SOCIAL AND NON-SOCIAL REWARD: NEURAL MECHANISMS IMPLICATED IN REWARD PROCESSING ACROSS DOMAINS AND CONTEXTS

EDITED BY: Johanna M. Jarcho, Jason M. Chein, Amanda E. Guyer, Regina Marie Sullivan and Marijn Van Wingerden

PUBLISHED IN: Frontiers in Behavioral Neuroscience

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88963-942-7
DOI 10.3389/978-2-88963-942-7

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

SOCIAL AND NON-SOCIAL REWARD: NEURAL MECHANISMS IMPLICATED IN REWARD PROCESSING ACROSS DOMAINS AND CONTEXTS

Topic Editors:
Johanna M. Jarcho, Temple University, United States
Jason M. Chein, Temple University, United States
Amanda E. Guyer, University of California, Davis, United States
Regina Marie Sullivan, New York University, United States
Marijn Van Wingerden, Heinrich Heine University of Düsseldorf, Germany

Citation: Jarcho, J. M., Chein, J. M., Guyer, A. E., Sullivan, R. M., Van Wingerden, M., eds. (2020). Social and Non-Social Reward: Neural Mechanisms Implicated in Reward Processing Across Domains and Contexts. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88963-942-7

Table of Contents

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 24 May 2019
doi: 10.3389/fnbeh.2019.00108

Associations Between Adolescents' Social Re-orientation Toward Peers Over Caregivers and Neural Response to Teenage Faces

Michele Morningstar[1,2], Connor Grannis[1], Whitney I. Mattson[1] and Eric E. Nelson[1,2]*

[1] Center for Biobehavioral Health, Nationwide Children's Hospital, Columbus, OH, United States, [2] Department of Pediatrics, The Ohio State University, Columbus, OH, United States

Adolescence is a period of intensive development in body, brain, and behavior. Potentiated by changes in hormones and neural response to social stimuli, teenagers undergo a process of social re-orientation away from their caregivers and toward expanding peer networks. The current study examines how relative relational closeness to peers (compared to parents) during adolescence is linked to neural response to the facial emotional expressions of other teenagers. Self-reported closeness with friends (same- and opposite-sex) and parents (mother and father), and neural response to facial stimuli during fMRI, were assessed in 8- to 19-year-old typically developing youth (n = 40, *mean* age = 13.90 years old, SD = 3.36; 25 female). Youth who reported greater relative closeness with peers than with parents showed decreased activation in the dorsolateral prefrontal cortex (dlPFC) during stimulus presentation, which may reflect lessened inhibitory control or regulatory response to peer-aged faces. Functional connectivity between the dlPFC and dorsal striatum was greatest in older youth who were closer to peers; in contrast, negative coupling between these regions was noted for both younger participants who were closer to peers and older participants who were closer to their parents. In addition, the association between relative closeness to peers and neural activation in regions of the social brain varied by emotion type and age. Results suggest that the re-orientation toward peers that occurs during adolescence is accompanied by changes in neural response to peer-aged social signals in social cognitive, prefrontal, and subcortical networks.

Keywords: adolescence, social development, peers, faces, social brain, relationships

OPEN ACCESS

Edited by:
Johanna M. Jarcho,
Temple University, United States

Reviewed by:
David Tai Hsu,
Stony Brook University, United States
Cecile D. Ladouceur,
University of Pittsburgh, United States

****Correspondence:***
Michele Morningstar
michele.morningstar@nationwidechildrens.org

Received: *04 March 2019*
Accepted: *02 May 2019*
Published: *24 May 2019*

Citation:
Morningstar M, Grannis C, Mattson WI and Nelson EE (2019) Associations Between Adolescents' Social Re-orientation Toward Peers Over Caregivers and Neural Response to Teenage Faces. Front. Behav. Neurosci. 13:108. doi: 10.3389/fnbeh.2019.00108

INTRODUCTION

Adolescence is often considered a second sensitive period of development, because it is a time when dramatic changes in emotion, cognition, and behavior take place (Crone and Dahl, 2012). Due in part to fluctuations in adrenarcheal and gonadal hormones during the teenage years (Forbes and Dahl, 2010; Byrne et al., 2017), marked structural and functional development occurs in numerous brain networks related to motivation (Forbes and Dahl, 2010; Goddings et al., 2012; Scherf et al., 2013), executive function (Crone, 2009; Ordaz et al., 2013; Satterthwaite et al., 2013), and social cognition (Blakemore, 2008). The neural maturation of detection, affective, and cognitive

regulation systems in the brain are thought to help guide the processing of increasingly complex socio-emotional stimuli during a period where teenagers begin to engage with broader social networks outside of their family environment [see social information processing network (SIPN) model; Nelson et al., 2005; Nelson et al., 2016].

In many contexts, adolescence is the apex of an inverted U-shaped maturational curve for affective or motivational responses, but represents only an intermediary point in the linear trajectory of higher cognitive functions (Casey et al., 2010a; Smith et al., 2014). For example, compared to children or adults, adolescents show heightened response to both threatening and rewarding stimuli in areas associated with motivational aspects of affective experience, such as the amygdala, striatum, anterior insula, and anterior cingulate cortex (Casey and Jones, 2010; Moore et al., 2012; van Duijvenvoorde et al., 2014; Smith et al., 2015, 2018; Braams et al., 2016; Guyer et al., 2016). However, prefrontal regions associated with cognitive regulation and the canalization of motivational responses continue to develop into adulthood, as does their neuromodulatory influence on subcortical affective systems (Steinberg, 2005; Crone, 2009; Casey et al., 2010b; Nelson and Guyer, 2011). In adolescence, immature prefrontal regulation of reward- and affect-related responses may be contributing to the heightened salience attributed to peers and other emotional stimuli (Guyer et al., 2009; Nelson and Guyer, 2011; Schriber and Guyer, 2016). Potentiated motivational responses to developmentally relevant stimuli, such as social cues from other youth, may be in fact an important mechanism that guides increases in engagement with peers (Larson and Richards, 1991; Nelson et al., 2016) during the teenage years.

Achieving independence from caregivers and integrating with peer networks is one of the more dramatic transitions that occurs during adolescence. Indeed, across both cultures and species, puberty is accompanied by a marked shift in social landscape, whereby individuals spend greater amounts of time with peers and less time in proximity to primary caretakers (Nelson et al., 2005; Forbes and Dahl, 2010; Crone and Dahl, 2012). This social re-orientation is likely encouraged by changes in emotional responses elicited by salient social cues, which promote adolescents' behavioral shift toward peers. For instance, though parents are the primary source of emotional support for 9- to 10-year-olds, youth's dependency on parents declines from early to mid-adolescence – with same-sex friends becoming the main source of support and intimacy for 15- to 16-year-olds (Hunter and Youniss, 1982; Furman and Buhrmester, 1992; Rice and Mulkeen, 1995; Lieberman et al., 1999; De Goede et al., 2009). At a physiological level, the presence of mothers has been found to buffer the cortisol stress response and modulate amygdala reactivity in children, but not in adolescents (Gee et al., 2014; Hostinar et al., 2015). Thus, the social re-orientation of adolescence is accompanied by a reconfiguration of the salience of social cues (Spear, 2000; Ladouceur, 2012), with peer-aged social signals becoming increasingly important relative to those of parents. This in turn promotes behavioral engagement with peers and associated social learning (Nelson et al., 2016), whereby teenagers adapt to the specific behavioral norms of new peer groups outside of the family environment to gain social acceptance (O'Brien and Bierman, 1988; Lamblin et al., 2017).

Changes in the valuation and salience of peers during adolescence may also guide the development of increasingly specialized neural networks for the processing of social information (Spear, 2000; Casey et al., 2010a; Nelson et al., 2016). Indeed, the maturation of perceptual and socio-emotional networks is thought to be guided by experience (Johnson et al., 2009; Leppanen and Nelson, 2009; Crone and Dahl, 2012; Pfeifer and Blakemore, 2012; Scherf and Scott, 2012; Dahl et al., 2018). In infancy, emotion and attention networks are attuned to salient social stimuli (Carver et al., 2003; Leppanen and Nelson, 2009) – such as caregiver faces and voices (Querleu et al., 1984; Bushneil et al., 1989; Carver et al., 2003; Tottenham et al., 2012) – when critical maturational changes are taking place within perceptual networks. Emotion-guided attention to caregivers is thought to play an important role in shaping the neuronal responses to these stimuli, which persist throughout subsequent developmental stages (Sugita, 2008; Leppanen and Nelson, 2009; Beauchemin et al., 2010; Nakato et al., 2011; Werker and Hensch, 2015). Similarly, when peers are gaining in emotional importance during adolescence, functional maturation is taking place in many brain areas involved in social cognition processes, such as the orbitofrontal and ventral lateral prefrontal cortex, amygdala, and posterior superior temporal sulcus (for reviews, see Paus, 2005; Blakemore, 2008; Burnett et al., 2011). These developmental changes coincide with increases in social cognition abilities, including mentalizing and the recognition of facial emotional expressions (Steinberg, 2005; Blakemore and Mills, 2014; Kilford et al., 2016; Foulkes and Blakemore, 2018). Therefore, the adolescent transition toward peers is likely to be mediated by relative shifts in emotion and motivation, and may promote social learning by guiding functional maturation of emerging social cognitive networks in the brain. However, though extensive work has examined both teenagers' changing relationships with peers and parents (e.g., Furman and Buhrmester, 1992; Steinberg and Morris, 2001) and their neural responses to socio-emotional stimuli (e.g., Burnett et al., 2009, 2011), the association between adolescents' social orientation toward peers versus parents and concomitant brain activation in response to peer-aged social stimuli has not been investigated.

The current study examines how age-related changes in self-reported emotional closeness to peers vs. parents in 40 typically developing adolescents (aged 8 to 19 years old) are associated with differential neural activation to peer-aged facial expressions of emotion. The SIPN model suggests that salience-related response in limbic structures may guide approach or avoidance behaviors toward developmentally relevant stimuli, such as socio-emotional cues from other teenagers (Nelson et al., 2005, 2016; Leppanen and Nelson, 2009). Thus, as youth re-orient toward their peers during adolescence, the facial non-verbal expressions of other teenagers are likely to be more salient and rewarding (e.g., Wright and Stroud, 2002; Chein et al., 2011; Picci and Scherf, 2016). For example, choosing to approach pictures of friends (over those of familiar peers or celebrities, using a joystick) has been associated with greater amygdala,

hippocampus, nucleus accumbens, and ventral medial prefrontal cortex activation in adolescents (Güroğlu et al., 2008), suggesting a valuation response to peers at this age. Similarly, adolescents showed more activation to videos of unfamiliar teenagers' emotions than of their parents' in mentalizing (temporal-parietal junction, posterior superior temporal sulcus) and subcortical emotion processing regions (ventral striatum, amygdala, and hippocampus; Saxbe et al., 2015). As such, we hypothesized that youth who reported greater closeness with their peers (compared to their parents) would also show increased neural response to peer-aged faces in reward- or affect-related regions (e.g., amygdala, ventral striatum, hippocampus) and social processing areas (e.g., temporal-parietal junction) of the brain.

In conjunction, response within cognitive-regulatory regions of the brain may be lower. Theories of adolescent neurodevelopment (including the SIPN and the dual-systems model; Nelson et al., 2016; Shulman et al., 2016) suggest that the motivational influence of peers on behavior during the teenage years may be due in part to insufficient prefrontal regulation of subcortical responses. As such, frontal cortical regions associated with cognitive regulation may not be as highly engaged in youth who show evidence of social re-orientation toward peers. However, there is likely to be change in the relative engagement of both the affective and cognitive-regulation node with peer-aged stimuli across development (Nelson et al., 2005). Further, given evidence of age-related changes in both peer relationships (Larson and Richards, 1991; Steinberg and Morris, 2001; Foulkes and Blakemore, 2018) and face processing (Cohen Kadosh and Johnson, 2007; Cohen Kadosh et al., 2011, 2013; Moore et al., 2012; Pfeifer and Blakemore, 2012), we expected that the association between peer experiences and neural response to teenagers' facial expressions of emotion would vary as a function of age from late childhood to late adolescence.

MATERIALS AND METHODS

Participants

The study sample included 40 typically developing youth (25 female) between the ages of 8 and 19 years old (M = 13.90, SD = 3.36). Because the timing of social re-orientation differs between individuals, we included participants within a broad age range to capture variation in social engagement across childhood and adolescence. Participants were recruited through a digital flyer distributed via email to employees of a large Midwestern children's hospital. Exclusion criteria included severe cognitive impairment and the presence of conditions or devices contraindicated for magnetic resonance imaging (MRI; e.g., braces, retainer, pacemaker), assessed via a metal screening form. Self-report of race indicated that 67.5% of the sample was Caucasian, 17.5% was Black or African American, and 15% was multiracial or of other ethnicities. Participants provided written assent or consent. Parents of participants younger than 18 provided written parental consent for their child's participation. All procedures were approved by the hospital Institutional Review Board.

Measures

Closeness to Peers and Parents

Closeness to peers and parents was assessed using the Network of Relationships Inventory – Relationship Qualities version (NRI) questionnaire (Furman and Buhrmester, 2009). Participants answered 30 questions about different aspects of their relationships with 6 people in their lives: best same-sex friend, best opposite-sex friend, boy/girlfriend, sibling, mother, and father (Since not all participants in our sample had a boy/girlfriend or a sibling, these relationships were excluded from further analyses). Relationship features are rated on a 5-point scale, from 1 = "never or hardly at all" to 5 = "always or extremely." The subscales for companionship, intimate disclosure, satisfaction, emotional support, and approval were averaged to create a "closeness score" for each relationship (Furman and Buhrmester, 2009). To assess relative closeness in different relationship types (e.g., peers compared to parents), we generated a closeness score for peers (average closeness with best same-sex and best opposite-sex friend; α = 0.93) and a closeness score for parents (average closeness with mother and father; α = 0.94) for each participant. Same- and opposite-sex friends were merged to obtain the peer closeness score, since the majority of youth report having meaningful opposite-sex friendships at this age (Kuttler et al., 1999). A Relative Closeness score was then obtained by subtracting closeness with parents from closeness with peers: positive values of Relative Closeness indicate greater closeness with peers than with parents, and negative values indicate greater closeness with parents than with peers.

Neural Response to Facial Expressions

Participants' neural response to facial stimuli was assessed in the context of a facial emotion recognition (ER) task. As part of a larger study, youth were presented with pictures of adolescents' facial expressions (conveying anger, fear, happiness, sadness, or neutral) and asked to identify the intended emotion from the above five labels while undergoing functional magnetic resonance imaging (fMRI). Facial stimuli were selected from the National Institute of Mental Health's Child Emotional Faces Picture Set (NIMH-ChEFS; Egger et al., 2011). Forty-five faces were produced by female adolescents (nine actors) and 45 by male adolescents (six actors), for a total of 90 facial expressions. Six faces were selected for each of the five emotional expressions. Within these six faces, three faces had their eyes averted away from the participant, and 3 faces had a straight eye gaze. The same child provided both the straight- and averted-gaze version of a stimulus. The stimuli were selected from the full dataset based on expression quality, judged by two research assistants (see **Supplementary Table 2** in **Supplementary Materials**).

Following training in a mock scanner, participants completed the ER task in the MRI scanner. Each trial was comprised of stimulus presentation (1 s in duration) followed by a 5-s response period. Participants viewed a computer monitor at the head of the magnet bore via a mirror attached to the head coil and responses were recorded using a Lumina handheld response device inside the scanner. Stimuli were presented in an event-related design with a jittered inter-trial interval between 1 and 8 s

(mean 4.5 s). A fixation cross was visible during the inter-trial interval and a pictogram of response labels was shown during the response period. The task was split into three runs of 30 faces, each lasting approximately 6 min. Each run contained a pseudorandomized order of faces that included a balanced number of stimuli per emotion type. Runs were presented in random order.

Image Acquisition and Processing

Magnetic resonance imaging data were collected on two Siemens 3 Tesla scanners running identical software, using standard 32- and 64-channel head coil arrays.[1] Imaging protocol included three-plane localizer scout images and an isotropic 3D T1-weighted anatomical scan covering the whole brain (MPRAGE). Imaging parameters for the MPRAGE were: 1 mm pixel dimensions, 176 sagittal slices, repetition time (TR) = 2200–2300 ms, echo time (TE) = 2.45–2.98 ms, field of view (FOV) = 248–256 mm. Functional MRI data were acquired with echo planar imaging (EPI) acquisitions, with a voxel size of 2.5 × 2.5 × 3.5–4 mm, and with the phase-encoding axis oriented in the anterior-posterior direction. During fMRI scans, dummy data were collected for 9.2 s while participants watched a blank screen. For fMRI scans, parameters were: TR = 1500 ms, TE = 30–43 ms, FOV = 240 mm.

Echo planar imaging images were preprocessed and analyzed in AFNI, version 18.0.11 (Cox, 1996). Functional images were corrected to the first volume, realigned to the AC/PC line, and coregistered to the T1 anatomical image. The image was subsequently normalized non-linearly to the Talairach template. After normalization, data were spatially smoothed with a Gaussian filter (FWHM, 6 mm kernel). Voxel-wise signal was scaled to a mean value of 100, and signal values above 200 were censored within each functional run. Volumes in which at least 10% of the voxels were considered to be signal outliers or contained movement greater than 1 mm between volumes were censored prior to analysis. Following this procedure, 4.1% of volumes were censored.[2]

Analysis

Relative Closeness With Peers and Parents

A general linear model was computed to examine the association between Relationship Type (within-subjects, two levels: peers vs. parents), Age (between-subjects; continuous, in years), and biological Sex (between-subjects, two levels: male vs. female) on NRI closeness scores. In addition, a regression was performed to examine the association between Age and NRI Relative Closeness scores.

Neural Response to Faces

Event-related response amplitudes were first estimated at the subject level. We convolved the hemodynamic response function with a base function that included a combined regressor for the presentation of the facial stimulus (1 s in duration) contrasted to the baseline fixation cross and response period. A regressor for stimulus emotion category (five levels) and nuisance regressors for motion (six affine directions) and scanner drift within the concatenated runs (3rd polynomial) were also included at the subject level. For group-level analyses, the contrast images produced for each participant were fit to a multivariate model (3dMVM in AFNI; Chen et al., 2014) of the effect of Emotion category, mean-centered Relative Closeness, and mean-centered Age on whole-brain activation, with participant Sex as a control variable. Within this model, we computed *F*-statistics for the main effects of Emotion, Age, Relative Closeness, and for the interactions of Relative Closeness × Age and Relative Closeness × Emotion. Cluster-size threshold corrections were estimated with the spatial autocorrelation function of 3dclustsim, based on Montecarlo simulations with study-specific smoothing estimates (Cox et al., 2016), with two-sided thresholding and first-nearest neighbor clustering, at $\alpha = 0.05$ and $p < 0.001$. The resulting cluster threshold of 27 voxels was applied to the results. Regions were identified at their peak activation point using the Talairach-Tournoux atlas.

RESULTS

Relative Closeness With Peers and Parents

There was a main effect of Relationship Type on closeness scores, $F(1, 37) = 21.21$, $p < 0.001$, $\eta^2 = 0.36$, such that participants reported generally greater closeness within their parental than peer relationships (**Table 1**). However, there was a significant interaction between Relationship Type and Age, $F(1, 37) = 15.66$, $p < 0.001$, $\eta^2 = 0.30$: parameter estimates suggested that closeness with peers increased with age ($B = 0.07$, $\beta = 0.29$, $p = 0.07$) and closeness with parents decreased with age ($B = -0.07$, $\beta = -0.47$, $p < 0.01$; see **Figure 1**). There was no main effect of Age ($p > 0.96$), Sex ($p > 0.60$), or interaction between Sex and Relationship Type ($p > 0.76$) on closeness. Further, Age predicted higher Relative Closeness scores, $\beta = 0.55$, $t(38) = 4.09$, $p < 0.001$, suggesting that older participants were closer to their peers (over parents) than were younger participants (**Figure 2**).

TABLE 1 | Closeness with peers, closeness with parents, and Relative Closeness scores on the NRI.

Relationship type	Mean	Standard deviation	Minimum	Maximum
Closeness to peers	3.52	0.81	1.60	5.00
Closeness to parents	3.87	0.49	2.97	4.67
Relative closeness to peers over parents (Relative Closeness)	−0.36	0.86	−2.17	1.80

[1]Due to scanner updates during data collection, five participants were tested on a different scanner than the other 35 participants. Results were highly similar to those presented in the manuscript when these participants were excluded from analyses (see **Supplementary Table 1** in **Supplementary Materials**).

[2]There were age effects on the amount of motion during the scan, such that age was negatively related to the fraction of censored volumes per participant ($\beta = -0.43$, $p = 0.006$). Including participants' fraction of total volumes censored as a covariate did not alter the results presented here (with the exception of the Age × Relative Closeness effect on the R-MTG cluster, which was just below cluster correction thresholds for size at 26 voxels).

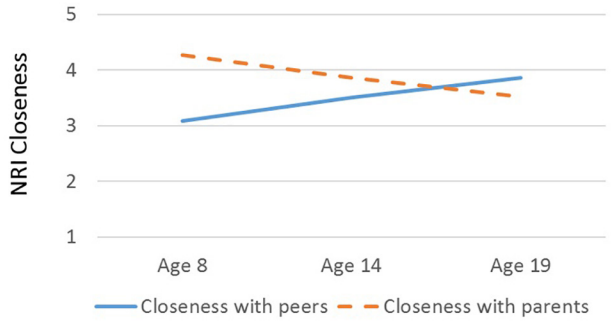


FIGURE 1 | Interaction between age (in years) and closeness scores on the Network of Relationships Inventory. Blue solid line, closeness to peers (same- and opposite-sex friend); orange dashed line, closeness to parents (mother and father). Plotted closeness scores are estimated from marginal means for different relationship types (peers vs. parents) at age 8, age 14, and age 19, with Sex held constant.

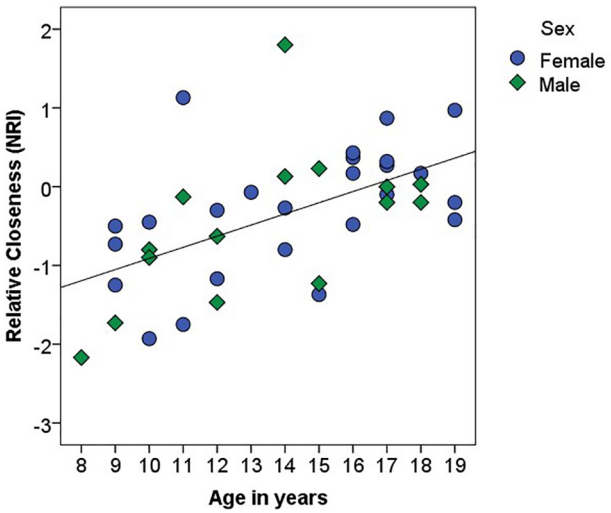


FIGURE 2 | Association between age (in years) and Relative Closeness on the Network of Relationships Inventory (NRI). Relative Closeness = closeness with peers – closeness with parents. Female participants are identified with blue circles; male participants are identified with green diamonds. The black line represents the linear relationship between the two variables (R^2 = 0.31).

Neural Response to Faces

There was a main effect of Emotion in several brain areas, including the medial frontal gyrus at midline, right inferior frontal gyrus, right and left insula, right superior temporal gyrus, and right and left temporo-parietal junction (**Table 2** and **Figure 3**). All of these clusters showed a similar emotion-specific pattern, whereby happy faces elicited relatively less activation than the other types of emotional faces (except for a cluster in the right insula, where neutral elicited relatively greater activation than the other emotions). There was no main effect of Age or Sex on brain activation to peer-aged faces. However, there was a main effect of Relative Closeness on activation in the left and right middle frontal gyri (L-MFG; R-MFG), where increased closeness with peers over parents was associated with lessened response to peer-aged faces (**Table 2** and **Figure 4**).

Further, there was an interaction of Relative Closeness and Emotion in the right inferior parietal lobule and supramarginal gyrus (i.e., temporo-parietal junction, or R-TPJ; **Table 2** and **Figure 5**). Parameter estimates for the effect of Relative Closeness on each emotion indicate that greater relative closeness with peers was associated with greater TPJ response to happy faces, $B = 0.10$, $\beta = 0.41$, $p = 0.03$, and lesser response to fearful faces, $B = -0.28$, $\beta = -0.50$, $p < 0.01$. Lastly, there was an interaction of Relative Closeness and Age in the bilateral orbitofrontal cortex at midline (B-OFC), the left inferior and middle temporal gyrus (L-MTG), and right middle temporal gyrus (R-MTG; **Table 2** and **Figure 6**). In all these clusters, activation to peer-aged faces was greatest in younger participants who were relatively closer to peers than parents, and in older participants who were relatively closer to parents than peers. Activation to peer-aged faces was lowest in younger participants who were relatively closer to parents than peers and in older participants who were relatively closer to peers than parents.

Functional Connectivity

To further understand their function in the context of the task, we conducted exploratory generalized psychophysiological interaction (gPPI) analyses (McLaren et al., 2012) to examine the functional connectivity of the two clusters in which a main effect of Relative Closeness with peers was noted (L-MFG and R-MFG). We first fit the same subject-level model to activation within those two regions of interest. We then performed a group-level model examining the effect of Age and Relative Closeness on functional connectivity with each of those seeds. Emotion and Sex were entered in the model as control variables. Identical cluster-size correction simulations were performed as above, with a resulting cluster threshold of 26 voxels.

For both the L-MFG and R-MFG seeds, there was an Age × Relative Closeness interaction on functional connectivity with the right precentral gyrus (R-PreCG; **Table 3** and **Figure 7**). In addition, there was also an Age × Relative Closeness interaction on functional connectivity between the R-MFG seed and both the right and left dorsal striatum (R-DS, L-DS; spanning the putamen and globus pallidus). Connectivity between seed regions and both the R-PreCG and dorsal striatum was strongest for older participants who were relatively closer to their peers than their parents. In contrast, a negative coupling between these regions was observed in younger participants who were closer to their peers, and in older participants who were closer to their parents.

DISCUSSION

The current study examined age-related changes in 8- to 19-year-olds' closeness with peers and parents, and investigated associations between relative closeness to peers and neural response to peer-aged facial expressions. Age was associated with increased relative closeness to peers over parents. Youth's neural activation to teenage faces in frontal and temporal regions, as well as the functional connectivity between the dorsolateral prefrontal

TABLE 2 | Effects of Relative Closeness, Age, and Emotion on neural activation to faces.

Effect structure	*F*	*k*	*x*	*y*	*z*	Generalized η^2	Brodmann area
Relative Closeness							
L middle frontal gyrus (L-MFG)	33.07	46	−39	49	11	0.17	10
R middle frontal gyrus (R-MFG)	28.76	43	29	19	41	0.19	8
Relative Closeness × Emotion							
R TPJ (R-TPJ)	7.42	34	59	−36	26	0.13	40
Relative Closeness × Age							
Bilateral orbitofrontal cortex (B-OFC)	33.01	97	4	24	−11	0.14	11, 32
L inferior/middle temporal gyrus (L-ITG)	25.11	41	−54	−21	−16	0.19	21
R middle temporal gyrus (R-MTG)	24.63	29	67	−29	−11	0.12	21
Emotion							
Bilateral cerebellum and lingual gyrus	31.76	2670	−11	−49	−16	0.32	N/A, 18
L precentral/postcentral gyrus	30.38	1436	−31	−29	51	0.31	4
R precentral/postcentral gyrus	44.60	1402	41	−26	49	0.45	4
Bilateral medial frontal gyrus	18.32	639	−6	6	49	0.13	6
R inferior frontal gyrus	10.03	339	34	4	29	0.07	44
L insula	16.56	287	−29	24	6	0.17	13
R insula	14.00	212	34	21	4	0.13	13
R insula/postcentral gyrus	21.00	285	41	−21	19	0.27	1
L TPJ	9.03	167	−51	−51	31	0.12	39
R TPJ	10.53	136	49	−51	31	0.15	39
R superior temporal gyrus	8.67	85	49	−34	6	0.08	21
L superior parietal lobule	8.64	66	−29	−56	44	0.08	7
R thalamus	11.13	50	16	−19	4	0.16	N/A
L medial frontal gyrus	8.93	46	−6	−14	51	0.08	6
Sex × Emotion							
L lingual gyrus	7.73	69	−6	−96	−1	0.04	18

Clusters listed here represent areas in which there were effects of Relative Closeness with peers, Age, Emotion, or their interactions on activation during stimulus presentation, controlling for Sex in the model. Clusters were formed using 3dclustsim at $p < 0.001$. Clusters of activation greater than the cluster size threshold of 27 voxels are presented here. There were no main effects of Age or Sex on activation. R, right; L, left; TPJ, temporal-parietal junction (e.g., supramarginal gyrus, angular gyrus, and inferior parietal lobule). k, cluster size in voxels. xyz coordinates represent the peak activation of the cluster, in Talairach-Tournoux space. η^2, eta squared.

cortex (dlPFC) and the dorsal striatum (DS), depended on youth's age and the extent of their orientation toward peers.

Closeness With Peers and Parents

Though younger participants reported greater closeness with their parents than with their peers, older adolescents showed the opposite pattern. Age was associated with greater relative closeness with peers over parents; by mid-adolescence (approximately age 16), the majority of youth had arguably shifted toward reporting closer relationships with their friends than their caregivers. These results are consistent with an extensive body of work demonstrating changes in support, intimacy, interaction frequency, and complexity of parental and peer relationships during adolescence (Hunter and Youniss, 1982; Larson and Richards, 1991; Furman and Buhrmester, 1992; Rice and Mulkeen, 1995; Lieberman et al., 1999; De Goede et al., 2009). The enhanced salience of peers likely reflects evolutionarily conserved motivational mechanisms that guide attention and behavior toward greater social networks. Though positive family relationships in adolescence are important for social competence and other positive achievement outcomes (Bell et al., 1985; Field et al., 2002), close friendships take on a primordial role for teenagers (Steinberg and Morris, 2001; Foulkes and Blakemore, 2018). Teenagers spend most of their day in peer interactions (Crockett et al., 1984), and the importance of social bonds increases across adolescence: indeed, intimacy within friendships was more closely tied to adjustment and social competence in relationships in 13- to 16-year-olds than in 10- to 13-year-olds (Buhrmester, 1990). Establishing oneself within peer networks is a particularly important task for adolescents, and may buffer the negative impact of social stressors like rejection (Masten et al., 2010; Silk et al., 2011).

Associations Between Relative Closeness With Peers and Neural Responses to Faces

As adolescents' social networks broaden with age, neural networks underlying reward evaluation, response inhibition, and affective processing undergo continued development (Yurgelun-Todd, 2007). There is increasing recognition that variations in the peer environment can contribute to individual differences in neurocognitive processing of social and emotional stimuli (Foulkes and Blakemore, 2018). In the framework of the SIPN model of adolescents' social and neural development, our hypothesis was that greater orientation toward peers (i.e., greater

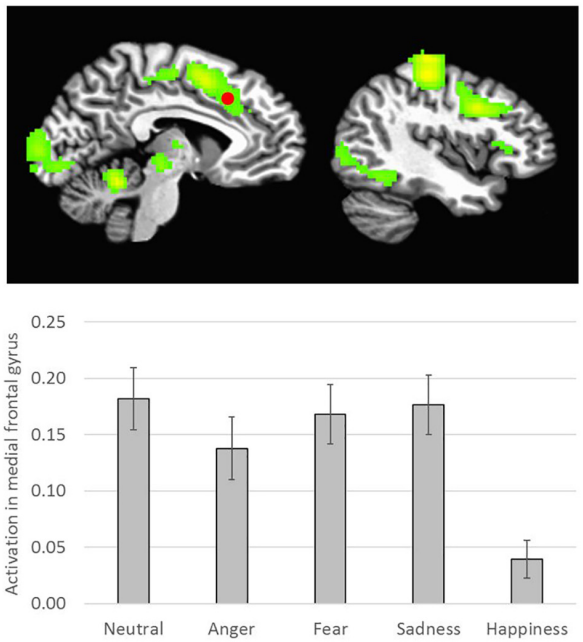


FIGURE 3 | Emotion-specific activation during stimulus presentation (i.e., *F* of Emotion). Clusters were formed using 3dclustsim at $p < 0.001$, with a cluster size threshold of 26 voxels. Brain images are rendered in the Talairach-Tournoux template space. Refer to **Table 2** for description of regions of activation. Bar graph represents estimated marginal means for effect of Emotion type on activation in the medial frontal gyrus (marked with a red dot on the brain image), with Sex, Relative Closeness, and Age held constant at the mean. Error bars represent the standard error of the mean.

relative closeness with peers than with parents) would be associated with increased response in reward- or affect-related nodes of the brain, but reduced activation in cognitive-regulatory regions. Results suggest that neural activation in, and functional connectivity between, these nodes varies with both relative closeness with peers and its interaction with age.

Contrary to our hypothesis, we did not find evidence that greater closeness with peers was associated with differential response in traditional affect-related regions of the brain, such as the amygdala or ventral striatum. However, individuals who reported greater relative closeness with peers over parents (collapsed across age) showed less activation in the dlPFC (i.e., R-MFG and L-MFG) than those who reported greater closeness with parents. Regions of the dlPFC have been implicated in many higher-order functions, such as working memory (e.g., Nelson et al., 2000; Cole and Schneider, 2007), decision-making (including risk-taking; e.g., Krain et al., 2006; Rao et al., 2008), emotion regulation (Golkar et al., 2012), and attentional or cognitive control (MacDonald et al., 2000; Cole and Schneider, 2007; Kompus et al., 2009; Kohn et al., 2014). The experimental paradigm we employed does not enable us to determine the precise function of the dlPFC in this task. However, the R-MFG and L-MFG clusters that varied by relative closeness with peers (located approximately in Brodmann areas 8 and 10) have been involved in the up- and down-regulation of emotional response (Li et al., 2018), impulse control in delay discounting tasks (Weygandt et al., 2015), the selection of "safe" choices in risk-taking paradigms (Chein et al., 2011; Crowley et al., 2015; Van Leijenhorst et al., 2010), and response inhibition in go-no-go (Li et al., 2006; Chikazoe et al., 2009) or Stroop tasks (Aarts et al., 2009). In the current study, it is possible that reduced activation in these regions is reflective of lessened inhibitory control responses to novel teenage faces – a pattern that would be expected in youth who were relatively closer to their peers than their parents. Alternatively, youth who are closer with peers may not need to engage as many emotion regulation or effortful control resources when responding to the facial expressions of peer-aged teenagers.

Though these interpretations are speculative and cannot be formally tested in the current study, functional connectivity analyses support the hypothesized inhibitory or regulatory function of the dlPFC. The coupling between both dlPFC seed regions and either the right precentral gyrus or the DS varied by participant age and their relative closeness with peers. Inhibitory control processes are thought to be mediated by a fronto-basal ganglia circuit (for reviews, see Verbruggen and Logan, 2008; Chikazoe, 2010) encompassing ventral and dorsal prefrontal regions and the globus pallidus in the DS (Aron and Poldrack, 2006; Dillon and Pizzagalli, 2007). Moreover, the DS itself has been found to contribute to aspects of reward processing and goal-directed action. Activation in the DS has been elicited by both reward and punishment (e.g., Bjork et al., 2004; Delgado, 2007; Münte et al., 2017), as well as the anticipation of rewards (e.g., Knutson et al., 2001; Spreckelmeyer et al., 2009). Further, the DS is thought to be implicated in the association between stimuli, actions, and rewards (O'Doherty, 2004; Haruno and Kawato, 2006; Balleine et al., 2007) and the encoding of the value of different outcomes (Delgado et al., 2003) in the context of reward-based learning.

Developmental neuroscience theories of adolescence have highlighted the "mismatch" in the timing of maturation between early-developing subcortical structures (including the striatum) and later-developing neocortical structures during the teenage years (Steinberg, 2005; Casey et al., 2011). Poor prefrontal regulatory influence on affect- or reward-related subcortical areas has been proposed to contribute to many phenotypic aspects of adolescence (e.g., Nelson et al., 2016; Shulman et al., 2016), including the heightened motivational salience of peers (Nelson and Guyer, 2011; Schriber and Guyer, 2016). In our sample, functional connectivity between the dlPFC and DS regions was strongest for older youth who were closer to their peers – those who, it may be argued, reported the developmentally expected patterns of orientation toward friends. In contrast, for youth who did not follow this pattern (and who were either closer to peers at a young age, or closer to parents in their late adolescence), there was a negative coupling between the dlPFC and the DS. Thus, younger youth who were closer to their peers showed lower dlPFC and greater DS activation in response to peer-aged faces, whereas older youth who were closer to their parents showed greater dlPFC and lower DS activation. It is possible that differences in connectivity for younger participants may be driven by immature structural connections between frontal and striatal regions; however, the presence of a similar pattern

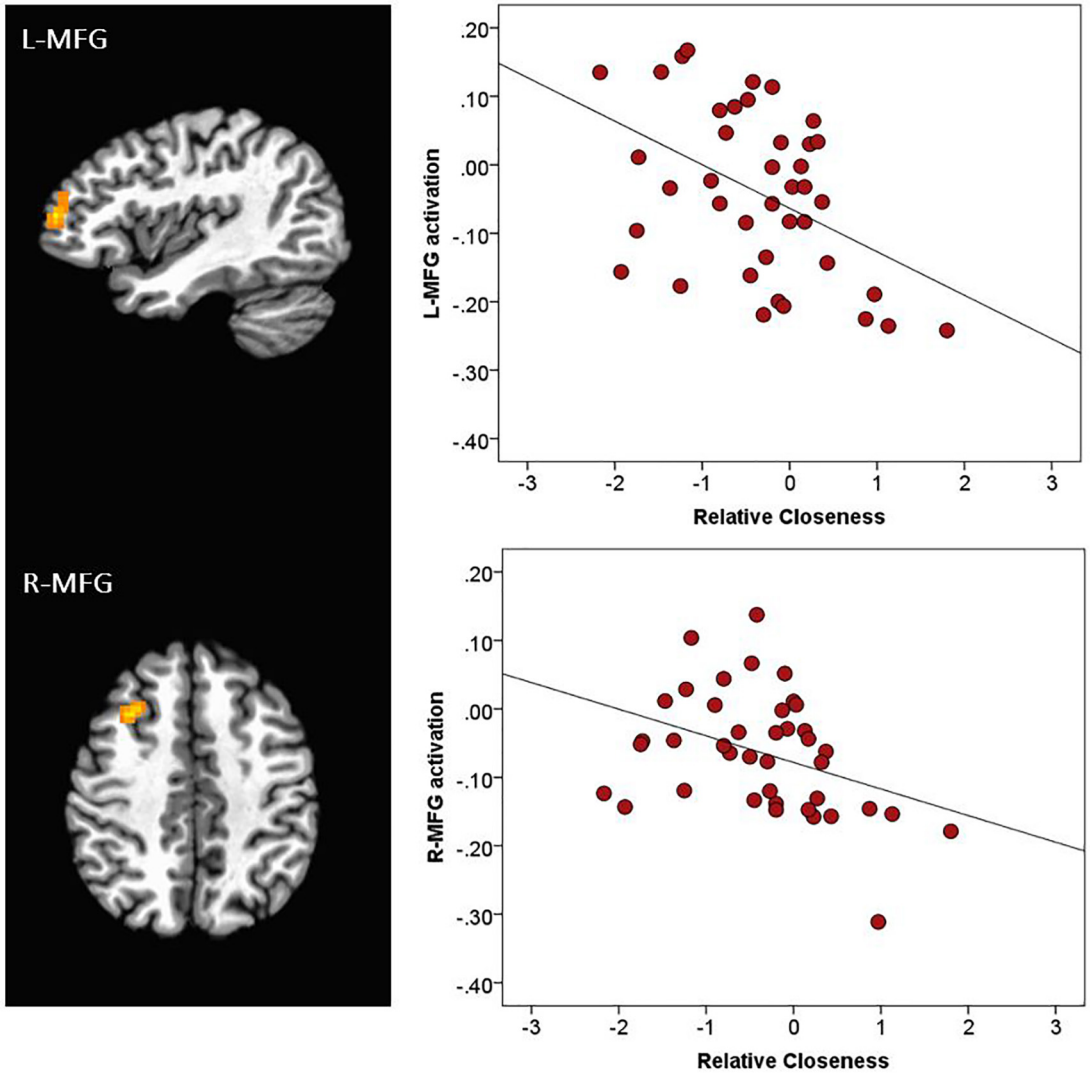


FIGURE 4 | Activation during stimulus presentation associated with participants' relative closeness with peers over parents. R, right; L, left. MFG, middle frontal gyrus. Clusters were formed using 3dclustsim at $p < 0.001$, with a cluster size threshold of 27 voxels. Brain images are rendered in the Talairach-Tournoux template space. Refer to **Table 2** for description of regions of activation. The black line on the scatterplots represents the linear relationship between neural activation and Relative Closeness (L-MFG: $R^2 = 0.20$; R-MFG: $R^2 = 0.15$).

for older adolescents suggests that variations in brain structure are not sufficient to explain these findings. Alternatively, these respective neural patterns may be associated with the facilitation of orientation toward peers (low inhibitory control paired with high response in valuation-related regions) or the hindrance of this behavioral tendency (high inhibitory control and low valuation response). This interpretation is strictly hypothetical, though it is in line with theoretical predictions about the interplay of changes in social behavior, the salience of peers, and the interaction of affective and cognitive-regulatory nodes of the brain (Nelson et al., 2016). To test this hypothesis, future studies should explore how social re-orientation is associated with dlPFC and DS activation in tasks that explicitly assess reward processing and inhibitory control in response to peer-aged social cues.

Further, the association between relative closeness with peers and neural activation to faces in several regions of the social brain was found to vary depending on either (a) stimulus emotion, or (b) participant age. Emotion-specific differences in closeness-related activation were found in the right TPJ, an area heavily involved in social cognitive functions like the perception and interpretation of others' affect and beliefs (Saxe and Wexler, 2005; Van Overwalle, 2009). Specifically, youth who were closer to their peers than their parents (regardless of their age) showed greater activation to happy faces, and less activation to fearful faces, in the TPJ. This finding is consistent with past work indicating that 14- to 18-year-olds who reported greater emotional closeness with their peers showed heightened TPJ response to social reward (Flores et al., 2018). Happy faces

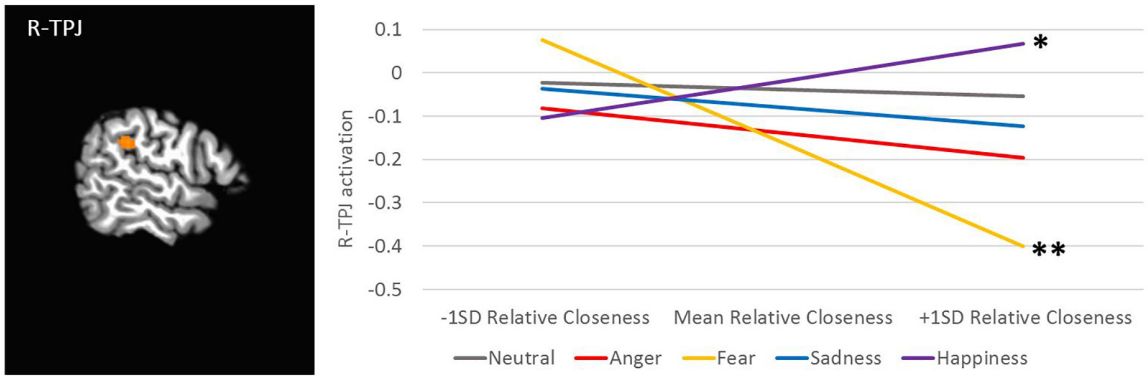


FIGURE 5 | Interaction between participants' relative closeness and facial emotion type on neural activation during stimulus presentation. R, right; TPJ, temporal-parietal junction. Cluster was formed using 3dclustsim at $p < 0.001$, with a cluster size threshold of 27 voxels. Brain image is rendered in the Talairach-Tournoux template space. Refer to **Table 2** for description of region of activation. Plotted activation in the line graph is estimated from marginal means for activation by emotion type at low levels of Relative Closeness (–1 standard deviation), mean levels of Relative Closeness, and high levels of Relative Closeness (+1 standard deviation), with Sex and Age held constant at the mean. SD, standard deviation. The significance of the slope for different emotions (i.e., slope ≠ 0) is noted as $*p < 0.05$, $**p < 0.01$.

TABLE 3 | Generalized psychophysiological interaction analyses on functional connectivity with clusters of Relative Closeness-related activation.

Structure	*F*	*k*	*x*	*y*	*z*	Generalized η^2	Brodmann area
Seed in L-MFG							
R precentral gyrus (R-PreCG)	24.41	27	59	1	19	0.17	6
Seed in R-MFG							
R precentral gyrus (R-PreCG)	37.87	35	64	−1	21	0.14	6
R dorsal striatum (R-DS)	31.91	116	21	−11	−1	0.13	N/A
L dorsal striatum (L-DS)	26.42	28	−24	−1	−6	0.11	N/A

Clusters listed here represent areas in which there was an interaction between Age and Relative Closeness on functional connectivity with the seed regions. Clusters were formed using 3dclustsim at $p < 0.001$. R, right; L, left. MFG, middle frontal gyrus. k, cluster size in voxels. xyz coordinates represent the peak activation of the cluster, in Talairach-Tournoux space. η^2, eta squared. Some clusters were noted in the cerebellum (culmen) but are not noted here (available from first author). There were no main effects of Age, Relative Closeness, or Emotion on functional connectivity with either seed. A main effect of Sex on functional connectivity with the L-MFG seed was noted in the right insula, such that coupling between the two regions was greater for girls than boys (additional details available from first author).

are generally considered to be rewarding social cues, whereas fearful faces may be aversive or socially threatening. Elevated TPJ response to positive social cues and reduced response to negative cues may underlie a tendency to recruit mentalizing networks more in the context of social approach signals, which may facilitate positive mutual engagement with peers.

Age-related variations in the association between relative closeness and brain activation were also noted in the orbitofrontal cortex (OFC) and the temporal lobes. Greater activation in these brain regions was noted for younger participants who were closer to their peers than parents, and older youth who were closer to their parents. The temporal lobes are extensively involved in multimodal and affective integration of social stimuli (Zilbovicius et al., 2006; Morin et al., 2014; Pitcher et al., 2017), while the medial portions of the OFC are generally implicated in valuation and reward (O'Doherty et al., 2001; Roelofs et al., 2008; Leppanen and Nelson, 2009; Murray and Wise, 2010). In the present context, this pattern of activation may indicate enhanced value and integrative processing of peer stimuli in young adolescents who are particularly drawn to their peers, but also in older adolescents and young adults who have not developed close bonds with their friends. Though speculative, it is possible that the increased activation in the above social brain regions reflects increased valuation of peer-aged cues for these two groups of teenagers who must either continue to orient toward peers or begin to do so.

Strengths and Limitations

To our knowledge, this is the first study that examines associations between youth's social orientation toward peers (i.e., emotional closeness with friends compared to parents) and their neural response to peer-aged facial expressions of emotion. Though the current study did not assess social behaviors with peers, results highlight potential neural markers of social re-orientation that may either accompany or facilitate behavioral approach toward peers during the teenage years (Nelson et al., 2016). However, limitations must be noted. First, we used youth's relative closeness to peers compared to their closeness with their parents as a proxy for social orientation tendencies; future studies will need to supplement this estimate of social development with objective measures of social experiences and behaviors, such as those obtained with ecological momentary assessment paradigms. Second, the current study only evaluated youth's neural response to peer-aged faces. A more stringent test of our hypothesis that individual variations in social orientation are associated with differential neural response to peer-aged cues requires the inclusion of adult faces as a comparison condition. The use of individualized stimuli obtained from participants' own friends and parents

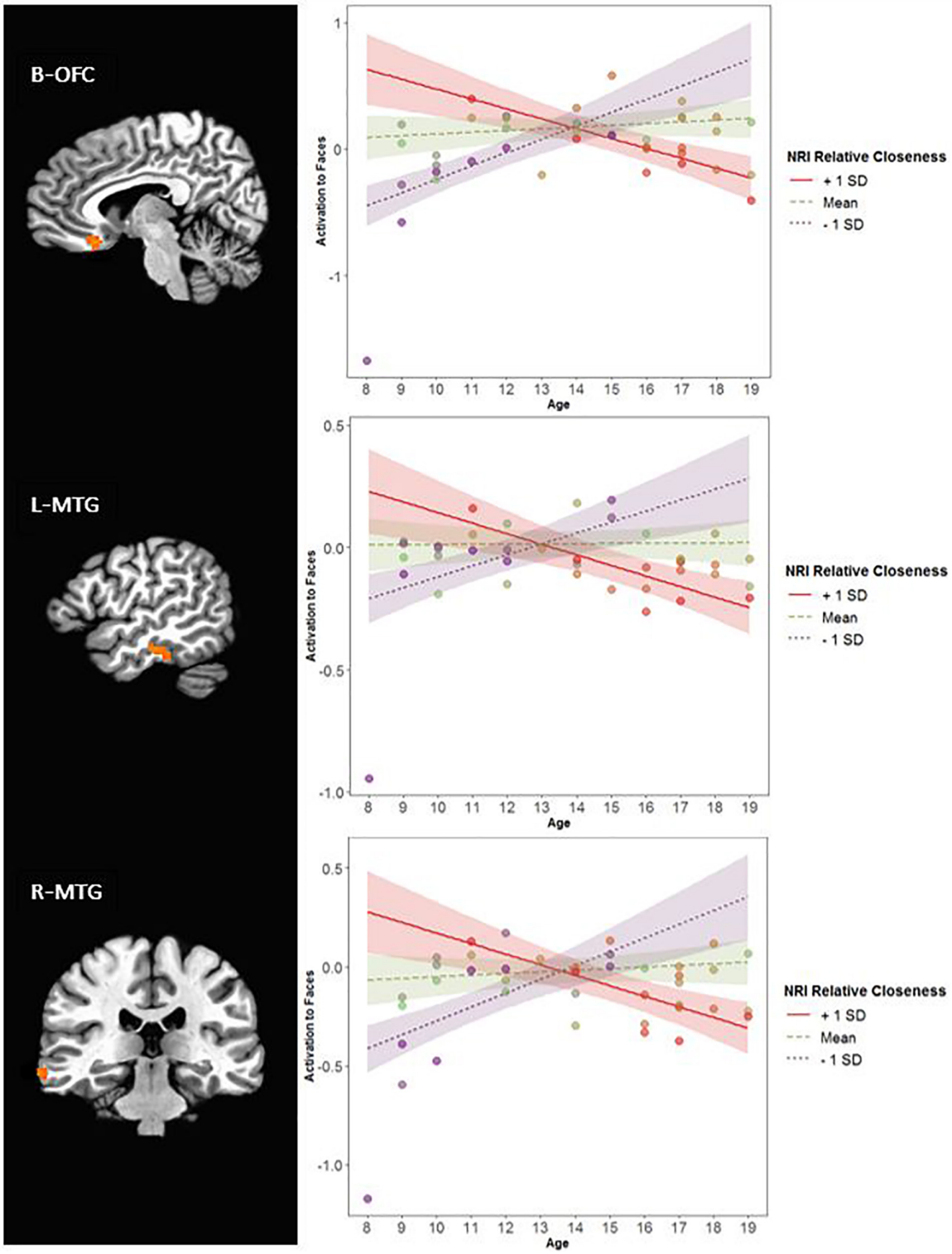


FIGURE 6 | Interaction between participants' relative closeness and age on neural activation during stimulus presentation. R, right; L, left; B, bilateral. OFC, orbitofrontal cortex; MTG, middle temporal gyrus. Clusters were formed using 3dclustsim at $p < 0.001$, with a cluster size threshold of 27 voxels. Brain images are rendered in the Talairach-Tournoux template space. Refer to **Table 2** for description of regions of activation. Plotted activation in the line graphs represents estimated activation at low levels of Relative Closeness (–1 standard deviation), mean levels of Relative Closeness, and high levels of Relative Closeness (+1 standard deviation). SD, standard deviation. Colored bands surrounding the regression lines represent 95% confidence intervals. Of note, all interactions remained significant when the 8-year-old participant with low activation in these regions was removed.

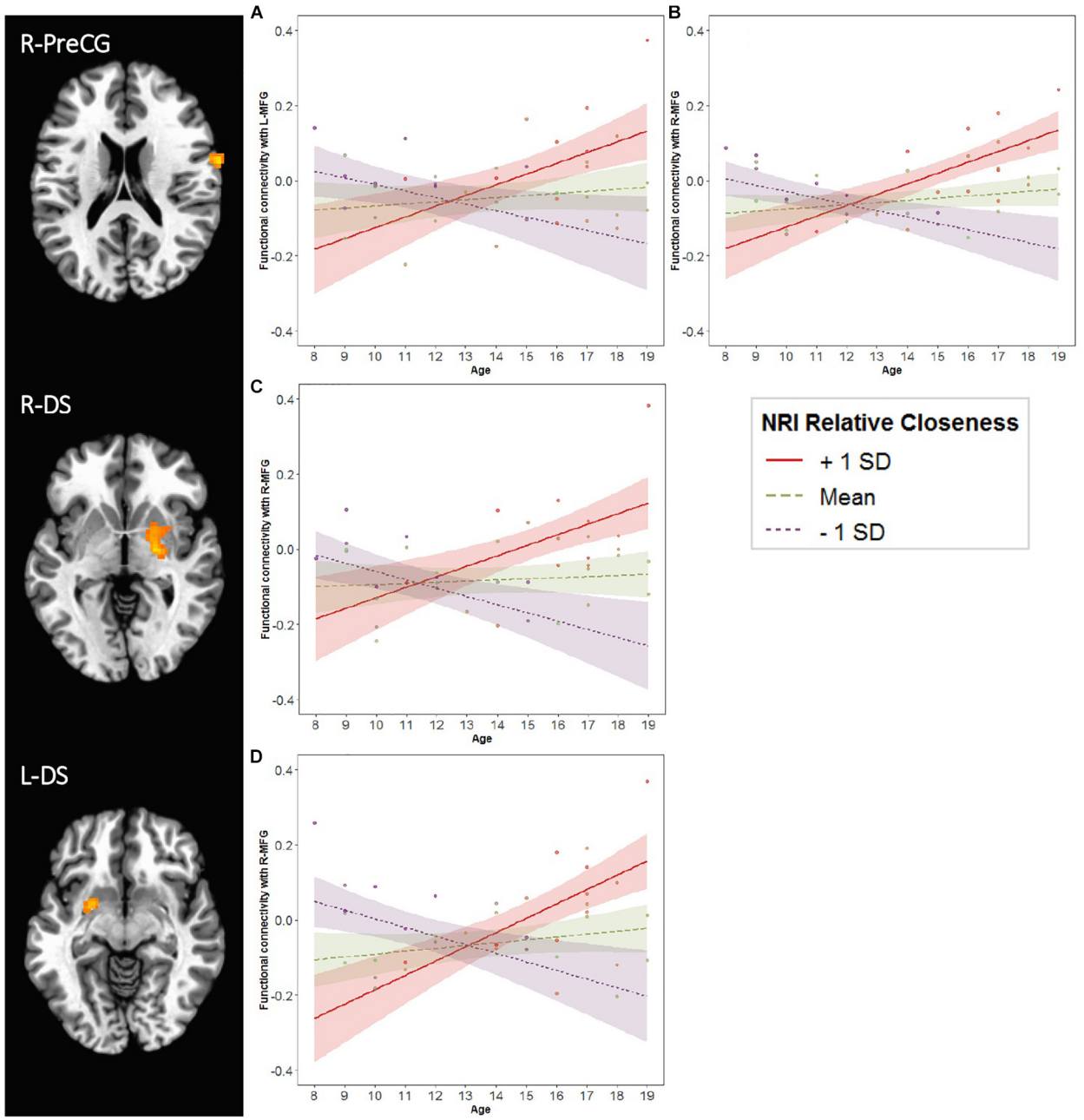


FIGURE 7 | Age and Relative Closeness-related changes in functional connectivity with left and right middle frontal gyrus (MFG). Generalized psychophysiological interactions were computed by placing a seed in each of the two MFG clusters (L-MFG and R-MFG; see **Table 2** and **Figure 4**). Brain regions above represent areas for which there was an interaction of Age × Relative Closeness on functional connectivity with the seeds. Clusters were formed using 3dclustsim at $p < 0.001$, with a cluster size threshold of 27 voxels. Refer to **Table 3** for description of regions of activation. Brain images are rendered in the Talairach-Tournoux template space. L, left; R, right. PreCG, precentral gyrus; DS, dorsal striatum. The line graphs illustrate the Age × Relative Closeness on functional connectivity between the R-PreCG and L-MFG (graph **A**), the R-PreCG and R-MFG (graph **B**), the R-DS and R-MFG (graph **C**), and the L-DS and R-MFG (graph **D**). SD, standard deviation; NRI, Network of Relationships Inventory.

would have also provided more specific information about the neural representation of social experiences in close relationships. Though adolescents' processing of unfamiliar peers' faces is relevant to the process of integrating with novel social groups during the teenage years, future work would benefit from the use of personally relevant stimuli in experimental paradigms assessing social cognition.

Third, the current study cannot pinpoint the extent to which changes in emotional closeness with others and neural responses to emotional faces are due to variations in adrenarcheal or

gonadal hormones (e.g., Whittle et al., 2015). Pubertal status, as well as the timing and tempo of pubertal development, are thought to play a large role in psychological and neural functioning (Angold et al., 1998; Lenroot and Giedd, 2010; Byrne et al., 2017). Though age and pubertal status are highly correlated, the assessment of pubertal maturation would add to our understanding of developmental changes in both social behavior and the neural processing of facial stimuli. Replication in a larger sample size would also strengthen our conclusions about age-related changes in brain activation patterns across late childhood and adolescence. Lastly, the present design does not enable tests of directionality. As individual differences in peer environments may influence neural response to social stimuli, so may individual differences in neurobiology affect adolescents' social behaviors and sensitivity to socio-emotional cues (Foulkes and Blakemore, 2018). Additional work in longitudinal frameworks would help clarify the association between neural response and social experiences in adolescence.

CONCLUSION

Adolescence is characterized by a myriad of changes in body, brain, and behavior. Among these transitions, the teenage years are marked by a social re-orientation toward peers – a process that is likely bolstered and accompanied by changes in how social stimuli from other adolescents are valuated and processed neurally. The results of the current study suggest that individual differences in teenagers' peer experiences (denoting social re-orientation toward friends, or a lack thereof) are associated with differential brain responses to peer-aged faces. Age was associated with greater relative closeness to peers than to parents, which can be conceptualized as a marker of having achieved the transition toward a broader peer network. Across all ages, greater relative closeness to peers itself was related to (a) lessened activation in frontal regions associated with inhibitory or regulatory functions, (b) reduced response to fearful social cues in the TPJ, and (c) greater response to positive social cues in the TPJ. In addition, both activation within regions of the social brain (orbitofrontal cortex, temporal lobes), and functional connectivity between dorsolateral prefrontal cortex and the dorsal striatum, varied as a function of youth's age and closeness to peers. Specifically, both increased activation in frontal and temporal regions involved in the evaluation of socio-emotional stimuli, and negative coupling between the dlPFC and DS, were noted in early adolescents who had transitioned toward peers, and late adolescents who had failed to do so. Though replication with extended study designs will be necessary, such neural response to peer-aged cues may support the positive valuation of peers that may be necessary to encourage motivational tendencies toward peer interactions.

In conclusion, engaging with peers and forming close social bonds is a crucial developmental task, which may be accompanied by changing neural response to peers' social signals in social cognitive, inhibitory control, and reward-related networks. Understanding the normative interrelated changes to neural systems and social behavior in adolescence is necessary for the characterization of typical developmental trajectories and deviations from those norms in teenagers who struggle to form meaningful peer relationships.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Institutional Review Board of the Research Institute at Nationwide Children's Hospital with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board.

AUTHOR CONTRIBUTIONS

All authors contributed to the study design, data collection, statistical analysis, and manuscript preparation.

FUNDING

This work was supported by Intramural funds at Nationwide Children's Hospital, Center for Biobehavioral Health and Fonds de recherche du Québec – Nature et technologies (Grant No. 207776).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2019.00108/full#supplementary-material

REFERENCES

Aarts, E., Roelofs, A., and van Turennout, M. (2009). Attentional control of task and response in lateral and medial frontal cortex: brain activity and reaction time distributions. *Neuropsychologia* 47, 2089–2099. doi: 10.1016/j.neuropsychologia.2009.03.019

Angold, A., Costello, E. J., and Worthman, C. M. (1998). Puberty and depression: the roles of age, pubertal status and pubertal timing. *Psychol. Med.* 28, 51–61.

Aron, A. R., and Poldrack, R. A. (2006). Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. *J. Neurosci.* 26, 2424–2433.

Balleine, B. W., Delgado, M. R., and Hikosaka, O. (2007). The role of the dorsal striatum in reward and decision-making. *J. Neurosci.* 27, 8161–8165.

Beauchemin, M., Gonzalez-Frankenberger, B., Tremblay, J., Vannasing, P., Martínez-Montes, E., Belin, P., et al. (2010). Mother and stranger: an electrophysiological study of voice processing in newborns. *Cereb. Cortex* 21, 1705–1711. doi: 10.1093/cercor/bhq242

Bell, N. J., Avery, A. W., Jenkins, D., Feld, J., and Schoenrock, C. J. (1985). Family relationships and social competence during late adolescence. *J. Youth Adolesc.* 14, 109–119. doi: 10.1007/BF02098651

Bjork, J. M., Knutson, B., Fong, G. W., Caggiano, D. M., Bennett, S. M., and Hommer, D. W. (2004). Incentive-elicited brain activation in adolescents: similarities and differences from young adults. *J. Neurosci.* 24, 1793–1802.

Blakemore, S. J. (2008). The social brain in adolescence. *Nat. Rev. Neurosci.* 9, 267–277. doi: 10.1038/nrn2353

Blakemore, S. J., and Mills, K. L. (2014). Is adolescence a sensitive period for sociocultural processing? *Annu. Rev. Psychol.* 65, 187–207. doi: 10.1146/annurev-psych-010213-115202

Braams, B. R., Peper, J. S., van der Heide, D., Peters, S., and Crone, E. A. (2016). Nucleus accumbens response to rewards and testosterone levels are related to alcohol use in adolescents and young adults. *Dev. Cogn. Neurosci.* 17, 83–93. doi: 10.1016/j.dcn.2015.12.014

Buhrmester, D. (1990). Intimacy of friendship, interpersonal competence, and adjustment during preadolescence and adolescence. *Child Dev.* 61, 1101–1111.

Burnett, S., Bird, G., Moll, J., Frith, C., and Blakemore, S. J. (2009). Development during adolescence of the neural processing of social emotion. *J. Cogn. Neurosci.* 21, 1736–1750. doi: 10.1162/jocn.2009.21121

Burnett, S., Sebastian, C., Cohen Kadosh, K., and Blakemore, S. J. (2011). The social brain in adolescence: evidence from functional magnetic resonance imaging and behavioural studies. *Neurosci. Biobehav. Rev.* 35, 1654–1664. doi: 10.1016/j.dcn.2014.07.009

Bushneil, I. W. R., Sai, F., and Mullin, J. T. (1989). Neonatal recognition of the mother's face. *Br. J. Dev. Psychol.* 7, 3–15.

Byrne, M. L., Whittle, S., Vijayakumar, N., Dennison, M., Simmons, J. G., and Allen, N. B. (2017). A systematic review of adrenarche as a sensitive period in neurobiological development and mental health. *Dev. Cogn. Neurosci.* 25, 12–28. doi: 10.1016/j.dcn.2016.12.004

Carver, L. J., Dawson, G., Panagiotides, H., Meltzoff, A. N., McPartland, J., Gray, J., et al. (2003). Age-related differences in neural correlates of face recognition during the toddler and preschool years. *Dev. Psychobiol.* 42, 148–159.

Casey, B. J., Duhoux, S., and Malter Cohen, M. (2010a). Adolescence: what do transmission, transition, and translation have to do with it? *Neuron* 67, 749–760. doi: 10.1016/j.neuron.2010.08.033

Casey, B. J., Jones, R. M., Levita, L., Libby, V., Pattwell, S. S., Ruberry, E. J., et al. (2010b). The storm and stress of adolescence: insights from human imaging and mouse genetics. *Dev. Psychobiol.* 52, 225–235. doi: 10.1002/dev.20447

Casey, B. J., and Jones, R. M. (2010). Neurobiology of the adolescent brain and behavior: implications for substance use disorders. *J. Am. Acad. Child Adolesc. Psychiatry* 49, 1189–1285. doi: 10.1016/j.jaac.2010.08.017

Casey, B. J., Jones, R. M., and Somerville, L. H. (2011). Braking and accelerating of the adolescent brain. *J. Res. Adolesc.* 21, 21–33.

Chein, J., Albert, D., O'Brien, L., Uckert, K., and Steinberg, L. (2011). Peers increase adolescent risk taking by enhancing activity in the brain's reward circuitry. *Dev. Sci.* 14, F1–F10. doi: 10.1111/j.1467-7687.2010.01035.x

Chen, G., Adleman, N. E., Saad, Z. S., Leibenluft, E., and Cox, R. W. (2014). Applications of multivariate modeling to neuroimaging group analysis: a comprehensive alternative to univariate general linear model. *Neuroimage* 99, 571–588. doi: 10.1016/j.neuroimage.2014.06.027

Chikazoe, J. (2010). Localizing performance of go/no-go tasks to prefrontal cortical subregions. *Curr. Opin. Psychiatry* 23, 267–272. doi: 10.1097/YCO.0b013e3283387a9f

Chikazoe, J., Jimura, K., Asari, T., Yamashita, K., Morimoto, H., Hirose, S., et al. (2009). Functional dissociation in right inferior frontal cortex during performance of go/no-go task. *Cereb. Cortex* 19, 146–152. doi: 10.1093/cercor/bhn065

Cohen Kadosh, K., Cohen Kadosh, R., Dick, F., and Johnson, M. H. (2011). Developmental changes in effective connectivity in the emerging core face network. *Cereb. Cortex* 21, 1389–1394. doi: 10.1093/cercor/bhq215

Cohen Kadosh, K., and Johnson, M. H. (2007). Developing a cortex specialized for face perception. *Trends Cogn. Sci.* 11, 367–369.

Cohen Kadosh, K., Johnson, M. H., Henson, R. N., Dick, F., and Blakemore, S. J. (2013). Differential face-network adaptation in children, adolescents and adults. *Neuroimage* 69, 11–20. doi: 10.1016/j.neuroimage.2012.11.060

Cole, M. W., and Schneider, W. (2007). The cognitive control network: integrated cortical regions with dissociable functions. *Neuroimage* 37, 343–360.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res.* 29, 162–173.

Cox, R. W., Reynolds, R. C., and Taylor, P. A. (2016). AFNI and clustering: false positive rates redux. *Brain Connect.* 7, 152–171. doi: 10.1089/brain.2016.0475

Crockett, L., Losoff, M., and Petersen, A. C. (1984). Perceptions of the peer group and friendship in early adolescence. *J. Early Adolesc.* 4, 155–181.

Crone, E. A. (2009). Executive functions in adolescence: inferences from brain and behavior. *Dev. Sci.* 12, 825–830. doi: 10.1111/j.1467-7687.2009.00918.x

Crone, E. A., and Dahl, R. E. (2012). Understanding adolescence as a period of social–affective engagement and goal flexibility. *Nat. Rev. Neurosci.* 13, 636–650. doi: 10.1038/nrn3313

Crowley, T. J., Dalwani, M. S., Mikulich-Gilbertson, S. K., Young, S. E., Sakai, J. T., Raymond, K. M., et al. (2015). Adolescents' neural processing of risky decisions: effects of sex and behavioral disinhibition. *PLoS One* 10:e0132322. doi: 10.1371/journal.pone.0132322

Dahl, R. E., Allen, N. B., Wilbrecht, L., and Suleiman, A. B. (2018). Importance of investing in adolescence from a developmental science perspective. *Nature* 554, 441–450. doi: 10.1038/nature25770

De Goede, I. H. A., Branje, S. J. T., Delsing, M. J. M. H., and Meeus, W. H. J. (2009). Linkages over time between adolescents' relationships with parents and friends. *J. Youth Adolesc.* 38, 1304–1315. doi: 10.1007/s10964-009-9403-2

Delgado, M. R. (2007). Reward-related responses in the human striatum. *Ann. N. Y. Acad. Sci.* 1104, 70–88.

Delgado, M. R., Locke, H. M., Stenger, V. A., and Fiez, J. A. (2003). Dorsal striatum responses to reward and punishment: effects of valence and magnitude manipulations. *Cogn. Affect. Behav. Neurosci.* 3, 27–38.

Dillon, D. G., and Pizzagalli, D. A. (2007). Inhibition of action, thought, and emotion: a selective neurobiological review. *Appl. Prev. Psychol.* 12, 99–114.

Egger, H. L., Pine, D. S., Nelson, E., Leibenluft, E., Ernst, M., Towbin, K. E., et al. (2011). The NIMH child emotional faces picture Set (NIMH-ChEFS): a new set of children's facial emotion stimuli. *Int. J. Methods in Psychiatr. Res.* 20, 145–156. doi: 10.1002/mpr.343

Field, T., Diego, M., and Sanders, C. (2002). Adolescents' parent and peer relationships. *Adolescence* 37, 121–130.

Flores, L. E., Eckstrand, K. L., Silk, J. S., Allen, N. B., Ambrosia, M., Healey, K. L., et al. (2018). Adolescents' neural response to social reward and real-world emotional closeness and positive affect. *Cogn. Affect. Behav. Neurosci.* 18, 705–717. doi: 10.3758/s13415-018-0598-0

Forbes, E. E., and Dahl, R. E. (2010). Pubertal development and behavior: hormonal activation of social and motivational tendencies. *Brain Cogn.* 72, 66–72. doi: 10.1016/j.bandc.2009.10.007

Foulkes, L., and Blakemore, S.-J. (2018). Studying individual differences in human adolescent brain development. *Nat. Neurosci.* 21, 315–323. doi: 10.1038/s41593-018-0078-4

Furman, W., and Buhrmester, D. (1992). Age and sex differences in perceptions of networks of personal relationships. *Child Dev.* 63, 103–115.

Furman, W., and Buhrmester, D. (2009). The network of relationships inventory: behavioral systems version. *Int. J. Behav. Dev.* 33, 470–478.

Gee, D. G., Gabard-Durnam, L., Telzer, E. H., Humphreys, K. L., Goff, B., Shapiro, M., et al. (2014). Maternal buffering of human amygdala-prefrontal circuitry during childhood but not during adolescence. *Psychol. Sci.* 25, 2067–2078. doi: 10.1177/0956797614550878

Goddings, A. L., Burnett Heyes, S., Bird, G., Viner, R. M., and Blakemore, S. J. (2012). The relationship between puberty and social emotion processing. *Dev. Sci.* 15, 801–811. doi: 10.1111/j.1467-7687.2012.01174.x

Golkar, A., Lonsdorf, T. B., Olsson, A., Lindstrom, K. M., Berrebi, J., Fransson, P., et al. (2012). Distinct contributions of the dorsolateral prefrontal and orbitofrontal cortex during emotion regulation. *PLoS One* 7:e48107. doi: 10.1371/journal.pone.0048107

Güroğlu, B., Haselager, G. J. T., van Lieshout, C. F. M., Takashima, A., Rijpkema, M., and Fernández, G. (2008). Why are friends special? Implementing a social interaction simulation task to probe the neural correlates of friendship. *Neuroimage* 39, 903–910.

Guyer, A. E., McClure-Tone, E. B., Shiffrin, N. D., Pine, D. S., and Nelson, E. E. (2009). Probing the neural correlates of anticipated peer evaluation in adolescence. *Child Dev.* 80, 1000–1015. doi: 10.1111/j.1467-8624.2009.01313.x

Guyer, A. E., Silk, J. S., and Nelson, E. E. (2016). The neurobiology of the emotional adolescent: from the inside out. *Neurosci. Biobehav. Rev.* 70, 74–85. doi: 10.1016/j.neubiorev.2016.07.037

Haruno, M., and Kawato, M. (2006). Different neural correlates of reward expectation and reward expectation error in the putamen and caudate nucleus during stimulus-action-reward association learning. *J. Neurophysiol.* 95, 948–959.

Hostinar, C. E., Johnson, A. E., and Gunnar, M. R. (2015). Parent support is less effective in buffering cortisol stress reactivity for adolescents compared to children. *Dev. Sci.* 18, 281–297. doi: 10.1111/desc.12195

Hunter, F. T., and Youniss, J. (1982). Changes in functions of three relations during adolescence. *Dev. Psychol.* 18, 806–811.

Johnson, M. H., Grossmann, T., and Cohen Kadosh, K. (2009). Mapping functional brain development: building a social brain through interactive specialization. *Dev. Psychol.* 45, 151–159. doi: 10.1037/a0014548

Kilford, E. J., Garrett, E., and Blakemore, S. J. (2016). The development of social cognition in adolescence: an integrated perspective. *Neurosci. Biobehav. Rev.* 70, 106–120. doi: 10.1016/j.neubiorev.2016.08.016

Knutson, B., Fong, G. W., Adams, C. M., Varner, J. L., and Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport* 12, 3683–3687.

Kohn, N., Eickhoff, S. B., Scheller, M., Laird, A. R., Fox, P. T., and Habel, U. (2014). Neural network of cognitive emotion regulation–an ALE meta-analysis and MACM analysis. *Neuroimage* 87, 345–355. doi: 10.1016/j.neuroimage.2013.11.001

Kompus, K., Hugdahl, K., Ohman, A., Marklund, P., and Nyberg, L. (2009). Distinct control networks for cognition and emotion in the prefrontal cortex. *Neurosci. Lett.* 467, 76–80. doi: 10.1016/j.neulet.2009.10.005

Krain, A. L., Wilson, A. M., Arbuckle, R., Castellanos, F. X., and Milham, M. P. (2006). Distinct neural mechanisms of risk and ambiguity: a meta-analysis of decision-making. *Neuroimage* 32, 477–484.

Kuttler, A. F., La Greca, A. M., and Prinstein, M. J. (1999). Friendship qualities and social-emotional functioning of adolescents with close, cross-sex friendships. *J. Res. Adolesc.* 9, 339–366.

Ladouceur, C. (2012). Neural systems supporting cognitive-affective interactions in adolescence: the role of puberty and implications for affective disorders. *Front. Integr. Neurosci.* 6:65. doi: 10.3389/fnint.2012.00065

Lamblin, M., Murawski, C., Whittle, S., and Fornito, A. (2017). Social connectedness, mental health and the adolescent brain. *Neurosci. Biobehav. Rev.* 80, 57–68. doi: 10.1016/j.neubiorev.2017.05.010

Larson, R., and Richards, M. H. (1991). Daily companionship in late childhood and early adolescence: changing developmental contexts. *Child Dev.* 62, 284–300.

Lenroot, R. K., and Giedd, J. N. (2010). Sex differences in the adolescent brain. *Brain Cogn.* 72, 46–55. doi: 10.1016/j.bandc.2009.10.008

Leppanen, J. M., and Nelson, C. A. (2009). Tuning the developing brain to social signals of emotions. *Nat. Rev. Neurosci.* 10, 37–47. doi: 10.1038/nrn2554

Li, C. S., Huang, C., Constable, R. T., and Sinha, R. (2006). Imaging response inhibition in a stop-signal task: neural correlates independent of signal monitoring and post-response processing. *J. Neurosci.* 26, 186–192.

Li, F., Yin, S., Feng, P., Hu, N., Ding, C., and Chen, A. (2018). The cognitive up- and down-regulation of positive emotion: Evidence from behavior, electrophysiology, and neuroimaging. *Biol. Psychol.* 136, 57–66. doi: 10.1016/j.biopsycho.2018.05.013

Lieberman, M., Doyle, A.-B., and Markiewicz, D. (1999). Developmental patterns in security of attachment to mother and father in late childhood and early adolescence: associations with peer relations. *Child Dev.* 70, 202–213.

MacDonald, A. W. III, Cohen, J. D., Stenger, V. A., and Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* 288, 1835–1838.

Masten, C. L., Telzer, E. H., Fuligni, A. J., Lieberman, M. D., and Eisenberger, N. I. (2010). Time spent with friends in adolescence relates to less neural sensitivity to later peer rejection. *Soc. Cogn. Affect. Neurosci.* 7, 106–114. doi: 10.1093/scan/nsq098

McLaren, D. G., Ries, M. L., Xu, G., and Johnson, S. C. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *Neuroimage* 61, 1277–1286. doi: 10.1016/j.neuroimage.2012.03.068

Moore, W. E. III, Pfeifer, J. H., Masten, C. L., Mazziotta, J. C., Iacoboni, M., and Dapretto, M. (2012). Facing puberty: associations between pubertal development and neural responses to affective facial displays. *Soc. Cogn. Affect. Neurosci.* 7, 35–43. doi: 10.1093/scan/nsr066

Morin, E. L., Hadj-Bouziane, F., Stokes, M., Ungerleider, L. G., and Bell, A. H. (2014). Hierarchical encoding of social cues in primate inferior temporal cortex. *Cereb. Cortex* 25, 3036–3045. doi: 10.1093/cercor/bhu099

Münte, T. F., Marco-Pallares, J., Bolat, S., Heldmann, M., Lütjens, G., Nager, W., et al. (2017). The human globus pallidus internus is sensitive to rewards – evidence from intracerebral recordings. *Brain Stimul.* 10, 657–663. doi: 10.1016/j.brs.2017.01.004

Murray, E. A., and Wise, S. P. (2010). Interactions between orbital prefrontal cortex and amygdala: advanced cognition, learned responses and instinctive behaviors. *Curr. opin. Neurobiol.* 20, 212–220. doi: 10.1016/j.conb.2010.02.001

Nakato, E., Otsuka, Y., Kanazawa, S., Yamaguchi, M. K., Honda, Y., and Kakigi, R. (2011). I know this face: neural activity during mother'face perception in 7-to 8-month-old infants as investigated by near-infrared spectroscopy. *Early Hum. Dev.* 87, 1–7. doi: 10.1016/j.earlhumdev.2010.08.030

Nelson, C. A., Monk, C. S., Lin, J., Carver, L. J., Thomas, K. M., and Truwit, C. L. (2000). Functional neuroanatomy of spatial working memory in children. *Dev. Psychol.* 36, 109–116.

Nelson, E. E., and Guyer, A. E. (2011). The development of the ventral prefrontal cortex and social flexibility. *Dev. Cogn. Neurosci.* 1, 233–245. doi: 10.1016/j.dcn.2011.01.002

Nelson, E. E., Jarcho, J. M., and Guyer, A. E. (2016). Social re-orientation and brain development: an expanded and updated view. *Dev. Cogn. Neurosci.* 17, 118–127. doi: 10.1016/j.dcn.2015.12.008

Nelson, E. E., Leibenluft, E., McClure, E. B., and Pine, D. S. (2005). The social re-orientation of adolescence: a neuroscience perspective on the process and its relation to psychopathology. *Psychol. Med.* 35, 163–174.

O'Brien, S. F., and Bierman, K. L. (1988). Conceptions and perceived influence of peer groups: interviews with preadolescents and adolescents. *Child Dev.* 59, 1360–1365.

O'Doherty, J. P. (2004). Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Curr. Opin. Neurobiol.* 14, 769–776.

O'Doherty, J. P., Kringelbach, M. L., Rolls, E. T., Hornak, J., and Andrews, C. (2001). Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat. Neurosci.* 4, 95–102.

Ordaz, S. J., Foran, W., Velanova, K., and Luna, B. (2013). Longitudinal growth curves of brain function underlying inhibitory control through adolescence. *J. Neurosci.* 33, 18109–18124.

Paus, T. (2005). Mapping brain maturation and cognitive development during adolescence. *Trends Cogn. Sci.* 9, 60–68.

Pfeifer, J. H., and Blakemore, S. J. (2012). Adolescent social cognitive and affective neuroscience: past, present, and future. *Soc. Cogn. Affect. Neurosci.* 7, 1–10. doi: 10.1093/scan/nsr099

Picci, G., and Scherf, K. S. (2016). From caregivers to peers: puberty shapes human face perception. *Psychol. Sci.* 27, 1461–1473.

Pitcher, D., Japee, S., Rauth, L., and Ungerleider, L. G. (2017). The superior temporal sulcus is causally connected to the amygdala: a combined TBS-fMRI study. *J. Neurosci.* 37, 1156–1161. doi: 10.1523/JNEUROSCI.0114-16.2016

Querleu, D., Lefebvre, C., Titran, M., Renard, X., Morillion, M., and Crepin, G. (1984). Reaction of the newborn infant less than 2 hours after birth to the maternal voice. *J. Gynécol. Obstét. Biol. Reprod.* 13, 125–134.

Rao, H., Korczykowski, M., Pluta, J., Hoang, A., and Detre, J. A. (2008). Neural correlates of voluntary and involuntary risk taking in the human brain: an fMRI study of the balloon analog risk task (BART). *Neuroimage* 42, 902–910.

Rice, K. G., and Mulkeen, P. (1995). Relationships with parents and peers: a longitudinal study of adolescent intimacy. *J. Adolesc. Res.* 10, 338–357. doi: 10.1007/s10964-013-0004-8

Roelofs, K., Minelli, A., Mars, R. B., van Peer, J., and Toni, I. (2008). On the neural control of social emotional behavior. *Soc. Cogn. Affect. Neurosci.* 4, 50–58. doi: 10.1093/scan/nsn036

Satterthwaite, T. D., Wolf, D. H., Erus, G., Ruparel, K., Elliott, M. A., Gennatas, E. D., et al. (2013). Functional maturation of the executive system during adolescence. *J. Neurosci.* 33, 16249–16261. doi: 10.1523/JNEUROSCI.2345-13.2013

Saxbe, D., Del Piero, L., Immordino-Yang, M. H., Kaplan, J., and Margolin, G. (2015). Neural correlates of adolescents' viewing of parents' and peers' emotions: associations with risk-taking behavior and risky peer affiliations. *Soc. Neurosci.* 10, 592–604. doi: 10.1080/17470919.2015.1022216

Saxe, R., and Wexler, A. (2005). Making sense of another mind: the role of the right temporo-parietal junction. *Neuropsychologia* 43, 1391–1399.

Scherf, K. S., and Scott, L. S. (2012). Connecting developmental trajectories: biases in face processing from infancy to adulthood. *Dev. Psychobiol.* 54, 643–663. doi: 10.1002/dev.21013

Scherf, K. S., Smyth, J. M., and Delgado, M. R. (2013). The amygdala: an agent of change in adolescent neural networks. *Horm. Behav.* 64, 298–313. doi: 10.1016/j.yhbeh.2013.05.011

Schriber, R. A., and Guyer, A. E. (2016). Adolescent neurobiological susceptibility to social context. *Dev. Cogn. Neurosci.* 19, 1–18. doi: 10.1016/j.dcn.2015.12.009

Shulman, E. P., Smith, A. R., Silva, K., Icenogle, G., Duell, N., Chein, J., et al. (2016). The dual systems model: review, reappraisal, and reaffirmation. *Dev. Cogn. Neurosci.* 17, 103–117. doi: 10.1016/j.dcn.2015.12.010

Silk, J. S., Stroud, L. R., Siegle, G. J., Dahl, R. E., Lee, K. H., and Nelson, E. E. (2011). Peer acceptance and rejection through the eyes of youth: pupillary, eyetracking and ecological data from the chatroom interact task. *Soc. Cogn. Affect. Neurosci.* 7, 93–105. doi: 10.1093/scan/nsr044

Smith, A. R., Rosenbaum, G. M., Botdorf, M. A., Steinberg, L., and Chein, J. M. (2018). Peers influence adolescent reward processing, but not response inhibition. *Cogn. Affect. Behav. Neurosci.* 18, 284–295.

Smith, A. R., Steinberg, L., and Chein, J. (2014). The role of the anterior insula in adolescent decision making. *Dev. Neurosci.* 36, 196–209. doi: 10.1159/000358918

Smith, A. R., Steinberg, L., Strang, N., and Chein, J. (2015). Age differences in the impact of peers on adolescents' and adults' neural response to reward. *Dev. Cogn. Neurosci.* 11, 75–82. doi: 10.1016/j.dcn.2014.08.010

Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neurosci. Biobehav. Rev.* 24, 417–463.

Spreckelmeyer, K. N., Krach, S., Kohls, G., Rademacher, L., Irmak, A., Konrad, K., et al. (2009). Anticipation of monetary and social reward differently activates mesolimbic brain structures in men and women. *Soc. Cogn. Affect. Neurosci.* 4, 158–165. doi: 10.1093/scan/nsn051

Steinberg, L. (2005). Cognitive and affective development in adolescence. *Trends Cogn. Sci.* 9, 69–74.

Steinberg, L., and Morris, A. S. (2001). Adolescent development. *Annu. Rev. Psychol.* 52, 83–110.

Sugita, Y. (2008). Face perception in monkeys reared with no exposure to faces. *Proc. Natl. Acad. Sci. U.S.A.* 105, 394–398. doi: 10.1073/pnas.0706079105

Tottenham, N., Shapiro, M., Telzer, E. H., and Humphreys, K. L. (2012). Amygdala response to mother. *Dev. Sci.* 15, 307–319.

van Duijvenvoorde, A. C., Op de Macks, Z. A., Overgaauw, S., Gunther Moor, B., Dahl, R. E., and Crone, E. A. (2014). A cross-sectional and longitudinal analysis of reward-related brain activation: effects of age, pubertal stage, and reward sensitivity. *Brain Cogn.* 89, 3–14. doi: 10.1016/j.bandc.2013.10.005

Van Leijenhorst, L., Gunther Moor, B., Op de Macks, Z. A., Rombouts, S. A., Westenberg, P. M., and Crone, E. A. (2010). Adolescent risky decision-making: neurocognitive development of reward and control regions. *Neuroimage* 51, 345–355. doi: 10.1016/j.neuroimage.2010.02.038

Van Overwalle, F. (2009). Social cognition and the brain: a meta-analysis. *Hum. Brain Mapp.* 30, 829–858. doi: 10.1002/hbm.20547

Verbruggen, F., and Logan, G. D. (2008). Response inhibition in the stop-signal paradigm. *Trends Cogn. Sci.* 12, 418–424. doi: 10.1016/j.tics.2008.07.005

Werker, J. F., and Hensch, T. K. (2015). Critical periods in speech perception: new directions. *Annu. Rev. Psychol.* 66, 173–196. doi: 10.1146/annurev-psych-010814-015104

Weygandt, M., Mai, K., Dommes, E., Ritter, K., Leupelt, V., Spranger, J., et al. (2015). Impulse control in the dorsolateral prefrontal cortex counteracts post-diet weight regain in obesity. *Neuroimage* 109, 318–327. doi: 10.1016/j.neuroimage.2014.12.073

Whittle, S., Simmons, J. G., Byrne, M. L., Strikwerda-Brown, C., Kerestes, R., Seal, M. L., et al. (2015). Associations between early adrenarche, affective brain function and mental health in children. *Soc. Cogn. Affect. Neurosci.* 10, 1282–1290. doi: 10.1093/scan/nsv014

Wright, D. S., and Stroud, J. N. (2002). Age differences in lineup identification accuracy: people are better with their own age. *Law Hum. Behav.* 26, 641–654.

Yurgelun-Todd, D. (2007). Emotional and cognitive changes during adolescence. *Curr. Opin. Neurobiol.* 17, 251–257.

Zilbovicius, M., Meresse, I., Chabane, N., Brunelle, F., Samson, Y., and Boddaert, N. (2006). Autism, the superior temporal sulcus and social perception. *Trends Neurosci.* 29, 359–366. doi: 10.1016/j.tins.2006.06.004

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling Editor declared a past co-authorship with one of the authors EN.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 31 May 2019
doi: 10.3389/fnbeh.2019.00120

Peer Victimization and Dysfunctional Reward Processing: ERP and Behavioral Responses to Social and Monetary Rewards

Brent I. Rappaport[1], Laura Hennefield[2], Autumn Kujawa[3], Kodi B. Arfer[4], Danielle Kelly[2], Emily S. Kappenman[5], Joan L. Luby[2] and Deanna M. Barch[1,2,6]*

[1]Department of Psychological & Brain Sciences, Washington University in St. Louis, St. Louis, MO, United States, [2]Department of Psychiatry, School of Medicine, Washington University in St. Louis, St. Louis, MO, United States, [3]Department of Psychology & Human Development, Vanderbilt University, Nashville, TN, United States, [4]Center for HIV Identification, Prevention, and Treatment Services, University of California, Los Angeles, Los Angeles, CA, United States, [5]Department of Psychology, San Diego State University, San Diego, CA, United States, [6]Department of Radiology, School of Medicine, Washington University in St. Louis, St. Louis, MO, United States

Peer victimization (or bullying) is a known risk factor for depression, especially among youth. However, the mechanisms connecting victimization experience to depression symptoms remains unknown. As depression is known to be associated with neural blunting to monetary rewards, aberrant responsiveness to social rewards may be a key deficit connecting socially stressful experiences with later depression. We, therefore, sought to determine whether adolescents' experiences with social stress would be related to their current response to social rewards over less socially relevant monetary rewards. Neural responses to monetary and social rewards were measured using event-related potentials (ERPs) to peer acceptance and rejection feedback (Island Getaway task) and to monetary reward and loss feedback (Doors task) in a sample of 56 late adolescents/emerging young adults followed longitudinally since preschool. In the Island Getaway task, participants voted whether to "keep" or "kick out" each co-player, providing an index of prosocial behavior, and then received feedback about how each player voted for the participant. Analyses tested whether early and recent peer victimization was related to response to rewards (peer acceptance or monetary gains), residualized for response to losses (peer rejection or monetary losses) using the reward positivity (RewP) component. Findings indicated that both experiencing greater early and greater recent peer victimization were significantly associated with participants casting fewer votes to keep other adolescents ("Keep" votes) and that greater early peer victimization was associated with reduced neural response to peer acceptance. Early and recent peer victimization were significantly more associated with neural response to social than monetary rewards. Together, these findings suggest that socially injurious experiences such as peer victimization, especially those occurring early in childhood, relate to two distinct but important findings: that early victimization is associated with later reduced response to peer acceptance, and is associated with later tendency to reject

OPEN ACCESS

Edited by:
Johanna M. Jarcho, Temple University, United States

Reviewed by:
Sarah Hope Lincoln, Harvard University, United States
Jonathan P. Stange, University of Illinois at Chicago, United States
Yiping Zhong, Hunan Normal University, China

***Correspondence:**
Brent I. Rappaport
brappaport@wustl.edu

Received: *26 February 2019*
Accepted: *17 May 2019*
Published: *31 May 2019*

Citation:
Rappaport BI, Hennefield L, Kujawa A, Arfer KB, Kelly D, Kappenman ES, Luby JL and Barch DM (2019) Peer Victimization and Dysfunctional Reward Processing: ERP and Behavioral Responses to Social and Monetary Rewards. Front. Behav. Neurosci. 13:120. doi: 10.3389/fnbeh.2019.00120

peers. Findings also suggest that there is evidence of specificity to reward processing of different types; thus, future research should expand studies of reward processing beyond monetary rewards to account for the possibility that individual differences may be related to other, more relevant, reward types.

Keywords: peer victimization, event-related potentials (ERP), reward, depression, adolescence, monetary reward, social reward

INTRODUCTION

Peer victimization (i.e., bullying) affects nearly one-fifth of high school students in the United States and over a third of adolescents worldwide (Modecki et al., 2014; US Center for Disease Control, 2018) and is an established risk factor for psychopathology. More specifically, victimized youth have a heightened risk for depression (Reijntjes et al., 2010; Takizawa et al., 2014; Klomek et al., 2015). Depression is associated with blunted neural responses to rewarding feedback in adults and adolescents (for meta-analyses, see Zhang et al., 2013; Keren et al., 2018). Though functional magnetic resonance imaging (fMRI) studies initially focused on hyporeactivity to monetary rewards, recent studies have extended the findings to *social* rewards (Olino et al., 2015; Kujawa et al., 2017), suggesting that depression is associated with anhedonia to multiple different reward types (Fussner et al., 2018). Some have proposed that this anhedonia is the result of interactions between the reward system and stress (Pizzagalli, 2014), showing that acute stress reduces striatal activation to monetary rewards (Ossewaarde et al., 2011; Porcelli et al., 2012). Therefore, peer victimization may lead to blunting of the brain's response to rewards. As a social experience, peer victimization might be expected to be more strongly related to aberrant responses to social rewards than monetary ones. This is because victimization could change the value associated with positive peer feedback, making youth glean less pleasure or sense of reward from social acceptance. On the other hand, peer victimization may be related to depression just as any other childhood (Mandelli et al., 2015) or lifetime stressor (Kendler et al., 1999), with the social component of the stressor irrelevant. If so, peer victimization may act similarly to other childhood stressors in contributing to risk for depression, and thus may be related to blunted responses to both monetary and social rewards. Either pattern of responses would inform the pathway through which victimization confers risk for depression. Identifying this pathway can lead to interventions aimed at preventing or reducing the occurrence of depression in victimization youth. As such, the goal of the current study was to determine whether peer victimization was similarly or differentially associated with brain response to social and monetary rewards in the same sample.

One measure of reward response studied in depression is reward-related activity, occurring in response to the presentation of reward feedback. This can be measured using event-related potentials (ERPs)—an EEG signal time-locked to a particular event, such as the onset of a stimulus. ERP signals consist of components related to specific cognitive, motor, sensory, or emotional processes (Luck and Kappenman, 2012), including the reward positivity (RewP), an ERP component related to the processing of rewarding feedback. The RewP is thought to arise from activity within the mesocorticolimbic circuit including the striatum, mPFC, amygdala and orbitofrontal cortex (Gehring and Willoughby, 2002; Carlson et al., 2011; Foti et al., 2011b; Becker et al., 2014; Weinberg et al., 2014; Proudfit, 2015). Blunted RewP to monetary rewards has been concurrently and prospectively associated with depression severity in patients (Foti et al., 2011a, 2014; Bress et al., 2012; Liu et al., 2014; Proudfit, 2015), in some cases predicting risk for later depression (Bress et al., 2013; Weinberg et al., 2014, 2015; Nelson et al., 2016). More recently, depression severity has been associated with blunted RewP to social rewards (Kujawa et al., 2017), with one study directly comparing RewP to monetary and social rewards and revealing morphologically similar, although not identical, waveforms of activation (Ethridge et al., 2017). This makes the RewP an interesting and well-validated ERP component to test whether peer victimization is similarly or differentially associated with aberrant brain responses to rewards of different types.

In addition to neural responses, prosocial behavior towards peers may also inform our understanding of the link between peer victimization and depression. For instance, social acceptance is related to more prosocial behavior (Tur-Porcar et al., 2018; Will et al., 2018) and prosocial behavior itself is associated with improved social acceptance and relationships (Crick, 1996; Layous et al., 2012). In contrast, social rejection is linked to more aggressive and less prosocial behavior (Di Giunta et al., 2018; Tur-Porcar et al., 2018) in addition to causing a reduction in prosocial behaviors such as donating money, volunteering, helpfulness, and cooperation (Twenge et al., 2007). These findings suggest that the way youth react behaviorally to negative social interactions could reduce their ability or motivation for positive engagement and further deteriorate their peer relationships, overtime worsening depression symptoms (Leadbeater and Hoglund, 2009). Thus, while it is important to examine potential neural mechanisms of risk, behavioral mechanisms likely contribute to the relationship between peer victimization and depression. To test this, the current study also assessed whether peer victimization was associated with reduced prosocial behavior towards other co-players during the social reward task.

There is a reason to believe that both recent and early life experiences with peer victimization could be associated with aberrant reward responding. Recent, acute experiences of peer victimization affect adolescents' schemas of peers and bias their interpersonal skills and attributions of peers (Schwartz et al., 1998; Camodeca and Goossens, 2005; Troop-Gordon and Ladd, 2005; Hoglund and Leadbeater, 2007). Despite peer

victimization research tending to focus on adolescence, there is evidence that peer relations are as complex and salient in preschool (Schaefer et al., 2010), and that peer victimization is moderately stable beginning in early childhood (Pouwels et al., 2016). Thus, peer victimization experienced early in life may similarly bias individuals' beliefs about others. This, in turn, could have long-lasting consequences for how victimized youth process and interpret social feedback, including peer acceptance and, subsequently, how their brain's reward system develops and responds to social rewards. In fact, early social stress has been shown to lead to reduced behavioral reward learning (Guyer et al., 2006; Sheridan et al., 2018) and neural responses to reward (Hanson et al., 2016). This line of reasoning suggests that both recent and early experiences of peer victimization are relevant to the development of neural and behavioral reactions to rewards—including social rewards. While few studies have tested for a relationship between peer victimization and reward functioning (but see Casement et al., 2014; Ethridge et al., 2018), fewer still have included measures of peer victimization in early childhood. However, one study demonstrated that peer victimization can have long-lasting associations with responses to monetary reward, showing that greater victimization in late childhood predicted blunted brain responses to reward at age 16 (Casement et al., 2014). Another study found that early experience of peer victimization resulted in increased neural responsivity to social rejection in adolescence (Rudolph et al., 2016). Thus, there is intriguing evidence supporting the possibility that peer victimization in early childhood has lasting effects on adolescents' responses to reward-related feedback; however, no study thus far has compared the relative strength of these associations between monetary and social rewards.

Given the literature reviewed above, the current study sought to examine the relationship between experiences of both early and recent peer victimization and current neural responses to social rewards (i.e., peer acceptance and rejection) compared to monetary rewards (i.e., gains and losses) in adolescents participating as part of a longitudinal study on early onset depression. We used two tasks to assess ERP responsivity to rewards: the Doors task was used to measure responses to monetary gains and losses, and the Island Getaway task was used to measure responses to social acceptance and rejection. Both tasks have been shown to elicit the Reward Positivity component (i.e., RewP). Behavioral responses on the Island Getaway task included voting to accept or reject other co-playing peers during the task. We tested the prediction that early and recent peer victimization would be more strongly related to blunted brain responses to social acceptance than to monetary gains. We also hypothesized that early and recent peer victimization would be related to less prosocial (acceptance) voting behavior. Finally, we tested the prediction that greater current depression symptoms would be related to reduced RewP responses in both tasks.

MATERIALS AND METHODS

Participants

Participants were drawn from the Preschool Depression Study (PDS), a prospective longitudinal investigation of young children and their families conducted at a midwestern university in the United States (Luby et al., 2009). Details of recruitment have been previously reported (Luby et al., 2009, 2014). To briefly summarize, 3- to 6-year-olds were recruited from primary care practices and preschools/daycares throughout the St. Louis metropolitan region using a validated screening checklist [Preschool Feelings Checklist (Luby et al., 2004)] to oversample preschoolers with symptoms of depression and healthy controls. Parental written consent and child assent were obtained before participation and the local Institutional Review Board approved all procedures. These children have participated in up to 10 in-person clinical and behavior assessment and five neuroimaging assessments. In the most recent wave of data collection, a task measuring ERP responses to social feedback was added. The current study reports on 56 adolescents (46% female, mean age = 18.05 ± 1.01, 57% Caucasian, 34% African American, 9% Other) from the PDS who had completed the current wave of the study, with data collection ongoing. Of those, 16 participants had current clinical diagnoses of major depressive disorder (MDD) and 13 of MDD not otherwise specified. Of the 56 participants, 13 reported taking psychotropic medications in the past year.

Measures

Social Reward Task

The Island Getaway task (Kujawa et al., 2014, 2017; Ethridge et al., 2017; Ethridge and Weinberg, 2018) was used to assess ERP and behavioral responses to peer acceptance or rejection. The original task was slightly modified to be age appropriate for the current sample. Task code is available at: http://arfer.net/projects/survivor. In the task, participants are told they are playing a game with real peers during which they will vote whether they wanted each peer (i.e., co-player) to continue on with them in the game, and then received feedback on how each co-player voted for them. Trials were divided into six rounds of voting. In the first round, participants created a profile including their photograph and demographic information and reviewed profiles of computerized co-players. In subsequent rounds, participants first responded to a poll question (e.g., "Who do you most admire?") and then reviewed co-player responses in order to facilitate an exchange of personal information for the remaining voting and feedback phases.

After reviewing each co-player's profile and poll response in each round, participants completed a voting and feedback phase during which they voted to either accept ("Keep") or reject ("Kick out") each co-player, and after each vote received feedback indicating whether that co-player had voted to accept or reject them. Acceptance feedback was indicated by an image of a green "thumbs up" and rejection feedback was indicated by a red "thumbs down." Each voting trial began with a co-player's profile presented until participants voted. To simulate variation in co-player response speed, co-player voting time was selected for each trial based on actual variability in participants' voting speeds from previously collected data. If participants voted faster than the simulated voting time for that co-player, the message "Waiting for [co-player's name] to vote..." was displayed. Lastly,

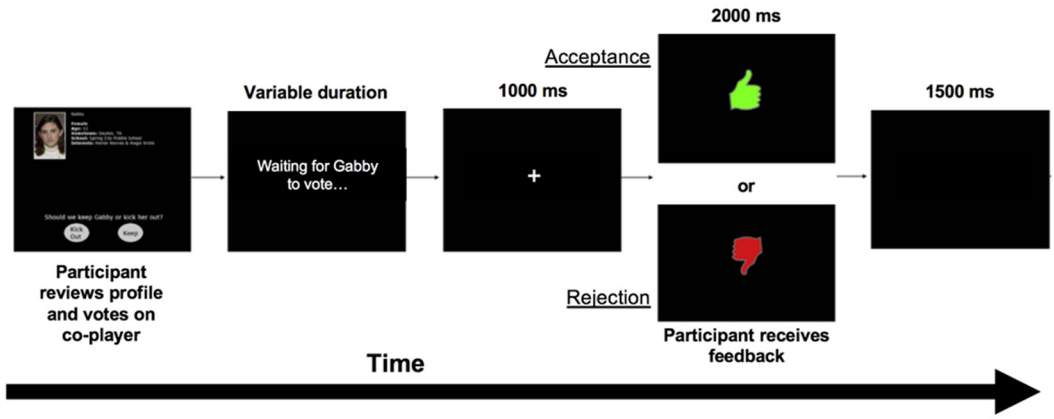


FIGURE 1 | Voting and feedback trial during the Island Getaway task.

a fixation cross was presented for 1,000 ms, followed by feedback displayed for 2,000 ms. A blank screen was presented for 1,500 ms before the start of the next trial (see **Figure 1**).

Co-players were randomly assigned a voting pattern for each participant, such that two co-players rejected the participant on most (four or five out of six) rounds, two co-players accepted the participant on most rounds, and the remaining seven co-players were equally likely to accept or reject the participant. To increase the unpredictability of feedback, all co-players voted both to keep and kick out the participant at least once (with the exception of the co-player excluded after the first round). After each of the rounds, participants were told which one of the co-players had been voted out of the game. The task included a total of 51 feedback trials split evenly between acceptance and rejection, with the last trial type determined randomly, though the proportion of rejection and acceptance feedback in each round varied slightly across participants.

Monetary Reward Task

The Doors Guessing Task (see **Supplementary Figure S1**) has been used in previous studies of older children, adolescents, and adults with depression (Foti et al., 2011a,b, 2014; Bress et al., 2012, 2015; Nelson et al., 2015). Participants were shown a graphic displaying two adjacent doors and told to select a door to win $0.50 or lose $0.25. Following each choice, a feedback stimulus (green up arrow or red down arrow) appeared on the screen informing the children whether they lost or gained money. The order and timing of all stimuli were as follows (see **Supplementary Figure S1**): (i) the text "Click for the next round" was presented until the participant pressed a button; (ii) a fixation cross was presented for 1,000 ms; (iii) the graphic of two doors was presented until a choice was made; (iv) a fixation cross was presented for 1,000 ms; (v) a feedback arrow was presented for 2,000 ms, and finally; (vi) a fixation cross was presented for 1,500 ms. A green upward arrow indicated a correct guess and a red downward arrow indicated an incorrect guess. Participants received negative feedback on exactly 50% of the trials, and positive feedback on exactly 50% of the trials.

Recent evidence supports the psychometric properties of the Island Getaway and Doors tasks, including internal consistency and convergent validity between the tasks (Levinson et al., 2017; Ethridge and Weinberg, 2018).

EEG Data Collection and Processing

Continuous EEG was recorded using the BrainVision ActiChamp, 32 channel active channel amplifier system (BrainVision LLC, Morrisville, NC, USA). The electrodes were mounted in an elastic cap using a subset of the International 10/20 System sites (FP1, F3, F7, FC1, FC5, FT9, C3, T7, CP1, CP5, TP9, P3, P7, O1, Fz, Cz, Pz, Oz, FP2, F4, F8, FC2, FC6, FT10, C4, T8, CP2, CP6, P4, P8, TP10, O2) with a ground electrode located at FPz. The electrooculogram (EOG) generated from blinks and eye movements were recorded from five facial electrodes placed around the eyes. The EEG was sampled at 500 Hz and all signals were digitized on a laboratory computer.

Depression Symptoms

Current depression symptoms were measured as the sum of core symptoms of MDD endorsed by a clinician on the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) at the current wave. Current depression symptoms were additionally measured using self-reported scores on the Child Depression Inventory–2 (CDI) if the participant was under 18 years old and Beck Depression Inventory–II (BDI) if the participant was 18 years old or older. CDI/BDI scores were calculated as the percentage of the raw score out of the total possible score, so as to make scores between the CDI and BDI comparable. Of the 56 participants, one was missing a CDI/BDI score. No participants were missing a score of core symptoms of MDD on the KSADS. Neural responses to monetary and social reward, as well as voting behavior, did not significantly differ from participants with missing CDI/BDI scores. Internal consistency was good for both CDI and BDI (Cronbach's alpha = 0.91 and 0.82, respectively).

Measures of Peer Victimization

Peer victimization was measured using the Global Peer Relations scale of the Health and Behavior Questionnaire (HBQ;

Armstrong and Goldstein, 2003). This scale includes items assessing peer acceptance/rejection and physical victimization, as well as relational victimization for children years old or older. Parents completed the child version (1.0) of the HBQ when children were 8 years old or younger, and the teen version (2.1) of the HBQ when children were 9 years old or older. Early experience of peer victimization was measured as the average score on this scale from the first three assessment waves, and recent experience of peer victimization was measured as the score on this scale from the previous wave (age range = 14.35–17.83 years). Internal consistency was good for the HBQ at early and recent assessment waves (Cronbach's alphas = 0.84–0.91). Of the 56 participants, two were missing a measure of early peer victimization, and one was missing a measure of recent peer victimization. Neural responses to monetary and social reward, as well as voting behavior, did not significantly differ from participants with missing peer victimization scores. The results for subtypes of peer victimization (i.e., physical victimization, rejection, and relational victimization) are presented in the **Supplemental Materials**.

Data Analysis

Off-line analysis was conducted using Brain Vision Analyzer 2 software (Brain Products, Gilching, Germany) and all data were re-referenced to the average of Tp9, Tp10, and Cz and band-pass filtered from 0.1 to 30 Hz. The EEG was corrected for EOG artifacts (Gratton et al., 1983) and physiological artifacts removed using an automatic procedure with a maximum allowed voltage step of 50 μv within a 400 ms interval length, maximum absolute different between any two points of 175 μv, and a minimum allowed activity of 0.50 μv within a 100 ms interval length. For both tasks, the EEG was segmented into 1,000 ms epochs, beginning 200 ms before and ending 800 ms after feedback onset. ERPs were quantified separately for the acceptance/gain and rejection/loss conditions as the mean activity at the Cz electrode site from 250 to 350 ms after feedback presentation in the Doors task and from 275 to 375 ms after feedback presentation in the Island Getaway task. This scoring is based on prior research showing that RewP is maximal in this time-frame and at this electrode for both tasks (Ethridge et al., 2017; Kujawa et al., 2017); of note, a study of the RewP response to monetary and social rewards in these two tasks found no difference in the psychometric properties of the RewP at Cz vs. frontal electrodes (i.e., Fz, FC1, FC2; Ethridge and Weinberg, 2018). A later time window is used for the Island Getaway task following studies that used principal component analysis to show that the RewP peaks approximately 25 ms later to social than monetary feedback (Ethridge et al., 2017; Kujawa et al., 2017; Babinski et al., 2019). Results were consistent when mean activity from 250 to 350 ms was used for the Island Getaway task (see **Supplementary Materials**). In line with previous work and recommendations (Meyer et al., 2017), residual scores for the RewP response to acceptance/gain accounting for RewP response to rejection/loss were calculated in R (version 3.5.0; R Core Team, 2013) to produce a score that was uncorrelated with RewP response to rejection/loss feedback. Residualized scores such as these are used to identify activity specific to reward response and account for other overlapping processes present in the ERP signal but unrelated to reward response (Luck and Kappenman, 2012). To test for associations between peer victimization and depression symptoms and brain and behavioral responses, robust linear regressions were fit using an M estimator from the MASS package (Venables and Ripley, 2002), and a robust f-test (Wald test) computed using the sfsmisc package (Maechler, 2018). Z tests were used to compare the regression coefficients of peer victimization predicting brain responses to social and monetary rewards (Paternoster et al., 1998).

RESULTS

Figure 2 depicts the grand average ERP waveforms and scalp distributions for the two tasks, as well as the time window extracted and used to measure the RewP for each task. As expected, electrocortical responses to rewards (i.e., monetary gains and social acceptance) were greater than those to losses (i.e., monetary losses and social rejection; $t_{(55)} = 6.056$, $p < 0.001$; $t_{(55)} = 2.802$, $p = 0.007$, respectively). Descriptive statistics are presented in **Table 1**. Early and recent peer victimization were moderately and significantly correlated [Spearman $r = 0.368$, 95% CI = (0.12, 0.58), $p = 0.007$]. Voting behavior and RewP were not significantly correlated [Spearman $r = 0.003$, 95% CI = (−0.27, 0.27), $p = 0.980$]. The results are consistent when outliers (i.e., participants with ERP responses outside 1.5 times the interquartile range) were removed (see **Supplemental Materials**; **Figure S2**).

Robust Linear Regressions With Peer Victimization

ERP Activity

Greater early peer victimization was significantly related to a more blunted RewP component to social acceptance [$\beta = -0.287$, 95% CI = (−0.551, −0.023), $p = 0.036$; see **Figure 3A**], and remained significant when current age was included as a covariate [$\beta = -0.273$, 95% CI = (−0.529, −0.018), $p = 0.039$]. Greater recent peer victimization was associated, though not significantly so, with a more blunted RewP component to social acceptance [$\beta = -0.207$, 95% CI = (−0.473, 0.058), $p = 0.127$; see **Figure 3A**].

Early and recent peer victimization were not significantly related to the RewP component for monetary gains [$\beta = 0.133$, 95% CI = (−0.120, 0.386), $p = 0.297$; $\beta = 0.184$, 95% CI = (−0.049, 0.417), $p = 0.121$, respectively]. When compared, early peer victimization showed a significantly stronger relationship with social rewards than monetary rewards ($Z = -2.25$, $p = 0.024$), as did recent peer victimization ($Z = -2.17$, $p = 0.030$).

The results were consistent when current depression (i.e., CDI/BDI and KSADS) was included as a covariate (see **Supplementary Materials**).

Voting Behavior

Greater early peer victimization was significantly related to fewer votes to accept (i.e., "keep") other co–players [$\beta = -0.325$, 95% CI = (−0.606, −0.044), $p = 0.025$; see **Figure 3B**], and remained

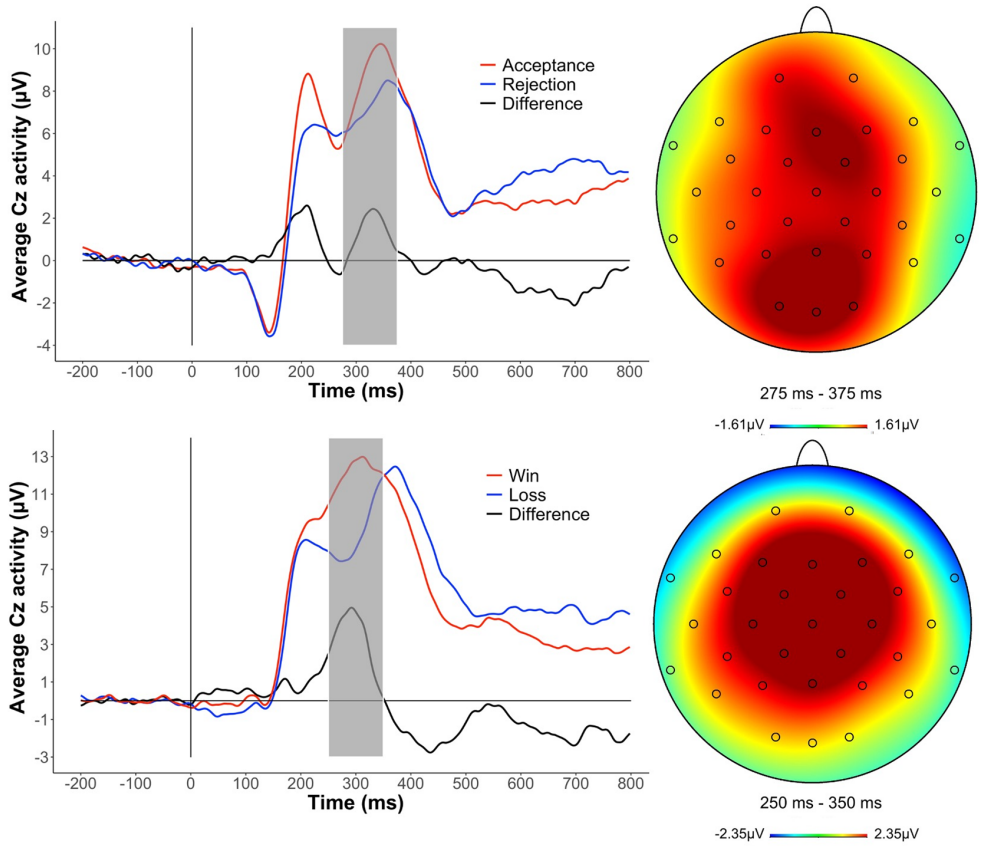


FIGURE 2 | Grand average event-related potential (ERP) waveforms and scalp distributions to social and monetary reward feedback at Cz electrode. Time window is highlighted in gray.

TABLE 1 | Descriptive statistics of peer victimization and depression measures.

	Mean	SD	Minimum	Maximum	95% CI for mean
Early HBQ peer victimization	1.43	0.47	1	3.51	(1.31, 1.56)
Recent HBQ peer victimization	1.33	0.46	1	3.2	(1.2, 1.45)
% CDI/BDI items	13.6	12.82	0	55.36	(10.14, 17.07)
N K-SADS MDD symptoms	2.27	2.52	0	9	(1.59, 2.94)

HBQ, Health and Behavior Questionnaire; CDI, Child Depression Inventory–2; BDI, Beck Depression Inventory–II; KSADS, Kiddie Schedule for Affective Disorders and Schizophrenia; MDD, major depressive disorder.

significant when current age was included as a covariate [$\beta = -0.363$, 95% CI = (−0.642, −0.083), $p = 0.013$]. Similarly, greater recent peer victimization was significantly related to fewer votes to accept other co–players [$\beta = -0.287$, 95% CI = (−0.542, −0.032), $p = 0.029$; see **Figure 3B**], and remained significant when accounting for current age as a covariate [$\beta = -0.288$, 95% CI = (−0.557, −0.018), $p = 0.038$]. Results were consistent when current depression (i.e., CDI/BDI and KSADS) was included as a covariate (see **Supplementary Materials**).

Robust Linear Regressions With Depression Symptoms

Neither measure of current depression were significantly related to RewP response to social acceptance [CDI/BDI: $\beta = -0.078$, CI = (−0.370, 0.215), $p = 0.603$; KSADS: $\beta = 0.108$, CI = (−0.177, 0.392), $p = 0.463$] or voting behavior [CDI/BDI: $\beta = 0.024$, CI = (−0.247, 0.294), $p = 0.864$; KSADS: $\beta = -0.083$, CI = (−0.339, −0.173), $p = 0.522$], nor were they significantly related to RewP response to monetary rewards [CDI/BDI: $\beta = -0.018$, CI = (−0.268, 0.232), $p = 0.891$] [KSADS: $\beta = 0.113$, CI = (−0.126, 0.353), $p = 0.354$]. Notably, current depression was associated with recent peer victimization, though not significantly [$\beta = 0.260$, CI = (−0.000, 0.520), $p = 0.061$].

DISCUSSION

The current study used previously validated social and non-social reward tasks to test the hypothesis that greater peer victimization

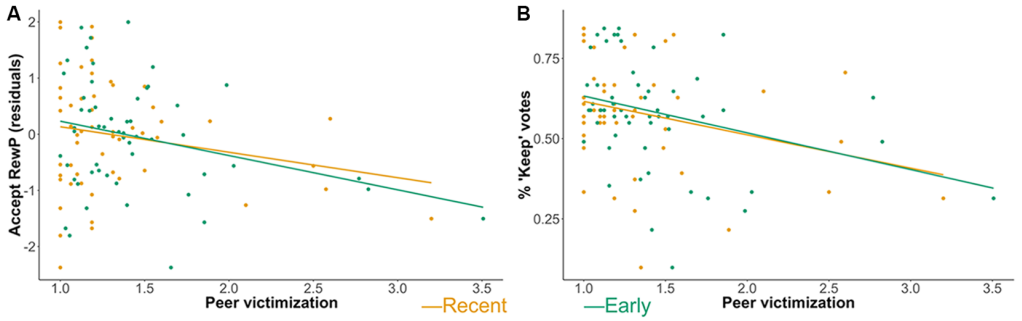


FIGURE 3 | Early and recent peer victimization and **(A)** RewP (residuals) to peer acceptance and **(B)** voting behavior.

would be associated with reduced brain responses exclusively to social rewards, whereas greater depression symptoms would be associated with reduced responses to both types of rewards. We found that, among a sample of late-adolescents/young-adults, early and recent peer victimization were related to brain responses to social rewards more so than to monetary rewards, and that greater early experience of peer victimization was related to reduced brain response (i.e., RewP) to peer acceptance. These findings suggest that—as a social stressor—peer victimization is associated with and potentially even shapes the way youth perceive peer interactions and relationships, possibly leading to decreased prosocial behaviors. Research shows that, in children who have experienced victimization, interpersonal skills worsen, attributions of peers become more negative, and they withdraw from or become hostile towards peers (Hymel et al., 1990; Schwartz et al., 1998; Camodeca and Goossens, 2005; Troop-Gordon and Ladd, 2005; Hoglund and Leadbeater, 2007; Bukowski et al., 2010). It is also possible that youth who get less pleasure out of social acceptance are at greater risk of being victimized. In either case, the results speak to the importance of understanding social reward processing throughout development, particularly the consequences of early life social stressors for brain development and behavioral outcomes.

We replicated effects showing that brain responses (i.e., RewP) to rewards were greater than to losses and grand average waveforms largely replicated waveforms from previous studies of both the Island Getaway and Doors tasks (Kujawa et al., 2014, 2017; Proudfit, 2015; Ethridge et al., 2017; Ethridge and Weinberg, 2018). Importantly, the dissociation that peer victimization was associated more strongly with reward response to social acceptance than with monetary rewards suggests that social stresses are linked specifically with deficits in responding to social rewards. Moreover, these results suggest that experience with peer victimization may affect the way social acceptance is represented and valued in the brain—making these experiences less rewarding—rather than leading to generalized blunting to rewards of different types. This emphasizes the importance of incorporating different types of rewards into research on reward-learning and the function of the brain's reward system. Focusing exclusively on monetary rewards may fail to detect more nuanced investigations of the mechanisms explaining the relationship between psychological stress and psychiatric symptoms. Developmentally, peer relations appear to be salient and rewarding starting in early childhood (Schaefer et al., 2010), suggesting that social rewards do not become salient only in adolescence. In light of this, future studies seeking to characterize deficits in reward function ought to account for different types of rewards.

Additionally, the relationship between peer victimization and reduced acceptance voting indicates that greater victimization is associated with less prosocial behavior, as in other studies of prosocial behavior (Twenge et al., 2007; Di Giunta et al., 2018; Tur-Porcar et al., 2018; Will et al., 2018). This could arise as a socially learned behavior, whereby an adolescent is averse to social acceptance for fear of being rejected in the future. It may also arise as a form of retribution, or getting back at other co-players that did not consistently vote to keep them in the game. On the other hand, voting to reject more often could be interpreted as a strategy for winning the game. This interpretation, however, suggests the possibility that adolescents are using different strategies to win the game: with more victimized youth using a strategy of winning through more "kick out" votes, and less victimized youth using a strategy of accepting other players in the hope they reciprocate. Therefore, whether these individual differences represent affective responses to rejection or a strategy, their behavior is no doubt unlikely to yield greater affiliation with the co-players, and—if taken as an indication of behavior in daily life—unlikely to yield more fulfilling social relationships. Although such reactions could be considered adaptive (i.e., a recently victimized child might reduce the frequency of further victimization by initiating fewer interactions), they are also reducing the overall number of social interactions and thus opportunities for peer acceptance. This could, in turn, increase their vulnerability for depression by making them more isolated and preventing future opportunities for positive social reinforcement. Overall, it appears that recent and early peer victimization biases youth towards more frequent rejection of peers, likely impacting their ability to form interpersonal relationships.

The current study provides further evidence that early life stressors can have consequences for corresponding neural processes and behaviors later in life. Specifically, that a social stressor such as peer victimization can have far-reaching

associations with later neural responses and behaviors. The literature on social reward thus far has been primarily focused with adolescence and young adulthood (Casement et al., 2014; Olino et al., 2015; Ethridge et al., 2017, 2018; Kujawa et al., 2017); however our findings suggest that peer victimization may have deleterious effects on youth as early as preschool. Furthermore, they identify possible mediators through which peer victimization is related to depression, or moderators of this relationship. For example, one study suggests a relationship between neural responses to social rejection and depression symptoms in highly victimized girls (Rudolph et al., 2016). Further studies are needed to clarify the causal relationship between peer victimization and depression and to test the role of blunted responding to social rewards and reduced prosocial behavior. Studies that collect information on peer relations and social reward responsivity early in childhood will be of particular importance.

We did not find, in contrast to other studies, that depression was significantly related to neural or behavioral responses to monetary or social rewards (Proudfit, 2015; Nelson et al., 2016; Kujawa et al., 2017). This could be a result of our study being underpowered to detect associations with depression symptoms. Alternatively, depression may be more strongly related with reward anticipation than feedback, in line with some recent fMRI findings (Stoy et al., 2012; Olino et al., 2014; Stringaris et al., 2015; Ubl et al., 2015), and theories that posit a stronger relationship between anhedonia and reward anticipation (Treadway et al., 2012). It is also possible that—in accordance with recent findings suggesting a stronger longitudinal than cross-sectional relationship between monetary reward-responsivity and depression severity (Kujawa et al., 2019)—blunted responses to monetary rewards will predict future depression symptoms. This presents an intriguing future direction to test whether blunted response to social and non-social reward differentially predict future depression severity. Nonetheless, the current findings support the role of a dysfunctional reward system as a neural correlate of social stress, if not also depression.

Limitations

Despite its strengths, the current study must be considered in light of its limitations. First, although peer victimization was significantly associated with ERP response to social reward and more weakly associated with depression severity, the study may have lacked variability in depression severity needed to detect associations with ERP activation. Second, parent-report of peer victimization was used. The literature suggests that a combination of parent, self, teacher, and peer report is ideal in capturing all aspects of youth's peer victimization (De Los Reyes and Prinstein, 2004); however, due to study limitations, we were unable to collect these supplementary reports. Third, recent peer victimization was used instead of current peer victimization due to concerns that the nature of victimization would be different once participants were no longer attending high school (i.e., over the age of 18) at the time of assessment, and that parents could be lacking information on their child's experience with victimization at this age. Fourth, the Doors task does not include a behavioral measure of reward responsivity, limiting our ability to infer how peer victimization is associated with behavioral responses to monetary rewards. Fifth, the RewP is a measure of reward response, accounting for response to losses (i.e., response to monetary gain/social acceptance residualized for response to monetary losses/social rejection) rather than a measure of reward exclusively. A common procedure in ERP research, this is done to isolate activity to the process of interest and account for other overlapping processes. This process does, however, limit the ability to measure the response to reward in isolation or compared to a neutral stimulus. Sixth, despite collecting information on psychotropic medication use in the past year, we did not collect information on medication use during the 48 h prior to the ERP tasks. Seventh, neither task used a measure of reward *learning*. That is, participants' ability to collect and integrate information to predict a positive outcome. Although the Island Getaway task included a measure of voting behavior, change in trial-to-trial voting was not examined. Future directions to address these limitations are discussed below.

Future Directions and Conclusions

There are a number of possible future directions to further inform the neural mechanisms underlying the relationship between peer victimization and psychopathology. FMRI studies could inform the location of brain activation linked with peer victimization and examine relationships between peer victimization and reward system network connectivity. Together with the current findings, such studies could identify neural consequences of peer victimization that put individuals at risk for depression. The current study assessed early peer victimization as that occurring between 3 and 7 years of age; future studies could further examine whether this represents a sensitive period. The current study also used an average measure of peer victimization over this period. Studies should seek to further clarify whether it is the chronicity or intensity of peer victimization that is most responsible for blunted reward responses.

Behaviorally, studies using ecological momentary assessment/experience sampling methods (EMA/ESMs) could test whether youth's behavioral reactions to such laboratory tasks are indeed indicative of their behavior in daily life. Such studies could examine the temporal course of peer victimization, blunted reward response, and behavior, thereby informing the causal relationship between them. Furthermore, other studies using predominately or entirely female samples (89%–100%) have found associations between peer victimization and non-social reward response (Casement et al., 2014; Ethridge et al., 2018). Unfortunately our study was underpowered to assess moderation effects by sex; however, an intriguing direction for future research would be to test whether peer victimization is associated with blunting to rewards in general in females, and more specifically with blunting to social rewards in males.

Finally, the behavioral finding that greater peer victimization is related to fewer acceptance votes appears to be a prime candidate for therapeutic intervention, and speaks to the potential effectiveness of social-emotional interventions aimed at curbing victimized youths' tendencies to withdraw or lash-out (e.g., Swearer et al., 2017). Further, the blunted neural response

may be a particularly useful diagnostic marker, indicating children at especially high risk of developing psychopathology in response to peer victimization. Future studies could additionally incorporate monetary reward tasks that involve a measure of behavior (e.g., monetary incentive delay task) to determine whether peer victimization is also unassociated with behavioral responses to non-social rewards. Overall, the current study emphasizes the meaningful specificity to reward processing of different types. Thus, future research should expand studies of reward processing beyond monetary rewards to account for the possibility that individual differences will be related to other, more domain-specific, types of reward.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Washington University School of Medicine Institutional Review Board with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Washington University School of Medicine Institutional Review Board.

AUTHOR CONTRIBUTIONS

BR, LH, AK, JL, and DB were responsible for study concept and design. KA was responsible for coding the Island Getaway task. BR, LH, DK, EK, JL, and DB were responsible for acquisition, analysis, or interpretation of data. BR and DB were responsible for drafting the manuscript and were responsible for statistical analysis. JL and DB obtained funding and supervised the article. BR, KA, DK, JL, and DB were responsible for administrative, technical, or material support. All authors contributed to manuscript revision, read and approved the submitted version.

FUNDING

This work was supported by National Institute of Mental Health Grant Nos. 2R01 MH064769-06 and R01 MH098454. The funder played no role in the design or conduct of the study. We did not receive any fees for open access publication.

ACKNOWLEDGMENTS

We thank the families participating in this study and the staff who helped make the project a success.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2019.00120/full#supplementary-material

REFERENCES

Armstrong, J. M., Goldstein, L. H., and The MacArthur Working Group on Outcome Assessment. (2003). *Manual for the MacArthur Health and Behavior Questionnaire (HBQ 1.0). MacArthur Foundation Research Network on Psychopathology and Development (David J. Kupfer, Chair).* Pittsburgh, PA: University of Pittsburgh.

Babinski, D. E., Kujawa, A., Kessel, E. M., Arfer, K. B., and Klein, D. N. (2019). Sensitivity to peer feedback in young adolescents with symptoms of ADHD: examination of neurophysiological and self-report measures. *J. Abnorm. Child Psychol.* 47, 605–617. doi: 10.1007/s10802-018-0470-2

Becker, M. P. I., Nitsch, A. M., Miltner, W. H. R., and Straube, T. (2014). A single-trial estimation of the feedback-related negativity and its relation to bold responses in a time-estimation task. *J. Neurosci.* 34, 3005–3012. doi: 10.1523/jneurosci.3684-13.2014

Bress, J. N., Foti, D., Kotov, R., Klein, D. N., and Hajcak, G. (2013). Blunted neural response to rewards prospectively predicts depression in adolescent girls: feedback negativity predicts depression. *Psychophysiology* 50, 74–81. doi: 10.1111/j.1469-8986.2012.01485.x

Bress, J. N., Meyer, A., and Hajcak, G. (2015). Differentiating anxiety and depression in children and adolescents: evidence from event-related brain potentials. *J. Clin. Child Adolesc. Psychol.* 44, 238–249. doi: 10.1080/15374416.2013.814544

Bress, J. N., Smith, E., Foti, D., Klein, D. N., and Hajcak, G. (2012). Neural response to reward and depressive symptoms in late childhood to early adolescence. *Biol. Psychol.* 89, 156–162. doi: 10.1016/j.biopsycho.2011.10.004

Bukowski, W. M., Laursen, B., and Hoza, B. (2010). The snowball effect: friendship moderates escalations in depressed affect among avoidant and excluded children. *Dev. Psychopathol.* 22, 749–757. doi: 10.1017/s095457941000043x

Camodeca, M., and Goossens, F. A. (2005). Aggression, social cognitions, anger and sadness in bullies and victims. *J. Child Psychol. Psychiatry* 46, 186–197. doi: 10.1111/j.1469-7610.2004.00347.x

Carlson, J. M., Foti, D., Mujica-Parodi, L. R., Harmon-Jones, E., and Hajcak, G. (2011). Ventral striatal and medial prefrontal BOLD activation is correlated with reward-related electrocortical activity: a combined ERP and fMRI study. *Neuroimage* 57, 1608–1616. doi: 10.1016/j.neuroimage.2011.05.037

Casement, M. D., Guyer, A. E., Hipwell, A. E., McAloon, R. L., Hoffmann, A. M., Keenan, K. E., et al. (2014). Girls' challenging social experiences in early adolescence predict neural response to rewards and depressive symptoms. *Dev. Cogn. Neurosci.* 8, 18–27. doi: 10.1016/j.dcn.2013.12.003

Crick, N. R. (1996). The role of overt aggression, relational aggression and prosocial behavior in the prediction of children's future social adjustment. *Child Dev.* 67, 2317–2327. doi: 10.2307/1131625

De Los Reyes, A., and Prinstein, M. J. (2004). Applying depression-distortion hypotheses to the assessment of peer victimization in adolescents. *J. Clin. Child Adolesc. Psychol.* 33, 325–335. doi: 10.1207/s15374424jccp3302_14

Di Giunta, L., Pastorelli, C., Thartori, E., Bombi, A. S., Baumgartner, E., Fabes, R. A., et al. (2018). Trajectories of Italian children's peer rejection: associations with aggression, prosocial behavior, physical attractiveness and adolescent adjustment. *J. Abnorm. Child Psychol.* 46, 1021–1035. doi: 10.1007/s10802-017-0373-7

Ethridge, P., Kujawa, A., Dirks, M. A., Arfer, K. B., Kessel, E. M., Klein, D. N., et al. (2017). Neural responses to social and monetary reward in early adolescence and emerging adulthood. *Psychophysiology* 54, 1786–1799. doi: 10.1111/psyp.12957

Ethridge, P., Sandre, A., Dirks, M. A., and Weinberg, A. (2018). Past-year relational victimization is associated with a blunted neural response to rewards in emerging adults. *Soc. Cogn. Affect. Neurosci.* 13, 1259–1267. doi: 10.1093/scan/nsy091

Ethridge, P., and Weinberg, A. (2018). Psychometric properties of neural responses to monetary and social rewards across development. *Int. J. Psychophysiol.* 132, 311–322. doi: 10.1016/j.ijpsycho.2018.01.011

Foti, D., Carlson, J. M., Sauder, C. L., and Proudfit, G. H. (2014). Reward dysfunction in major depression: multimodal neuroimaging evidence for refining the melancholic phenotype. *Neuroimage* 101, 50–58. doi: 10.1016/j.neuroimage.2014.06.058

Foti, D., Kotov, R., Klein, D. N., and Hajcak, G. (2011a). Abnormal neural sensitivity to monetary gains versus losses among adolescents at risk for depression. *J. Abnorm. Child Psychol.* 39, 913–924. doi: 10.1007/s10802-011-9503-9

Foti, D., Weinberg, A., Dien, J., and Hajcak, G. (2011b). Event-related potential activity in the basal ganglia differentiates rewards from nonrewards: temporospatial principal components analysis and source localization of the feedback negativity. *Hum. Brain Mapp.* 32, 2207–2216. doi: 10.1002/hbm.21182

Fussner, L. M., Mancini, K. J., and Luebbe, A. M. (2018). Depression and approach motivation: differential relations to monetary, social and food reward. *J. Psychopathol. Behav. Assess.* 40, 117–129. doi: 10.1007/s10862-017-9620-z

Gehring, W. J., and Willoughby, A. R. (2002). The medial frontal cortex and the rapid processing of monetary gains and losses. *Science* 295, 2279–2282. doi: 10.1126/science.1066893

Gratton, G., Coles, M. G. H., and Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalogr. Clin. Neurophysiol.* 55, 468–484. doi: 10.1016/0013-4694(83)90135-9

Guyer, A. E., Kaufman, J., Hodgdon, H. B., Masten, C. L., Jazbec, S., Pine, D. S., et al. (2006). Behavioral alterations in reward system function. *J. Am. Acad. Child Adolesc. Psychiatry* 45, 1059–1067. doi: 10.1097/01.chi.0000227882.50404.11

Hanson, J. L., Albert, D., Iselin, A.-M. R., Carré, J. M., Dodge, K. A., and Hariri, A. R. (2016). Cumulative stress in childhood is associated with blunted reward-related brain activity in adulthood. *Soc. Cogn. Affect. Neurosci.* 11, 405–412. doi: 10.1093/scan/nsv124

Hoglund, W. L., and Leadbeater, B. J. (2007). Managing threat: do social-cognitive processes mediate the link between peer victimization and adjustment problems in early adolescence? *J. Res. Adolesc.* 17, 525–540. doi: 10.1111/j.1532-7795.2007.00533.x

Hymel, S., Rubin, K. H., Rowden, L., and LeMare, L. (1990). Children's peer relationships: longitudinal prediction of internalizing and externalizing problems from middle to late childhood. *Child Dev.* 61, 2004–2021. doi: 10.1111/j.1467-8624.1990.tb03582.x

Kendler, K. S., Karkowski, L. M., and Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *Am. J. Psychiatry* 156, 837–841. doi: 10.1176/ajp.156.6.837

Keren, H., O'Callaghan, G., Vidal-Ribas, P., Buzzell, G. A., Brotman, M. A., Leibenluft, E., et al. (2018). Reward processing in depression: a conceptual and meta-analytic review across fMRI and EEG studies. *Am. J. Psychiatry* 175, 1111–1120. doi: 10.1176/appi.ajp.2018.17101124

Klomek, A. B., Sourander, A., and Elonheimo, H. (2015). Bullying by peers in childhood and effects on psychopathology, suicidality, and criminality in adulthood. *Lancet Psychiatry* 2, 930–941. doi: 10.1016/s2215-0366(15)00223-0

Kujawa, A., Arfer, K. B., Klein, D. N., and Proudfit, G. H. (2014). Electrocortical reactivity to social feedback in youth: a pilot study of the Island Getaway task. *Dev. Cogn. Neurosci.* 10, 140–147. doi: 10.1016/j.dcn.2014.08.008

Kujawa, A., Hajcak, G., and Klein, D. N. (2019). Reduced reward responsiveness moderates the effect of maternal depression on depressive symptoms in offspring: evidence across levels of analysis. *J. Child Psychol. Psychiatry* 60, 82–90. doi: 10.1111/jcpp.12944

Kujawa, A., Kessel, E. M., Carroll, A., Arfer, K. B., and Klein, D. N. (2017). Social processing in early adolescence: associations between neurophysiological, self-report, and behavioral measures. *Biol. Psychol.* 128, 55–62. doi: 10.1016/j.biopsycho.2017.07.001

Layous, K., Nelson, S. K., Oberle, E., Schonert-Reichl, K. A., and Lyubomirsky, S. (2012). Kindness counts: prompting prosocial behavior in preadolescents boosts peer acceptance and well-being. *PLoS One* 7:e51380. doi: 10.1371/journal.pone.0051380

Leadbeater, B. J., and Hoglund, W. L. (2009). The effects of peer victimization and physical aggression on changes in internalizing from first to third grade. *Child Dev.* 80, 843–859. doi: 10.1111/j.1467-8624.2009.01301.x

Levinson, A. R., Speed, B. C., Infantolino, Z. P., and Hajcak, G. (2017). Reliability of the electrocortical response to gains and losses in the doors task: reliability of ERPs to gain and loss. *Psychophysiology* 54, 601–607. doi: 10.1111/psyp.12813

Liu, W., Wang, L., Shang, H., Shen, Y., Li, Z., Cheung, E. F., et al. (2014). The influence of anhedonia on feedback negativity in major depressive disorder. *Neuropsychologia* 53, 213–220. doi: 10.1016/j.neuropsychologia.2013.11.023

Luby, J. L., Gaffrey, M. S., Tillman, R., April, L. M., and Belden, A. C. (2014). Trajectories of preschool disorders to full DSM depression at school age and early adolescence: continuity of preschool depression. *Am. J. Psychiatry* 171, 768–776. doi: 10.1176/appi.ajp.2014.13091198

Luby, J. L., Heffelfinger, A., Koenig-McNaught, A. L., Brown, K., and Spitznagel, E. (2004). The preschool feelings checklist: a brief and sensitive screening measure for depression in young children. *J. Am. Acad. Child Adolesc. Psychiatry* 43, 708–717. doi: 10.1097/01.chi.0000121066.29744.08

Luby, J. L., Si, X., Belden, A. C., Tandon, M., and Spitznagel, E. (2009). Preschool depression: homotypic continuity and course over 24 months. *Arch. Gen. Psychiatry* 66, 897–905. doi: 10.1001/archgenpsychiatry.2009.97

Luck, S. J., and Kappenman, E. S. (2012). *The Oxford Handbook of Event-Related Potential Components.* New York, NY: Oxford University Press.

Maechler, M. (2018). *sfsmisc: Utilities from "Seminar fuer Statistik" ETH Zurich.* Available online at: https://CRAN.R-project.org/package=sfsmisc. Accessed January 9, 2019.

Mandelli, L., Petrelli, C., and Serretti, A. (2015). The role of specific early trauma in adult depression: a meta-analysis of published literature. Childhood trauma and adult depression. *Eur. Psychiatry* 30, 665–680. doi: 10.1016/j.eurpsy.2015.04.007

Meyer, A., Lerner, M. D., De Los Reyes, A., Laird, R. D., and Hajcak, G. (2017). Considering ERP difference scores as individual difference measures: issues with subtraction and alternative approaches: difference scores and ERPs. *Psychophysiology* 54, 114–122. doi: 10.1111/psyp.12664

Modecki, K. L., Minchin, J., Harbaugh, A. G., Guerra, N. G., and Runions, K. C. (2014). Bullying prevalence across contexts: a meta-analysis measuring cyber and traditional bullying. *J. Adolesc. Health* 55, 602–611. doi: 10.1016/j.jadohealth.2014.06.007

Nelson, B. D., Perlman, G., Hajcak, G., Klein, D. N., and Kotov, R. (2015). Familial risk for distress and fear disorders and emotional reactivity in adolescence: an event-related potential investigation. *Psychol. Med.* 45, 2545–2556. doi: 10.1017/s0033291715000471

Nelson, B. D., Perlman, G., Klein, D. N., Kotov, R., and Hajcak, G. (2016). Blunted neural response to rewards as a prospective predictor of the development of depression in adolescent girls. *Am. J. Psychiatry* 173, 1223–1230. doi: 10.1176/appi.ajp.2016.15121524

Olino, T. M., McMakin, D. L., Morgan, J. K., Silk, J. S., Birmaher, B., Axelson, D. A., et al. (2014). Reduced reward anticipation in youth at high-risk for unipolar depression: a preliminary study. *Dev. Cogn. Neurosci.* 8, 55–64. doi: 10.1016/j.dcn.2013.11.005

Olino, T. M., Silk, J. S., Osterritter, C., and Forbes, E. E. (2015). Social reward in youth at risk for depression: a preliminary investigation of subjective and neural differences. *J. Child Adolesc. Psychopharmacol.* 25, 711–721. doi: 10.1089/cap.2014.0165

Ossewaarde, L., Qin, S., Van Marle, H. J. F., van Wingen, G. A., Fernández, G., and Hermans, E. J. (2011). Stress-induced reduction in reward-related prefrontal cortex function. *Neuroimage* 55, 345–352. doi: 10.1016/j.neuroimage.2010.11.068

Paternoster, R., Brame, R., Mazerolle, P., and Piquero, A. (1998). Using the correct statistical test for the equality of regression coefficients. *Criminology* 36, 859–866. doi: 10.1111/j.1745-9125.1998.tb01268.x

Pizzagalli, D. A. (2014). Depression, stress, and anhedonia: toward a synthesis and integrated model. *Annu. Rev. Clin. Psychol.* 10, 393–423. doi: 10.1146/annurev-clinpsy-050212-185606

Porcelli, A. J., Lewis, A. H., and Delgado, M. R. (2012). Acute stress influences neural circuits of reward processing. *Front. Neurosci.* 6:157. doi: 10.3389/fnins.2012.00157

Pouwels, J. L., Souren, P. M., Lansu, T. A. M., and Cillessen, A. H. N. (2016). Stability of peer victimization: a meta-analysis of longitudinal research. *Dev. Rev.* 40, 1–24. doi: 10.1016/j.dr.2016.01.001

Proudfit, G. H. (2015). The reward positivity: from basic research on reward to a biomarker for depression: the reward positivity. *Psychophysiology* 52, 449–459. doi: 10.1111/psyp.12370

R Core Team. (2013). *R: A Language and Environment for Statistical Computing.* Vienna, Austria: R Foundation for Statistical Computing. Available online at: http://www.R-project.org/. Accessed January 9, 2019.

Reijntjes, A., Kamphuis, J. H., Prinzie, P., and Telch, M. J. (2010). Peer victimization and internalizing problems in children: a meta-analysis of longitudinal studies. *Child Abuse Negl.* 34, 244–252. doi: 10.1016/j.chiabu.2009.07.009

Rudolph, K. D., Miernicki, M. E., Troop-Gordon, W., Davis, M. M., and Telzer, E. H. (2016). Adding insult to injury: neural sensitivity to social exclusion is associated with internalizing symptoms in chronically peer-victimized girls. *Soc. Cogn. Affect. Neurosci.* 11, 829–842. doi: 10.1093/scan/nsw021

Schaefer, D. R., Light, J. M., Fabes, R. A., Hanish, L. D., and Martin, C. L. (2010). Fundamental principles of network formation among preschool children. *Soc. Networks* 32, 61–71. doi: 10.1016/j.socnet.2009.04.003

Schwartz, D., Dodge, K. A., Coie, J. D., Hubbard, J. A., Cillessen, N., Lemerise, E. A., et al. (1998). Social-cognitive and behavioral correlates of aggression and victimization in boys' play groups. *J. Abnorm. Child Psychol.* 26, 431–440. doi: 10.1023/A:1022695601088

Sheridan, M. A., McLaughlin, K. A., Winter, W., Fox, N., Zeanah, C., and Nelson, C. A. (2018). Early deprivation disruption of associative learning is a developmental pathway to depression and social problems. *Nat. Commun.* 9:2216. doi: 10.1038/s41467-018-04381-8

Stoy, M., Schlagenhauf, F., Sterzer, P., Bermpohl, F., Hägele, C., Suchotzki, K., et al. (2012). Hyporeactivity of ventral striatum towards incentive stimuli in unmedicated depressed patients normalizes after treatment with escitalopram. *J. Psychopharmacol.* 26, 677–688. doi: 10.1177/0269881111416686

Stringaris, A., Vidal-Ribas Belil, P., Artiges, E., Lemaitre, H., Gollier-Briant, F., Wolke, S., et al. (2015). The brain's response to reward anticipation and depression in adolescence: dimensionality, specificity, and longitudinal predictions in a community-based sample. *Am. J. Psychiatry* 172, 1215–1223. doi: 10.1176/appi.ajp.2015.14101298

Swearer, S. M., Martin, M., Brackett, M., and Palacios, R. A. (2017). Bullying intervention in adolescence: the intersection of legislation, policies, and behavioral change. *Adolesc. Res. Rev.* 2, 23–35. doi: 10.1007/s40894-016-0037-9

Takizawa, R., Maughan, B., and Arseneault, L. (2014). Adult health outcomes of childhood bullying victimization: evidence from a five-decade longitudinal British birth cohort. *Am. J. Psychiatry* 171, 777–784. doi: 10.1176/appi.ajp.2014.13101401

Treadway, M. T., Bossaller, N. A., Shelton, R. C., and Zald, D. H. (2012). Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. *J. Abnorm. Psychol.* 121, 553–558. doi: 10.1037/a0028813

Troop-Gordon, W., and Ladd, G. W. (2005). Trajectories of peer victimization and perceptions of the self and schoolmates: precursors to internalizing and externalizing problems. *Child Dev.* 76, 1072–1091. doi: 10.1111/j.1467-8624.2005.00898.x

Tur-Porcar, A. M., Doménech, A., and Mestre, V. (2018). Family linkages and social inclusion. Predictors of prosocial behavior in childhood. *An. Psicol.* 34:340. doi: 10.6018/analesps.34.2.308151

Twenge, J. M., Baumeister, R. F., DeWall, C. N., Ciarocco, N. J., and Bartels, J. M. (2007). Social exclusion decreases prosocial behavior. *J. Pers. Soc. Psychol.* 92, 56–66. doi: 10.1037/0022-3514.92.1.56

Ubl, B., Kuehner, C., Kirsch, P., Ruttorf, M., Diener, C., and Flor, H. (2015). Altered neural reward and loss processing and prediction error signalling in depression. *Soc. Cogn. Affect. Neurosci.* 10, 1102–1112. doi: 10.1093/scan/nsu158

US Center for Disease Control. (2018). Featured topic: bullying research. Available online at: https://www.cdc.gov/violenceprevention/youthviolence/bullyingresearch/index.html. Accessed April 15, 2018.

Venables, W. N., and Ripley, B. D. (2002). *Modern Applied Statistics With S.* 4th Edn. New York, NY: Springer.

Weinberg, A., Liu, H., Hajcak, G., and Shankman, S. A. (2015). Blunted neural response to rewards as a vulnerability factor for depression: results from a family study. *J. Abnorm. Psychol.* 124, 878–889. doi: 10.1037/abn0000081

Weinberg, A., Riesel, A., and Proudfit, G. H. (2014). Show me the Money: the impact of actual rewards and losses on the feedback negativity. *Brain Cogn.* 87, 134–139. doi: 10.1016/j.bandc.2014.03.015

Will, G.-J., Crone, E. A., van Lier, P. A. C., and Güroglu, B. (2018). Longitudinal links between childhood peer acceptance and the neural correlates of sharing. *Dev. Sci.* 21:e12489. doi: 10.1111/desc.12489

Zhang, W.-N., Chang, S.-H., Guo, L.-Y., Zhang, K.-L., and Wang, J. (2013). The neural correlates of reward-related processing in major depressive disorder: a meta-analysis of functional magnetic resonance imaging studies. *J. Affect. Disord.* 151, 531–539. doi: 10.1016/j.jad.2013.06.039

Conflict of Interest Statement: JL receives royalties from Guilford Press.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling Editor declared a past co-authorship with one of the authors BR.

frontiers in Behavioral Neuroscience

CORRECTION
published: 23 June 2020
doi: 10.3389/fnbeh.2020.00100

Corrigendum: Peer Victimization and Dysfunctional Reward Processing: ERP and Behavioral Responses to Social and Monetary Rewards

Brent I. Rappaport[1], Laura Hennefield[2], Autumn Kujawa[3], Kodi B. Arfer[4], Danielle Kelly[2], Emily S. Kappenman[5], Joan L. Luby[2] and Deanna M. Barch[1,2,6]*

[1] Department of Psychological & Brain Sciences, Washington University in St. Louis, St. Louis, MO, United States, [2] Department of Psychiatry, School of Medicine, Washington University in St. Louis, St. Louis, MO, United States, [3] Department of Psychology & Human Development, Vanderbilt University, Nashville, TN, United States, [4] Center for HIV Identification, Prevention, and Treatment Services, University of California, Los Angeles, Los Angeles, CA, United States, [5] Department of Psychology, San Diego State University, San Diego, CA, United States, [6] Department of Radiology, School of Medicine, Washington University in St. Louis, St. Louis, MO, United States

OPEN ACCESS

Edited and reviewed by:
Johanna M. Jarcho,
Temple University, United States

***Correspondence:**
Brent I. Rappaport
brappaport@wustl.edu

Specialty section:
This article was submitted to Motivation and Reward, a section of the journal Frontiers in Behavioral Neuroscience

Received: 28 April 2020
Accepted: 22 May 2020
Published: 23 June 2020

Citation:
Rappaport BI, Hennefield L, Kujawa A, Arfer KB, Kelly D, Kappenman ES, Luby JL and Barch DM (2020) Corrigendum: Peer Victimization and Dysfunctional Reward Processing: ERP and Behavioral Responses to Social and Monetary Rewards. Front. Behav. Neurosci. 14:100. doi: 10.3389/fnbeh.2020.00100

Keywords: peer victimization, event-related potentials (ERP), reward, depression, adolescence, monetary reward, social reward

A Corrigendum on

Peer Victimization and Dysfunctional Reward Processing: ERP and Behavioral Responses to Social and Monetary Rewards

by Rappaport, B. I., Hennefield, L., Kujawa, A., Arfer, K. B., Kelly, D., Kappenman, E. S., et al. (2019). Front. Behav. Neurosci. 13:120. doi: 10.3389/fnbeh.2019.00120

In the original article, there was a mistake in **Figure 2** as published. In the original article, we had stated that "all data were re-referenced to the average of Tp9 and Tp10" in the Data Analysis section of the Materials and Methods. Although this was our intention, we recently discovered that our scripts had in fact been re-referencing the data to the average of Tp9, Tp10, and Cz electrodes accidentally. Repeating the analyses using the correct referencing and same trials from the original paper yields identical results to those reported in the original article. The corrected **Figure 2** appears below. The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

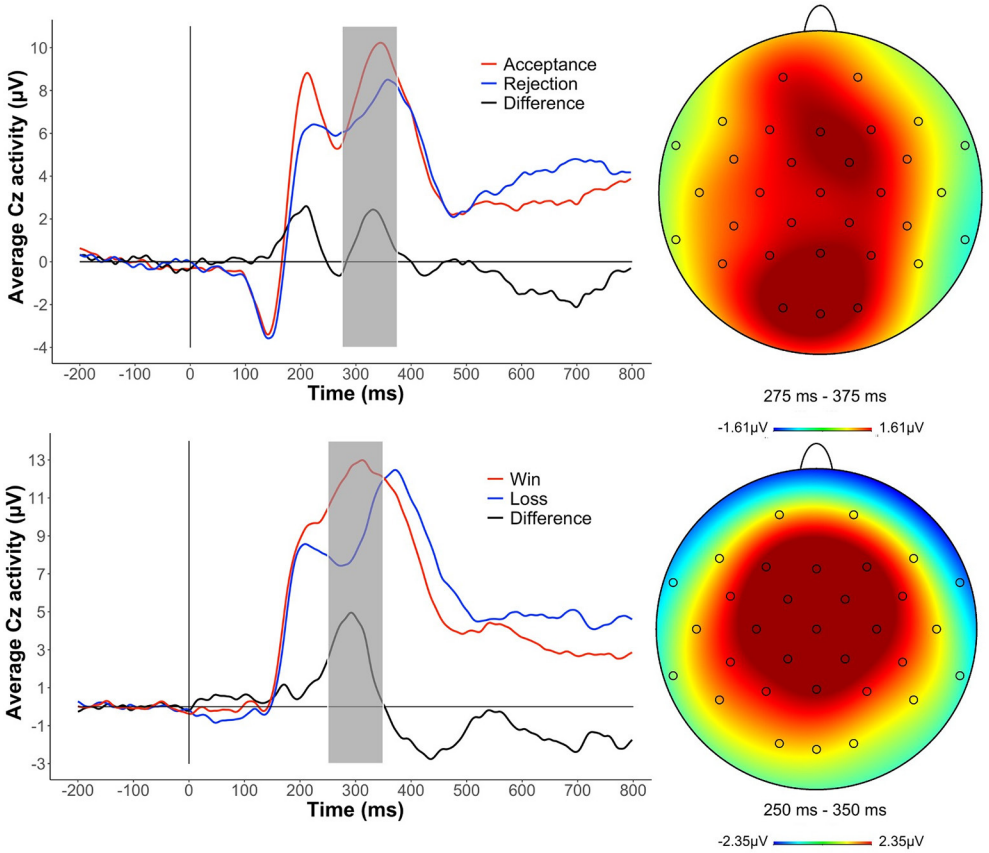


FIGURE 2 | Grand average event-related potential (ERP) waveforms and scalp distributions to social and monetary reward feedback at Cz electrode. Time window is highlighted in gray.

frontiers in Behavioral Neuroscience

REVIEW
published: 21 June 2019
doi: 10.3389/fnbeh.2019.00133

Social and Non-social Mechanisms of Inequity Aversion in Non-human Animals

Lina Oberliessen and Tobias Kalenscher*

Comparative Psychology, Institute of Experimental Psychology, Heinrich Heine University, Düsseldorf, Germany

Research over the last decades has shown that humans and other animals reveal behavioral and emotional responses to unequal reward distributions between themselves and other conspecifics. However, cross-species findings about the mechanisms underlying such inequity aversion are heterogeneous, and there is an ongoing discussion if inequity aversion represents a truly social phenomenon or if it is driven by non-social aspects of the task. There is not even general consensus whether inequity aversion exists in non-human animals at all. In this review article, we discuss variables that were found to affect inequity averse behavior in animals and examine mechanistic and evolutionary theories of inequity aversion. We review a range of moderator variables and focus especially on the comparison of social vs. non-social explanations of inequity aversion. Particular emphasis is placed on the importance of considering the experimental design when interpreting behavior in inequity aversion tasks: the tasks used to probe inequity aversion are often based on impunity-game-like designs in which animals are faced with unfair reward distributions, and they can choose to accept the unfair offer, or reject it, leaving them with no reward. We compare inequity-averse behavior in such impunity-game-like designs with behavior in less common choice-based designs in which animals actively choose between fair and unfair rewards distributions. This review concludes with a discussion of the different mechanistic explanations of inequity aversion, especially in light of the particular features of the different task designs, and we give suggestions on experimental requirements to understand the "true nature" of inequity aversion.

Keywords: inequity aversion, animals, social vs. non-social theories, moderator variables, task design, choice task

OPEN ACCESS

Edited by:
Regina Marie Sullivan,
New York University, United States

Reviewed by:
Masahiko Haruno,
Tamagawa University, Japan
Johannes Hewig,
University of Wuerzburg, Germany

****Correspondence:***
Lina Oberliessen
lina.hilden@hotmail.de

Received: *16 February 2019*
Accepted: *05 June 2019*
Published: *21 June 2019*

Citation:
Oberliessen L and Kalenscher T (2019) Social and Non-social Mechanisms of Inequity Aversion in Non-human Animals. Front. Behav. Neurosci. 13:133. doi: 10.3389/fnbeh.2019.00133

THE CONCEPT OF INEQUITY AVERSION

Other-regarding preferences, i.e., the consideration of the well-being of others when making decisions, are pertinent in human behavior and economic decision making (Fehr and Schmidt, 1999). Such decisions are not solely based on egoistic, materialistic motives, but others' outcomes are considered as well. Other-regarding preferences have often been studied with economic games (e.g., Yamagishi et al., 2009; Margittai et al., 2015; Strombach et al., 2015). For instance, in the dictator game, participants are asked to split an endowment between themselves and a co-player. Decades of research with the dictator game has shown that people across many cultures and socio-economic groups voluntarily share money and other resources with others (Bolton et al., 1998; Engel, 2011). Another game is the ultimatum game (Güth et al., 1982) in which one player, the proposer, splits a sum of money between herself and another player, the responder.

The responder can decide whether to accept or reject the share. If she accepts, both players can keep their share. If she rejects, both players receive nothing. Several thousand replications of the ultimatum game (Güth and Schmidt, 2013) have revealed that the vast majority of responders rejects offers that are perceived unfair, i.e., they forego own-payoffs, to punish unfair proposers. Yet another game is the impunity game (Bolton and Zwick, 1995). In this game, one player, the proposer, can share an endowment between herself and a second player, the responder. The responder can either accept or reject the offer. If she accepts the offer, both players keep their share, if she rejects, the responder receives nothing while the proposer keeps her share. Unfair offers are often rejected by responders (Bolton and Zwick, 1995), thus leaving them empty-handed with no economic consequences for the proposer. Rejections are puzzling at first sight, but are likely fueled by an emotional response to unfairness, revealing that responders derive more disutility from small, but unfair gains than from no gains at all.

Even though such fairness-driven behaviors appear economically unreasonable on the surface because of their costliness (recipients forego rewards or accept costs to punish fairness violators), they are often considered the consequence of so-called inequity aversion (IA), an affective, cognitive and behavioral response to unequal outcomes (Oberliessen et al., 2016). Generally, two forms of IA can be distinguished: (1) aversion against outcome distributions that yield a higher payoff for a partner relative to one's own payoff, given matched efforts to obtain the payoff (disadvantageous IA); and (2) aversion against outcomes that produce a lower payoff for a partner relative to one's own payoff (advantageous IA; Oberliessen et al., 2016).

But what is the benefit of costly IA if it does not increase, or even lowers, an organism's immediate (economic or Darwinian) fitness? IA has been hypothesized to function as a mechanism to ensure the sharing of payoffs and, thus, to enable and maintain long term cooperation with non-kin. It is proposed to serve as an unfairness detector, protecting individuals from exploitation (Brosnan, 2006, 2011; Brosnan and de Waal, 2014). Cooperation allows individuals to achieve goals that they could not achieve alone (e.g., teamwork in humans, or cooperative hunting and cooperative breeding in non-human animals) and offers the possibility to exchange favors over time (direct, indirect and generalized reciprocity; e.g., delousing behavior in monkeys; Stevens and Hauser, 2004; Brosnan and de Waal, 2014).

INEQUITY AVERSION IN NON-HUMAN ANIMALS

This explanation already foreshadows, and the examples imply, that IA might not solely occur in humans, but can also be expected in social non-human animal species that engage in cooperative behaviors. Indeed, evidence has accumulated over the last years suggesting that disadvantageous IA exists in various social species. In 2003, Brosnan and de Waal (2003) published a pioneering study testing the response of brown capuchin monkeys to unequal rewards. In this study, two monkeys in adjacent cages could both exchange a token for a food reward with a human experimenter. In the equity condition, both individuals received a piece of cucumber reward for successfully exchanging the token. In the inequity condition, one of the monkeys received a more valuable grape while the other monkey continued to receive the lower valued piece of cucumber for performing the same token exchange task. As a consequence, the disadvantaged monkey refused to exchange the token, or rejected the cucumber reward entirely, tentatively reminiscent of the behavior of human responders in the impunity game (see below for critical discussion). Since this early study, IA was replicated in capuchin monkeys (van Wolkenten et al., 2007; Fletcher, 2008; Takimoto et al., 2010; Takimoto and Fujita, 2011), and reported in macaques (Massen et al., 2012; Hopper et al., 2013), chimpanzees (Brosnan et al., 2005, 2010), cotton top tamarins (Neiworth et al., 2009), dogs (Range et al., 2009, 2012; Brucks et al., 2016; see McGetrick and Range, 2018 for an overview), wolves (Essler et al., 2017), crows (Wascher and Bugnyar, 2013), rabbits (Heidary et al., 2008) and rats (Oberliessen et al., 2016).

However, some studies failed to demonstrate disadvantageous IA in non-human animals, for example in capuchin monkeys (Dubreuil et al., 2006; Roma et al., 2006; Fontenot et al., 2007; Silberberg et al., 2009), chimpanzees, bonobos, orangutans, and gorillas (Bräuer et al., 2006, 2009), cleaner fish (Raihani et al., 2012), keas (Heaney et al., 2017), and dogs (Horowitz, 2012). While the lack of IA in less cooperative species like orangutans (Bräuer et al., 2009; Brosnan et al., 2011) or squirrel monkeys (Talbot et al., 2011; Freeman et al., 2013) might not come unexpected, given the hypothesis that IA is primarily a mechanism for maintaining cooperation, it is hard to explain its absence in cooperative species like capuchin monkeys, dogs, chimpanzees and cleaner fish (see **Table 1** for an overview of all studies). Consequently, there is an ongoing, relatively heated debate about the true nature of IA, whether it truly serves to maintain cooperation, and whether it even exists at all in non-human animals.

ONE CONCEPT—MANY THEORIES

In this section, we will more closely consider different theories of IA that have been proposed to account for the heterogeneous results. Some of these theories refer to social motives, but others explain previous alleged IA-like behaviors with non-social cognitive mechanisms.

Social Hypotheses: Maintaining Cooperation vs. Social Disappointment

Brosnan (2006, 2011) posits that fairness preferences, ultimately leading to IA, are advantageous for an organism because, as mentioned above, they serve as a mechanism to ensure the sharing of payoffs and thus, to enable and maintain long term cooperation with non-kin. However, other authors offer different, more mechanistic interpretations of the animals' behavior in the above-mentioned tasks. The social disappointment hypothesis (Engelmann et al., 2017) suggests that, rather than being sensitive to the relative advantage of the conspecific, animals actually respond to

TABLE 1 | Evidence for and against inequity aversion in non-human animal species using different task designs.

Reference	Species	Task type	Disadvantageous IA	Advantageous IA
Brosnan and de Waal (2003)	Capuchin monkeys	Impunity	+	
van Wolkenten et al. (2007)	Capuchin monkeys	Impunity	+	
Fletcher (2008)	Capuchin monkeys	Choice	+	
Takimoto et al. (2010)	Capuchin monkeys	Choice		+
Takimoto and Fujita (2011)	Capuchin monkeys	Choice		+
Dubreuil et al. (2006)	Capuchin monkeys	No task	–	
Roma et al. (2006)	Capuchin monkeys	No task	–	
Fontenot et al. (2007)	Capuchin monkeys	No task	–	
Silberberg et al. (2009)	Capuchin monkeys	Impunity	–	
De Waal et al. (2008)	Capuchin monkeys	Choice		+
Hopper et al. (2013)	Macaques	Impunity	+	
Massen et al. (2012)	Macaques	Impunity	+	
Ballesta and Duhamel (2015)	Macaques	Choice		+
Chang S. W. et al. (2011)	Macaques	Choice		–
Brosnan et al. (2005)	Chimpanzees	Impunity	+	
Brosnan et al. (2010)	Chimpanzees	Impunity	+	
Jensen et al. (2007)	Chimpanzees	Choice + impunity	–	–
Kaiser et al. (2012)	Chimpanzees	Choice + impunity	–	–
Bräuer et al. (2006)	Chimpanzees, bonobos, orangutans, gorillas	No task	–	
Bräuer et al. (2009)	Chimpanzees, bonobos, orangutans, gorillas	Impunity	–	
Horner et al. (2011)	Chimpanzees	Choice		+
Neiworth et al. (2009)	Tamarins	Impunity	+	
Freeman et al. (2013)	Marmosets, owl monkeys, squirrel monkeys	Impunity	–	
Brosnan et al. (2011)	Orangutans	Impunity	–	
Range et al. (2009)	Dogs	Impunity	+	
Range et al. (2012)	Dogs	Impunity	+	
Horowitz (2012)	Dogs	Choice	–	–
Brucks et al. (2016)	Dogs	Impunity	+	
Essler et al. (2017)	Wolves	Impunity	+	
Wascher and Bugnyar (2013)	Crows	Impunity	+	
Heidary et al. (2008)	Rabbits	No task (histopathology)	+	
Oberliessen et al. (2016)	Rats	Choice	+	
Márquez et al. (2015)	Rats	Choice		+
Hernandez-Lallement et al. (2015, 2016)	Rats	Choice		+
Hernandez-Lallement et al. (2016)	Rats	Choice		+
Hernandez-Lallement et al. (2018)	Rats	Choice		+
Raihani et al. (2012)	Cleaner fish	Impunity	–	
Heaney et al. (2017)	Keas	Impunity	–	

For each species tested on IA, the particular task type is specified. "Impunity" refers to impunity-like tasks (e.g., token exchange tasks) in which pairs of animals are confronted with equal or unequal outcomes, and they can choose to reject rewards and/or refuse further task performance. "Choice" refers to tasks in which an actor animal can actively choose between an equal and an unequal reward distribution. "No task" implies that equal, respectively unequal rewards are offered by an experimenter for free, and the animals can decide to accept or reject these food rewards. A "+" means that the particular authors found evidence for the respective kind of IA, a "–"means that there was no such evidence.

reward expectations triggered by the human experimenter. According to this hypothesis, the actor animal would simply be disappointed by the experimenter because she is not rewarding it as well as well as he could obviously have. Engelmann et al. (2017) tested their hypothesis in an experiment with chimpanzees. They used a two-by-two design in which food was either distributed by an experimenter or a machine and with a partner present or absent. In accordance with their hypothesis, they found that chimpanzees were more likely to reject food when it was distributed by an experimenter compared to a machine. Rejection rates were unaffected by the presence or absence of a partner chimpanzee. Hence, the authors concluded that the refusal of the less preferred food item stemmed from the social disappointment in the experimenter and not from the violation of the animals' sense of fairness.

However, this conclusion can be debated, too. First, Engelmann et al.'s (2017) result might be species- and context-specific; for instance, while chimpanzees might emotionally respond to violations of reward expectations associated with their human experimenter, other animals, like rodents and birds, might be less sensitive to their experimenter's behavior. In addition, this hypothesis is, at closer inspection, not very parsimonious, but makes relatively strong assumptions about the animals' computational capabilities: disappointment by the experimenter's bad rewarding performance requires the ability to actually realize that the experimenter could have performed better in providing higher quality of rewards. Finally, the social disappointment hypothesis seems more about the source of unfairness sentiments than about the existence of such sentiments *per se*: the hypothesis is perfectly consistent with the idea that the chimpanzees actually felt treated unfairly, it just predicts that they attributed this negative state to the experimenter, and not to the conspecific; hence, the animals would still show a form of IA.

One way to resolve these ambiguities would be to design tasks without experimenter interference, e.g., tasks in which two individuals have to negotiate the distribution of rewards over successive trials (e.g., Brosnan et al., 2006; Melis et al., 2009). Promising approaches on rule observance and conflict resolution have recently been developed for mice (e.g., Choe et al., 2017), but the implications for IA are still elusive. Future research should focus on the development of inter-conspecific negotiation tasks.

Frustration Hypothesis

Other authors proposed that non-social motives might also explain the animals' behavior in IA tasks. For example, Roma et al. (2006) suggested that frustration rather than IA might account for some of the findings. They investigated pairs of capuchin monkeys and offered the "model" monkey grape or cucumber while the "witness" monkey always received cucumber. The authors found that the witnesses' rejections of cucumber were not dependent on whether the model received grape or cucumber, i.e., they found no evidence of behaviorally measurable sensitivity to inequity. However, they also observed that, when cucumber was offered to the model monkeys who were used to grapes, they showed higher rejection rates of cucumber than the witnesses. This finding suggests that previous experience with a more valuable reward (grape) results in a relative devaluation of the less valuable reward, and, hence, its rejection. Thus, rejections might reflect frustration about the poor reward rather than feelings of unfairness. Nevertheless, it should be noted that the experimental setup differed to the one of Brosnan and de Waal (2003) as the animals received the rewards for free, i.e., without an effort requirement or token exchange. This lack of a cost requirement might be crucial because other research has shown that effort seems to be an important moderator of the magnitude of the IA response (van Wolkenten et al., 2007; Wascher and Bugnyar, 2013). This raises the question of whether the lack of any effort requirement in Roma et al.'s (2006) experiment might explain the absence of IA. Nevertheless, this consideration does not entirely disqualify frustration as a potential, non-social moderator of the animals' rejection behavior in IA tasks.

Reward Expectation Hypothesis

A related non-social explanation of the rejection of unequal rewards in IA tasks is the reward expectation hypothesis (Bräuer et al., 2006; see also Dubreuil et al., 2006; Neiworth et al., 2009). The hypothesis states that seeing another individual receiving a more valuable reward raises the expectation of receiving the same valuable reward. Deliveries of less valuable rewards thus violate the animal's reward expectation. By consequence, reward rejections or refusals of task performance could also be caused by failed expectations and negative reward prediction errors, and, hence, cannot with certainty be attributed to IA. A recent human study provided further evidence for the importance of expectations (Vavra et al., 2018). Participants in an ultimatum game were provided with explicit information on what kind of offers to expect by a certain proposer. The authors showed four different distributions, manipulating both the mean and the variance of these expected sets of offers. They found that 50% of the participants systematically changed their behavior as a function of their reward expectations (Vavra et al., 2018). As only the offer expectations differed between conditions, social processes alone cannot explain the changes in behavior corresponding to these offer expectations.

However, this line of reasoning still leaves room for social processes underlying rejection behavior in IA tasks. In standard reinforcement learning, non-human animals derive reward expectations purely from own-experience with past rewards. But in Brosnan and de Waal's original experiment as well as in follow-up studies, subjects never received the more valuable reward, so any elevated reward expectations based on own-reward history is unlikely. The reward-expectation hypothesis therefore specifically states that own-reward expectations would be influenced by the perception of rewards delivered to others. But the assumption that perceiving rewards delivered to others vicariously elevates own-reward expectations actually require the existence of social comparison processes, and, hence, implies social cognition; this hypothesis, therefore, cannot qualify as a non-social explanation of the variance in rejection behavior in IA tasks.

Yet, it is still possible that the mere presentation of more valuable rewards raised reward expectations beyond vicarious reward tracking. However, van Wolkenten et al. (2007) pointed out that the more valuable reward in the original task by Brosnan and de Waal (2003) and others was equally visible in both the inequity and equity conditions (the experimenter visibly stored the rewards in front of the experimental cages; van Wolkenten et al., 2007). This symmetry in reward presentation means that a putative presentation-effect on reward expectation is insufficient to explain the higher rejection rates in the inequity compared to the equity condition as the animals could see (and thus expect) the more valuable reward in both conditions. Nonetheless, admittedly, it is still possible that the accessibility of the more valuable reward to the conspecific (inequity condition; the reward is merely visible in the equity condition) might affect the level of expectation (see e.g., Brosnan et al., 2010). Consequently, the fact remains that reward expectation, like frustration, might be another plausible, non-social, moderator of IA.

Reference-Dependent Reward Valuation and Loss Aversion

Chen and Santos (2006) offer yet another non-social mechanism to account for the rejection behavior in all types of IA tasks. They suggest that reference-dependent reward valuation and loss-aversion can account for the evolution of IA. Reference-dependent reward valuation refers to the subjective evaluation of reward magnitude, or reward quality, relative to a benchmark criterion, such as a standard reward; i.e., a given reward magnitude might be valued differently, depending on whether it is higher or lower than the reference reward magnitude (Marsh and Kacelnik, 2002; Chen et al., 2006). Loss-aversion describes the overweighting of negative reward magnitudes during reward evaluation, i.e., reward magnitudes that are lower than expected, or the overweighting of actual losses, respectively (note that losses are difficult to implement in animal research; most research

on loss aversion in animals operationalizes losses as negative deviations from a reference point; Chen et al., 2006).

Chen and Santos (2006) maintain that the monkeys' behavior in the original IA task (e.g., Brosnan and de Waal, 2003) could be explained by translating reference-dependency and loss aversion concepts to the social domain; that is, they assume a socially generated reference point. According to this idea, the payoff to the other individual in Brosnan and de Waal's (2003) task might become the reference point against which own-rewards are evaluated. Own-rewards below this reference-point, i.e., cucumber instead of grape, would then be perceived as a loss, generating frustration and loss avoidance, and hence rejection (Chen and Santos, 2006).

Summary

Thus, in summary, there are a number of social explanations for the animals' rejection patterns in IA tasks, including genuine fairness preferences and social disappointment, but a range of non-social motives have also been proposed to account for the animals' behavior, including frustration, reward expectation, reference-point dependency and loss aversion. Note that the different social and non-social motives are not necessarily mutually exclusive, but might work in concert to influence behavior in IA tasks. Furthermore, it is worthwhile pointing out that particularly the non-social explanations are conceptually similar. Reward expectation might be considered a direct result of reference-dependent reward valuation, and hence frustration might occur as a result of loss aversion. The two social explanations mainly differ in the causal attribution of IA, as both assume a form of social disappointment: Either in the human experimenter who rewards below his best or in the relative unfairness between subject and partner. Interestingly, the explanation by Brosnan (2006, 2011) can also be seen as a (social) subcategory of reference-dependent reward valuation (the reference point is the outcome of the partner) and, in addition to that, any form of disappointment might eventually result in frustration.

In the next section, we will consider further moderators of IA. We especially highlight the importance of considering the particular characteristics of the different experimental designs used to elicit inequity aversion. We attempt to link these moderator variables, especially the task design, to the abovementioned theories on IA and provide suggestions for future research.

THE EXPERIMENTAL DESIGN AND OTHER MODERATORS OF INEQUITY AVERSION

There are a number of variables that moderate the extent, or even existence, of IA. As already mentioned, effort seems to be an important moderator of the magnitude of the IA response (van Wolkenten et al., 2007; Wascher and Bugnyar, 2013). Furthermore, the quality of the relationship between the pairs of animals tested in an IA task has been shown to influence the level of IA (Brosnan et al., 2005; De Waal et al., 2008; but see Massen et al., 2012; Brosnan et al., 2015). Social hierarchy position also seems to moderate the level of IA, such that higher rank is associated with more pronounced IA (Brosnan et al., 2010; Oberliessen et al., 2016; but see Massen et al., 2012). Further social moderators are sex (Brosnan et al., 2010) and personality (Brosnan et al., 2015): male chimpanzees, more than females, responded to violations of inequity, refusing to complete the interaction with the experimenter when the partner received a better reward (Brosnan et al., 2010). Chimpanzees that were rated higher in the extraversion dimension and lower in the agreeableness dimension were more likely to respond to inequity (Brosnan et al., 2015). In a recent human study, the sensitivity to pain was also identified as a factor to predict the experience of unfairness (the more pain-sensitive, the more experienced unfairness; Wang et al., 2019).

Perhaps the most important influencing factor of IA is the experimental setting in which IA is probed. Almost all of the above-mentioned studies on IA in animals are variants of the original experiment by Brosnan and de Waal (2003) in which pairs of animals are confronted with equal or unequal outcomes, and they can choose to reject rewards and/or refuse further task performance. These tasks strongly resemble the design structure of the impunity game (Bolton and Zwick, 1995) developed for humans (see above) because, in both the animal and human tasks, individuals engage in costly refusals of their own reward with no economic consequence to the conspecific/proposer. Due to their prevalence in the non-human animal literature, the different theories about the cognitive mechanisms underlying non-human IA mostly explain the behavioral particularities in impunity-like tasks. Here, we propose that the use of a different task design might enrich the discussion, and shed light on some of the open questions regarding the true (social or non-social) nature of IA. In particular, we suggest that a different IA paradigm—choice-based IA task designs—might be a promising complement to the existing IA literature as they offer the potential to avoid some of the interpretational caveats mentioned in the preceding section.

Design of Choice-Based Tasks

In a choice-based task (see **Figure 1**), an actor animal can actively choose between an equal and an unequal reward distribution, either leaving a conspecific better off (unequal distribution), or equally well off, than the actor animal (equal distribution; see e.g., Fletcher, 2008; Oberliessen et al., 2016). Importantly, the actor animal's choice is non-costly, i.e., its reward is equal in both reward distributions and thus, independent of the animal's decision. Preferences for equality are compared between two conditions: a social condition with a conspecific present, and a non-social control condition in which the outcome distributions are identical to the social condition, but the conspecific is absent; e.g., rewards are dropped in an empty, adjacent chamber or compartment. Using such choice-based tasks, it has been shown that both rats (Oberliessen et al., 2016) and capuchin monkeys (Fletcher, 2008) preferred equal over unequal outcome distributions when paired with a conspecific, and that this preference for equal distributions was weaker, or entirely absent, in a non-social control condition with no conspecific present.

In this type of designs, the subject can reveal its fairness preference by its choice, and thus control if inequity occurs at

all. The clear advantage of such choice-based IA designs is that the animals do not need to forego own rewards to express their aversion to inequity; thus, they differ from the impunity-like flavor of previous IA tasks that involved costly refusals of own-rewards. This is an important design feature as egoistic desires to maximize food intake in standard impunity-like IA tasks might override any faint, but non-zero IA motives; by consequence, an existent IA preference in an impunity-like task might be masked by an overly strong dislike of sacrificing own-rewards, and it might thus remain undetected.

The Added Value of Choice-Based Tasks

Choice-based tasks allow to control for some of the alternative factors discussed above that are supposed to influence IA. First of all, because the reward distributions and, hence, rewards to the actor animal, are identical between the social and the non-social condition, frustration effects and violations of reward expectation are unlikely to account for the higher preference for equal-reward outcomes in the social compared to the non-social control condition (but see below for more in-depth discussion of possible further frustration and reward expectation effects in choice-based tasks). Hence, differences in behavior between conditions can more plausibly be attributed to the social component of the task (however, note that many impunity-like IA tasks also had a non-social control condition).

Another reason why fairness-preferences in choice-based tasks cannot easily be explained by frustration effects or violations of reward expectations is the invariance in own-reward value; that is, frustration and reward expectations should only occur if the animal had previous experience with more valuable rewards. However, because own-reward quality and magnitude, as well as delay-to-reward and other reward parameters, are always identical in all trials, irrespective of the actor animal's choice, the subjects in choice-based tasks have no previous experience with better rewards, making frustration and expectation effects unlikely.

For the same reason, reference-point-dependence and loss-aversion (Chen and Santos, 2006) are also unlikely explanations of equity preferences in choice-based tasks. Because of the invariance in own-reward outcomes, choice-based tasks entail no reference-dependent reward evaluation or negative deviations from a standard reward (i.e., losses).

A counterargument holds that, at closer inspection, some design features of choice-based tasks might actually prompt frustration, reward expectancy and/or reference-dependency effects, albeit in more subtle ways: the total reward magnitude, i.e., the sum of rewards to the actor animal and the conspecific (or empty compartment, respectively), is higher after unfair than fair choices. This difference in total reward magnitude might affect the level of expectation, it might set a reward magnitude standard, and the actor animal might be frustrated because of the inaccessibility of the reward in the other compartment. These reward expectation, reference and frustration motives might bias choice away from the unfair alternative.

However, if these non-social mechanisms indeed favored equity preferences in choice-based IA task, their influence on choice should be stronger in the non-social control than the social condition, for the following reason: in the social condition, the conspecific has access to the reward and consumes it swiftly, but in the non-social condition, the reward is just dropped in an adjacent compartment without being consumed by an (absent) conspecific. Because of the lack of reward consumption in the control condition, the inaccessible reward in the other compartment is displayed longer than in the social condition. This means that the difference in reward magnitude, and, in particular, the inaccessibility of reward, is more salient in the control than the social condition. By consequence, frustration effects and other non-social drivers of preferences should favor equity choices in the control condition more than in the social condition. Yet, this is inconsistent with the choice data, revealing clear preferences for equity choices in the social, but not the non-social condition. Thus, we consider it implausible that non-social aspects of the task explain the condition-effects on equity preferences.

Finally, disappointment in the human experimenter (Engelmann et al., 2017) can be ruled out in choice-based tasks since the experimenter is not responsible for the choice of reward distributions and is present in both the social and the non-social control condition, or he is even entirely absent if tasks are fully automated.

Of course, there might be additional factors that could bias choices towards one or the other alternative in choice-based IA tasks. For example, the actor animal's perception of the conspecific's reward consumption might incite reward expectancy or might shift reference points, and the fact that the conspecific consumes a reward that the actor animal cannot access might be perceived as frustrating by the actor. It remains to be determined whether these factors are of social nature (e.g., frustration as a consequence of envy-like emotions about the conspecific's reward consumption), or non-social nature (e.g., the conspecific's reward consumption might simply cue the availability of higher rewards that are, however, inaccessible to the actor rat), and it should be investigated if these factors indeed play a role in influencing choice behavior in choice-based IA tasks at all.

Do Choice-Based Tasks Measure Inequity Aversion?

One crucial question is, whether choice-based tasks actually measure the same thing as impunity-like tasks. That is, is a rejection of an unfair offer in an impunity-like task driven by the same mental and affective mechanisms as preference for equity outcomes in a choice-based task, or are the animals' decisions in the respective tasks qualitatively different? Rejections of unfair offers in impunity-like tasks clearly have an affective flavor, while preferences for equal outcomes in choice-based tasks do not necessarily reveal strong emotions. However, empirical evidence that impunity-like tasks involve stronger negative emotions than choice-based tasks is elusive; hence, putative differences in the affective domain between task designs are somewhat speculative.

The answer to the question whether impunity-like or choice-based tasks measure the same form of IA also depends on the particular definition of IA used. Fehr and Schmidt (1999), who developed a theory of IA for human decision-makers, defined

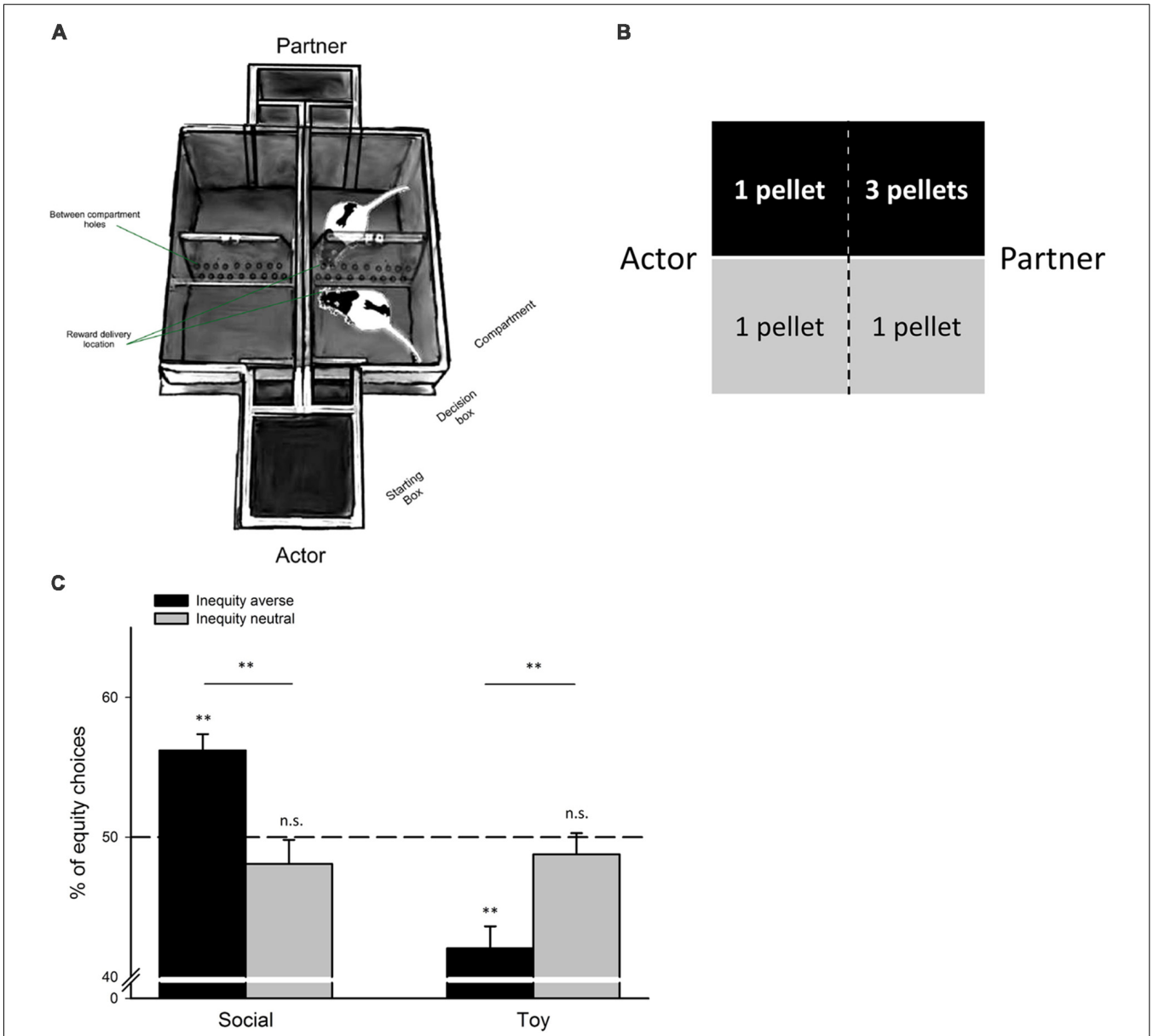


FIGURE 1 | Choice-based disadvantageous inequity aversion task for rats. **(A)** Double T-maze apparatus for quantifying disadvantageous IA in rats. Pairs of rats are trained in this task. The actor rat chooses to enter either an equal-reward compartment, or an unequal-reward compartment. The partner is always directed towards the opposite compartment facing the actor. Actor's and partner's compartments are separated by a transparent, perforated wall, allowing rats to see, hear and smell each other, but neither rat can access the other rat's compartment. The actor rat selects the reward distribution for both rats by entering one of the two compartments in each trial: entering the equal reward compartment produces one food pellet for each rat, entering the unequal-reward compartment yields one food pellet for the actor rat, and three food pellets for the partner rat. Thus, the actor's decisions are non-costly because its own-payoff is always identical and independent of its choice, but it can choose between a fair outcome (both rats receive the same reward magnitude), or an unfair outcome (the partner rat receives a higher reward than the actor rat). In a non-social control condition (the toy condition), reward contingencies, payoff matrix and all other features of the task are identical, but the partner rat is replaced by an inanimate toy rat. Adapted from Hernandez-Lallement et al. (2015, 2016) with friendly permission by Frontiers in Neuroscience, **(B)** illustration of the payoff matrix, **(C)** rats were classified as inequity averse, or inequity neutral, depending on their individual sensitivity to unequal reward distributions (see Oberliessen et al., 2016 for details). Unlike inequity-neutral rats, inequity-averse rats preferred equal over unequal outcomes in the social, but not in the non-social control condition, the toy condition (**$p < 0.01$; n.s., not significant). Adapted from Oberliessen et al. (2016) with friendly permission by Elsevier.

inequity aversion as the resistance against inequitable outcomes. They stressed that the aversion against inequity can, but does not have to, go along with the willingness to forego material payoffs for the sake of fairness.

It is also conceivable that IA is a special form of temporal discounting (Stevens and Hauser, 2004; for an overview of temporal discounting see Kalenscher and Pennartz, 2008): IA might be the rejection of a sooner smaller reward (an unequal

small payoff) compared to a more valuable reward in the future (fair, high rewards in a successful long-term cooperation).

Both definitions of IA entail the willingness of the decision-maker to incur costs for the sake of equity. Since decisions in the impunity-like designs of IA are costly, but decisions in choice-based tasks are not necessarily costly, the construct measured in the former class of tasks comes closer to the definition of IA as put forward by Fehr and Schmidt (1999) or the idea of temporal discounting. Future research should manipulate the costs of the fair option in choice-based designs, and investigate whether animals are also willing to forego own-payoff for the sake of equitable outcomes in these tasks.

In conclusion, we argue that the use of choice-based IA tasks may shed light on some of the remaining open questions raised by experiments using impunity-like IA tasks. We want to stress that we do not consider choice-based IA tasks superior to impunity-like tasks; they merely complement the existing research. We maintain that the combination of both tasks should be the way forward in future research.

ADVANTAGEOUS INEQUITY AVERSION

This review focused primarily on moderators and mechanisms of disadvantageous IA, and its putative ultimate reasons. The motivation for prioritizing the coverage of disadvantageous over advantageous IA, the aversion against outcomes that produce a lower payoff for a partner relative to one's own payoff, is that advantageous IA is rarely found (and tested) in impunity-like tasks (Jensen et al., 2007; Horowitz, 2012; Kaiser et al., 2012). However, there are several choice-based IA tasks prompting advantageous IA (also labeled as prosociality or mutual-reward preferences) in different non-human animals, e.g., rats (Hernandez-Lallement et al., 2015, 2016, 2018; Márquez et al., 2015), capuchin monkeys (De Waal et al., 2008; Takimoto et al., 2010; Takimoto and Fujita, 2011), chimpanzees (Horner et al., 2011), and rhesus macaques (Ballesta and Duhamel, 2015; but see Chang S. W. et al., 2011). Similar to disadvantageous IA, the expression of the animals' aversion against advantageous inequity in choice-based tasks is not costly: the own-reward to the deciding animal is always identical and independent of the choice of a fair or unfair alternative. To date, it is unclear if a principle mental component underlies preferences for equal reward distributions in disadvantageous and advantageous IA settings in non-human animals.

This review mainly focuses on IA in non-human animals. It is important to note that IA has been extensively studied in humans, too, with a vast, partly diverging literature in several different disciplines, including economics and psychology. The terminology and experimental methodology used and covered in this review are largely consistent with the literature in economics, where advantageous IA is defined as preference for fair vs. unfair outcomes, and where IA is mainly investigated by means of economic games (e.g., Fehr and Schmidt, 1999). By contrast, psychologists often label advantageous IA *guilt* and frequently focus on self-reports which can be linked to behavioral intentions underlying other-regarding preferences (e.g., Schmitt et al., 2000), and related concepts, like, e.g., *morality*, *justice*, or *ethics*. We argue that studying IA in animals is not only interesting by itself, but paves the way for harmonizing semantic differences between disciplines as well as highlighting conceptual similarities.

NEURAL SUBSTRATES OF IA

Parallel to behavioral studies on IA, another field of research evolved with the technical progress of cognitive neurosciences. Modern neuroimaging methods offer more and more possibilities to directly study brain processes during social decision making (mainly in humans), and thus to learn more about the underlying mechanisms and brain structures. Although this should not be the focus of this review, we consider it worthwhile to shortly touch on this topic and present some interesting results (note that we do not claim to provide a comprehensive overview; for more details, see Ruff and Fehr, 2014). Several studies which investigated neural responses to disadvantageous and advantageous IA in humans suggest that the dorsolateral prefrontal cortex seems to be particularly involved in encoding and interpreting payoff inequalities and implementing inequality averse behaviors (Sanfey et al., 2003; Hsu et al., 2005; Haruno and Frith, 2010; Tricomi et al., 2010; Chang L. J. et al., 2011; Fliessbach et al., 2012; Cappelen et al., 2014; Güroğlu et al., 2014; Haruno et al., 2014; Yu et al., 2014; Nihonsugi et al., 2015; Holper et al., 2018). Tricomi et al. (2010) found that inequality averse preferences were also correlated with activity in the valuation network (Bartra et al., 2013), mainly ventral striatum and ventromedial prefrontal cortex in humans, suggesting that own-reward activity in the valuation system was modulated by the degree of inequality relative to a better or worse reward received by another participant. A recent study by Gao et al. (2018) even distinguished between neural correlates of advantageous vs. disadvantageous IA. They found that the processing of advantageous inequity involved the left anterior insula, the right dorsolateral prefrontal cortex, and the dorsomedial prefrontal cortex. Disadvantageous inequity correlated with activity in the left posterior insula, the right amygdala, and the dorsal anterior cingulate cortex.

In the animal domain, a study on rhesus monkeys provided evidence that striatal neurons play a role in identifying the social actor and own reward in a social setting (Báez-Mendoza et al., 2013), consistent with the human evidence presented by Tricomi et al. (2010). As mentioned above, the amygdala also seems to play an important role in social decision making (Gao et al., 2018). In line with amygdala's hypothesized role in social cognition, Chang et al. (2015) could show that basolateral amygdala neurons signaled social preferences in rhesus macaques and mirrored the value of rewards delivered to self and others when monkeys were free to choose. In line with this finding, Hernandez-Lallement et al. (2016) found that basolateral amygdala lesions abolished mutual reward preferences in rats.

Thus, in summary, evidence from cognitive neuroscience suggests that the brain's valuation system, including ventromedial prefrontal cortex and ventral striatum, as well as a range of structures involved in planning and

cognition (dorsolateral prefrontal cortex), emotional processing (amygdala) and the appraisal of negative events (insula) are involved in processing IA in humans as well as non-human animals.

CONCLUSIONS

The main purpose of this review is to highlight some of the open questions and, especially, locate potentially essential differences in the various task designs used to probe IA in non-human animals. Future studies should investigate how animals perform in both impunity-like and choice-based variants of disadvantageous IA tasks to learn about the effect of design-specific differences on IA expression, and to test whether the level of IA in the choice-based task can predict the probability to reject rewards in the impunity-like task, or vice versa. Thus, identifying the commonalities and differences in behavior between both types of tasks will help to better differentiate between theories of IA, and to better understand the actual mental mechanisms underlying IA. Furthermore, future research should compare preferences for fair outcomes in disadvantageous IA tasks with preferences for fairness in advantageous IA tasks with the same individuals. This would help to untangle whether both forms of IA are positively or negatively correlated (respectively correlated at all). It is possible that highly disadvantageously inequity averse individuals do also show higher scores of advantageous IA. On the other hand, it is also conceivable that a high sensitivity of being disadvantaged goes along with a reduced sensitivity towards others being disadvantaged. The clarification of this issue might be further supported by additional neuroscientific studies. Isolating the differences, commonalities, moderators and predictors of each type of IA will yield important insights into the mechanistic underpinnings of IA.

AUTHOR CONTRIBUTIONS

LO developed the first concept of the article, wrote the article and revised the article. TK revised the concept of the article, wrote the article, and revised the article.

FUNDING

This work was supported by a grant from the Studienstiftung des Deutschen Volkes to LO and by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) to TK (Grant No. KA 2675/5-3).

REFERENCES

Báez-Mendoza, R., Harris, C. J., and Schultz, W. (2013). Activity of striatal neurons reflects social action and own reward. *Proc. Natl. Acad. Sci. U S A* 110, 16634–16639. doi: 10.1073/pnas.1211342110

Ballesta, S., and Duhamel, J. R. (2015). Rudimentary empathy in macaques' social decision-making. *Proc. Natl. Acad. Sci. U S A* 112, 15516–15521. doi: 10.1073/pnas.1504454112

Bartra, O., McGuire, J. T., and Kable, J. W. (2013). The valuation system: a coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. *Neuroimage* 76, 412–427. doi: 10.1016/j.neuroimage.2013.02.063

Bolton, G. E., Katok, E., and Zwick, R. (1998). Dictator game giving: rules of fairness versus acts of kindness. *Int. J. Game Theor.* 27, 269–299. doi: 10.1007/s001820050072

Bolton, G. E., and Zwick, R. (1995). Anonymity versus punishment in ultimatum bargaining. *Games Econ. Behav.* 10, 95–121. doi: 10.1006/game.1995.1026

Bräuer, J., Call, J., and Tomasello, M. (2006). Are apes really inequity averse? *Proc. R. Soc. B Biol. Sci.* 273, 3123–3128. doi: 10.1098/rspb.2006.3693

Bräuer, J., Call, J., and Tomasello, M. (2009). Are apes inequity averse? New data on the token-exchange paradigm. *Am. J. Primatol.* 71, 175–181. doi: 10.1002/ajp.20639

Brosnan, S. F. (2006). Nonhuman species' reactions to inequity and their implications for fairness. *Soc. Justice Res.* 19, 153–185. doi: 10.1007/s11211-006-0002-z

Brosnan, S. F. (2011). A hypothesis of the co-evolution of cooperation and responses to inequity. *Front. Neurosci.* 5:43. doi: 10.3389/fnins.2011.00043

Brosnan, S. F., and de Waal, F. B. M. (2003). Monkeys reject unequal pay. *Nature* 425, 297–299. doi: 10.1038/nature01963

Brosnan, S. F., and de Waal, F. B. M. (2014). Evolution of responses to (un)fairness. *Science* 346:1251776. doi: 10.1126/science.1251776

Brosnan, S. F., Flemming, T. E., Talbot, C., Mayo, L., and Stoinski, T. S. (2011). Orangutans (*Pongo pygmaeus*) do not form expectations based on their partner's outcomes. *Folia Primatol.* 82, 56–70. doi: 10.1159/000328142

Brosnan, S. F., Freeman, C., and de Waal, F. B. M. (2006). Partner's behavior, not reward distribution, determines success in an unequal cooperative task in capuchin monkeys. *Am. J. Primatol.* 68, 713–724. doi: 10.1002/ajp.20261

Brosnan, S. F., Hopper, L. M., Richey, S., Freeman, H. D., Talbot, C. F., Gosling, S. D., et al. (2015). Personality influences responses to inequity and contrast in chimpanzees. *Anim. Behav.* 101, 75–87. doi: 10.1016/j.anbehav.2014.12.019

Brosnan, S. F., Schiff, H. C., and de Waal, F. B. M. (2005). Tolerance for inequity may increase with social closeness in chimpanzees. *Proc. R. Soc. B Biol. Sci.* 272, 253–258. doi: 10.1098/rspb.2004.2947

Brosnan, S. F., Talbot, C., Ahlgren, M., Lambeth, S. P., and Schapiro, S. J. (2010). Mechanisms underlying responses to inequitable outcomes in chimpanzees, Pan troglodytes. *Anim. Behav.* 79, 1229–1237. doi: 10.1016/j.anbehav.2010.02.019

Brucks, D., Essler, J. L., Marshall-Pescini, S., and Range, F. (2016). Inequity aversion negatively affects tolerance and contact-seeking behaviours towards partner and experimenter. *PLoS One* 11:e0153799. doi: 10.1371/journal.pone.0153799

Cappelen, A. W., Eichele, T., Hugdahl, K., Specht, K., Sørensen, E. Ø., and Tungodden, B. (2014). Equity theory and fair inequality: a neuroeconomic study. *Proc. Natl. Acad. Sci. U S A* 111, 15368–15372. doi: 10.1073/pnas.1414602111

Chang, S. W., Fagan, N. A., Toda, K., Utevsky, A. V., Pearson, J. M., and Platt, M. L. (2015). Neural mechanisms of social decision-making in the primate amygdala. *Proc. Natl. Acad. Sci. U S A* 112, 16012–16017. doi: 10.1073/pnas.1514761112

Chang, L. J., Smith, A., Dufwenberg, M., and Sanfey, A. G. (2011). Triangulating the neural, psychological, and economic bases of guilt aversion. *Neuron* 70, 560–572. doi: 10.1016/j.neuron.2011.02.056

Chang, S. W., Winecoff, A. A., and Platt, M. L. (2011). Vicarious reinforcement in rhesus macaques (*Macaca mulatta*). *Front. Neurosci.* 5:27. doi: 10.3389/fnins.2011.00027

Chen, M. K., Lakshminarayanan, V., and Santos, L. R. (2006). How basic are behavioral biases? Evidence from capuchin monkey trading behavior. *J. Polit. Econ.* 114, 517–537. doi: 10.1086/503550

Chen, M. K., and Santos, L. R. (2006). Some thoughts on the adaptive function of inequity aversion: an alternative to Brosnan's social hypothesis. *Soc. Justice Res.* 19, 201–207. doi: 10.1007/s11211-006-0004-x

Choe, I. H., Byun, J., Kim, K. K., Park, S., Kim, I., Jeong, J., et al. (2017). Mice in social conflict show rule-observance behavior enhancing

long-term benefit. *Nat. Commun.* 8:1176. doi: 10.1038/s41467-017-01091-5

De Waal, F. B., Leimgruber, K., and Greenberg, A. R. (2008). Giving is self-rewarding for monkeys. *Proc. Natl. Acad. Sci. U S A* 105, 13685–13689. doi: 10.1073/pnas.0807060105

Dubreuil, D., Gentile, M. S., and Visalberghi, E. (2006). Are capuchin monkeys (Cebus apella) inequity averse? *Proc. Biol. Sci.* 273, 1223–1228. doi: 10.1098/rspb.2005.3433

Engel, C. (2011). Dictator games: a meta study. *Exp. Econ.* 14, 583–610. doi: 10.1007/s10683-011-9283-7

Engelmann, J. M., Clift, J. B., Herrmann, E., and Tomasello, M. (2017). Social disappointment explains chimpanzees' behaviour in the inequity aversion task. *Proc. R. Soc. B* 284:20171502. doi: 10.1098/rspb.2017.1502

Essler, J. L., Marshall-Pescini, S., and Range, F. (2017). Domestication does not explain the presence of inequity aversion in dogs. *Curr. Biol.* 27, 1861–1865. doi: 10.1016/j.cub.2017.05.061

Fehr, E., and Schmidt, K. M. (1999). A theory of fairness, competition, and cooperation. *Q. J. Econ.* 114, 817–868. doi: 10.1162/003355399556151

Fletcher, G. E. (2008). Attending to the outcome of others: disadvantageous inequity aversion in male capuchin monkeys (*Cebus apella*). *Am. J. Primatol.* 70, 901–905. doi: 10.1002/ajp.20576

Fliessbach, K., Phillipps, C. B., Trautner, P., Schnabel, M., Elger, C. E., Falk, A., et al. (2012). Neural responses to advantageous and disadvantageous inequity. *Front. Hum. Neurosci.* 6:165. doi: 10.3389/fnhum.2012.00165

Fontenot, M. B., Watson, S. L., Roberts, K. A., and Miller, R. W. (2007). Effects of food preferences on token exchange and behavioural responses to inequality in tufted capuchin monkeys, *Cebus apella*. *Anim. Behav.* 74, 487–496. doi: 10.1016/j.anbehav.2007.01.015

Freeman, H. D., Sullivan, J., Hopper, L. M., Talbot, C. F., Holmes, A. N., Schultz-Darken, N., et al. (2013). Different responses to reward comparisons by three primate species. *PLoS One* 8:e76297. doi: 10.1371/journal.pone.0076297

Gao, X., Yu, H., Sáez, I., Blue, P. R., Zhu, L., Hsu, M., et al. (2018). Distinguishing neural correlates of context-dependent advantageous-and disadvantageous-inequity aversion. *Proc. Natl. Acad. Sci. U S A* 115, E7680–E7689. doi: 10.1073/pnas.1802523115

Güroğlu, B., Will, G. J., and Crone, E. A. (2014). Neural correlates of advantageous and disadvantageous inequity in sharing decisions. *PLoS One* 9:e107996. doi: 10.1371/journal.pone.0107996

Güth, W., and Schmidt, M. G. (2013). "More than thirty years ofultimatum bargaining experiments: Motives, variations, and a survey of the recent literature," in *Jena Economic Research Papers* (Jena, Germany: Max Planck Institute of Economics), 2013–2035.

Güth, W., Schmittberger, R., and Schwarze, B. (1982). An experimental analysis of ultimatum bargaining. *J. Econ. Behav. Organ.* 3, 367–388. doi: 10.1016/0167-2681(82)90011-7

Haruno, M., and Frith, C. D. (2010). Activity in the amygdala elicited by unfair divisions predicts social value orientation. *Nat. Neurosci.* 13, 160–161. doi: 10.1038/nn.2468

Haruno, M., Kimura, M., and Frith, C. D. (2014). Activity in the nucleus accumbens and amygdala underlies individual differences in prosocial and individualistic economic choices. *J. Cogn. Neurosci.* 26, 1861–1870. doi: 10.1162/jocn_a_00589

Heaney, M., Gray, R. D., and Taylor, A. H. (2017). Kea show no evidence of inequity aversion. *R. Soc. Open Sci.* 4:160461. doi: 10.1098/rsos.160461

Heidary, F., Mahdavi, M. R. V., Momeni, F., Minaii, B., Rogani, M., Fallah, N., et al. (2008). Food inequality negatively impacts cardiac health in rabbits. *PLoS One* 3:e3705. doi: 10.1371/journal.pone.0003705

Hernandez-Lallement, J., van Wingerden, M., and Kalenscher, T. (2018). Towards an animal model of callousness. *Neurosci. Biobehav. Rev.* 91, 121–129. doi: 10.1016/j.neubiorev.2016.12.029

Hernandez-Lallement, J., van Wingerden, M., Marx, C., Srejic, M., and Kalenscher, T. (2015). Rats prefer mutual rewards in a prosocial choice task. *Front. Neurosci.* 8:443. doi: 10.3389/fnins.2014.00443

Hernandez-Lallement, J., van Wingerden, M., Marx, C., Schäble, S., and Kalenscher, T. (2016). Basolateral amygdala lesions abolish mutual reward preferences in rats. *Neurobiol. Learn. Mem.* 127:443. doi: 10.1016/j.nlm.2015.11.004

Holper, L., Burke, C. J., Fausch, C., Seifritz, E., and Tobler, P. N. (2018). Inequality signals in dorsolateral prefrontal cortex inform social preference models. *Soc. Cogn. Affect. Neurosci.* 13, 513–524. doi: 10.1093/scan/nsy020

Hopper, L. M., Lambeth, S. P., Schapiro, S. J., Bernacky, B. J., and Brosnan, S. F. (2013). The ontogeny of social comparisons in rhesus macaques (*Macaca mulatta*). *J. Primatol.* 2:109. doi: 10.4172/2167-6801.1000109

Horner, V., Carter, J. D., Suchak, M., and de Waal, F. B. (2011). Spontaneous prosocial choice by chimpanzees. *Proc. Natl. Acad. Sci. U S A* 108, 13847–13851. doi: 10.1073/pnas.1111088108

Horowitz, A. (2012). Fair is fine, but more is better: limits to inequity aversion in the domestic dog. *Soc. Justice Res.* 25, 195–212. doi: 10.1007/s11211-012-0158-7

Hsu, M., Bhatt, M., Adolphs, R., Tranel, D., and Camerer, C. F. (2005). Neural systems responding to degrees of uncertainty in human decision-making. *Science* 310, 1680–1683. doi: 10.1126/science.1115327

Jensen, K., Call, J., and Tomasello, M. (2007). Chimpanzees are rational maximizers in an ultimatum game. *Science* 318, 107–109. doi: 10.1126/science.1145850

Kaiser, I., Jensen, K., Call, J., and Tomasello, M. (2012). Theft in an ultimatum game: chimpanzees and bonobos are insensitive to unfairness. *Biol. Lett.* 8, 942–945. doi: 10.1098/rsbl.2012.0519

Kalenscher, T., and Pennartz, C. M. (2008). Is a bird in the hand worth two in the future? The neuroeconomics of intertemporal decision-making. *Prog. Neurobiol.* 84, 284–315. doi: 10.1016/j.pneurobio.2007.11.004

Margittai, Z., Strombach, T., van Wingerden, M., Joëls, M., Schwabe, L., and Kalenscher, T. (2015). A friend in need: time-dependent effects of stress on social discounting in men. *Horm. Behav.* 73, 75–82. doi: 10.1016/j.yhbeh.2015.05.019

Márquez, C., Rennie, S. M., Costa, D. F., and Moita, M. A. (2015). Prosocial choice in rats depends on food-seeking behavior displayed by recipients. *Curr. Biol.* 25, 1736–1745. doi: 10.1016/j.cub.2015.05.018

Marsh, B., and Kacelnik, A. (2002). Framing effects and risky decisions in starlings. *Proc. Natl. Acad. Sci. U S A* 99, 3352–3355. doi: 10.1073/pnas.042491999

Massen, J. J. M., van den Berg, L. M., Spruijt, B. M., and Sterck, E. H. M. (2012). Inequity aversion in relation to effort and relationship quality in long-tailed Macaques (*Macaca fascicularis*). *Am. J. Primatol.* 74, 145–156. doi: 10.1002/ajp.21014

McGetrick, J., and Range, F. (2018). Inequity aversion in dogs: a review. *Learn. Behav.* 46, 479–500. doi: 10.3758/s13420-018-0338-x

Melis, A. P., Hare, B., and Tomasello, M. (2009). Chimpanzees coordinate in a negotiation game. *Evol. Hum. Behav.* 30, 381–392. doi: 10.1016/j.evolhumbehav.2009.05.003

Neiworth, J. J., Johnson, E. T., Whillock, K., Greenberg, J., and Brown, V. (2009). Is a sense of inequity an ancestral primate trait? Testing social inequity in cotton top tamarins (*Saguinus oedipus*). *J. Comp. Psychol.* 123, 10–17. doi: 10.1037/a0012662

Nihonsugi, T., Ihara, A., and Haruno, M. (2015). Selective increase of intention-based economic decisions by noninvasive brain stimulation to the dorsolateral prefrontal cortex. *J. Neurosci.* 35, 3412–3419. doi: 10.1523/JNEUROSCI.3885-14.2015

Oberliessen, L., Hernandez-Lallement, J., Schäble, S., van Wingerden, M., Seinstra, M., and Kalenscher, T. (2016). Inequity aversion in rats, *Rattus norvegicus*. *Anim. Behav.* 115, 157–166. doi: 10.1016/j.anbehav.2016.03.007

Raihani, N. J., McAuliffe, K., Brosnan, S. F., and Bshary, R. (2012). Are cleaner fish, Labroides dimidiatus, inequity averse? *Anim. Behav.* 84, 665–674. doi: 10.1016/j.anbehav.2012.06.023

Range, F., Horn, L., Virányi, Z., and Huber, L. (2009). The absence of reward induces inequity aversion in dogs. *Proc. Natl. Acad. Sci. U S A* 106, 340–345. doi: 10.1073/pnas.0810957105

Range, F., Leitner, K., and Virányi, Z. (2012). The influence of the relationship and motivation on inequity aversion in dogs. *Soc. Justice Res.* 25, 170–194. doi: 10.1007/s11211-012-0155-x

Roma, P. G., Silberberg, A., Ruggiero, A. M., and Suomi, S. J. (2006). Capuchin monkeys, inequity aversion, and the frustration effect. *J. Comp. Psychol.* 120, 67–73. doi: 10.1037/0735-7036.120.1.67

Ruff, C. C., and Fehr, E. (2014). The neurobiology of rewards and values in social decision making. *Nat. Rev. Neurosci.* 15, 549–562. doi: 10.1038/nrn3776

Sanfey, A. G., Rilling, J. K., Aronson, J. A., Nystrom, L. E., and Cohen, J. D. (2003). The neural basis of economic decision-making in the ultimatum game. *Science* 300, 1755–1758. doi: 10.1126/science.1082976

Schmitt, M., Behner, R., Montada, L., Müller, L., and Müller-Fohrbrodt, G. (2000). Gender, ethnicity and education as privileges: exploring the generalizability of the existential guilt reaction. *Soc. Justice Res.* 13, 313–337. doi: 10.1023/A:1007640925819

Silberberg, A., Crescimbene, L., Addessi, E., Anderson, J. R., and Visalberghi, E. (2009). Does inequity aversion depend on a frustration effect? A test with capuchin monkeys (*Cebus apella*). *Anim. Cogn.* 12, 505–509. doi: 10.1007/s10071-009-0211-6

Stevens, J. R., and Hauser, M. D. (2004). Why be nice? Psychological constraints on the evolution of cooperation. *Trends Cogn. Sci.* 8, 60–65. doi: 10.1016/j.tics.2003.12.003

Strombach, T., Weber, B., Hangebrauk, Z., Kenning, P., Karipidis, I. I., Tobler, P. N., et al. (2015). Social discounting involves modulation of neural value signals by temporoparietal junction. *Proc. Natl. Acad. Sci. U S A* 112, 1619–1624. doi: 10.1073/pnas.1414715112

Takimoto, A., and Fujita, K. (2011). I acknowledge your help: capuchin monkeys' sensitivity to others' labor. *Anim. Cogn.* 14, 715–725. doi: 10.1007/s10071-011-0406-5

Takimoto, A., Kuroshima, H., and Fujita, K. (2010). Capuchin monkeys (*Cebus apella*) are sensitive to others' reward: an experimental analysis of food-choice for conspecifics. *Anim. Cogn.* 13, 249–261. doi: 10.1007/s10071-009-0262-8

Talbot, C. F., Freeman, H. D., Williams, L. E., and Brosnan, S. F. (2011). Squirell monkeys' response to inequitable outcomes indicates a behavioural convergence within the primates. *Biol. Lett.* 7, 680–682. doi: 10.1098/rsbl.2011.0211

Tricomi, E., Rangel, A., Camerer, C. F., and O'Doherty, J. P. (2010). Neural evidence for inequality-averse social preferences. *Nature* 463, 1089–1092. doi: 10.1038/nature08785

van Wolkenten, M., Brosnan, S. F., and de Waal, F. B. M. (2007). Inequity responses of monkeys modified by effort. *Proc. Natl. Acad. Sci. U S A* 104, 18854–18859. doi: 10.1073/pnas.0707182104

Vavra, P., Chang, L. J., and Sanfey, A. G. (2018). Expectations in the Ultimatum Game: distinct effects of mean and variance of expected offers. *Front. Psychol.* 9:992. doi: 10.3389/fpsyg.2018.00992

Wang, H., Li, K., and Xie, X. (2019). Individual differences in pain sensitivity predict the experience of unfairness. *J. Health Psychol.* 24, 953–963. doi: 10.1177/1359105316685902

Wascher, C. A., and Bugnyar, T. (2013). Behavioral responses to inequity in reward distribution and working effort in crows and ravens. *PLoS One* 8:e56885. doi: 10.1371/journal.pone.0056885

Yamagishi, T., Horita, Y., Takagishi, H., Shinada, M., Tanida, S., and Cook, K. S. (2009). The private rejection of unfair offers and emotional commitment. *Proc. Natl. Acad. Sci. U S A* 106, 11520–11523. doi: 10.1073/pnas.0900636106

Yu, R., Calder, A. J., and Mobbs, D. (2014). Overlapping and distinct representations of advantageous and disadvantageous inequality. *Hum. Brain Mapp.* 35, 3290–3301. doi: 10.1002/hbm.22402

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 21 June 2019
doi: 10.3389/fnbeh.2019.00132

Infant Trauma Alters Social Buffering of Threat Learning: Emerging Role of Prefrontal Cortex in Preadolescence

*Patrese A. Robinson-Drummer[1,2†], Maya Opendak[1,2†], Anna Blomkvist[1,2,3], Stephanie Chan[1,2,4], Stephen Tan[1,2,4], Cecilia Delmer[1,2,4], Kira Wood[1], Aliza Sloan[1,2,5], Lily Jacobs[1,2,6], Eliana Fine[2,6], Divija Chopra[1,2,4], Chaim Sandler[2,6], Giselle Kamenetzky[1,2,7] and Regina M. Sullivan[1,2]**

[1]Emotional Brain Institute, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, United States, [2]Department of Child and Adolescent Psychiatry, Child Study Center at NYU Langone Medical Center, NYU School of Medicine, New York, NY, United States, [3]Department of Psychology, Stockholm University, Stockholm, Sweden, [4]Department of Neural Science, New York University, New York, NY, United States, [5]Department of Psychology, Florida Atlantic University, Boca Raton, FL, United States, [6]Department of Biology, Yeshiva University, New York, NY, United States, [7]Instituto de Investigaciones Médicas A Lanari, IDIM-CONICET, Universidad de Buenos Aires, Combatientes de Malvinas 3150 (CP 1427), Buenos Aires, Argentina

OPEN ACCESS

Edited by:
Jee Hyun Kim,
Florey Institute of Neuroscience and Mental Health, Australia

Reviewed by:
Brittany R. Howell,
University of Minnesota Twin Cities, United States
Timothy J. Jarome,
Virginia Tech, United States

***Correspondence:**
Regina M. Sullivan
regina.sullivan@nyumc.org

†These authors have contributed equally to this work and are joint first authors

Received: *21 February 2019*
Accepted: *04 June 2019*
Published: *21 June 2019*

Citation:
Robinson-Drummer PA, Opendak M, Blomkvist A, Chan S, Tan S, Delmer C, Wood K, Sloan A, Jacobs L, Fine E, Chopra D, Sandler C, Kamenetzky G and Sullivan RM (2019) Infant Trauma Alters Social Buffering of Threat Learning: Emerging Role of Prefrontal Cortex in Preadolescence. Front. Behav. Neurosci. 13:132. doi: 10.3389/fnbeh.2019.00132

Within the infant-caregiver attachment system, the primary caregiver holds potent reward value to the infant, exhibited by infants' strong preference for approach responses and proximity-seeking towards the mother. A less well-understood feature of the attachment figure is the caregiver's ability to reduce fear *via* social buffering, commonly associated with the notion of a "safe haven" in the developmental literature. Evidence suggests this infant system overlaps with the neural network supporting social buffering (attenuation) of fear in the adults of many species, a network known to involve the prefrontal cortex (PFC). Here, using odor-shock conditioning in young developing rats, we assessed when the infant system transitions to the adult-like PFC-dependent social buffering of threat system. Rat pups were odor-shock conditioned (0.55 mA–0.6 mA) at either postnatal day (PN18; dependent on mother) or 28 (newly independent, weaned at PN23). Within each age group, the mother was present or absent during conditioning, with PFC assessment following acquisition using ^{14}C 2-DG autoradiography and cue testing the following day. Since the human literature suggests poor attachment attenuates the mother's ability to socially buffer the infants, half of the pups at each age were reared with an abusive mother from PN8–12. The results showed that for typical control rearing, the mother attenuated fear in both PN18 and PN28 pups, although the PFC [infralimbic (IL) and ventral prelimbic (vPL) cortices] was only engaged at PN28. Abuse rearing completely disrupted social buffering of pups by the mother at PN18. The results from PN28 pups showed that while the mother modulated learning in both control and abuse-reared pups, the behavioral and PFC effects were attenuated after maltreatment. Our data suggest that pups transition to the adult-like PFC social support circuit after independence from the mother (PN28), and this circuit remains functional after

early-life trauma, although its effectiveness appears reduced. This is in sharp contrast to the effects of early life trauma during infancy, where social buffering of the infant is more robustly impacted. We suggest that the infant social buffering circuit is disengaged by early-life trauma, while the adolescent PFC-dependent social buffering circuit may use a safety signal with unreliable safety value.

Keywords: early-life trauma, social buffering, social support, threat, fear, prefrontal cortex, infralimbic, prelimbic

INTRODUCTION

For infants, the mother and other significant caregivers serve as potent reward stimuli and induce robust proximity-seeking in the infant, regardless of the quality of care received. This infant attachment to the caregiver is learned during a sensitive period and rodent work suggests there is a unique neural network that robustly supports learning proximity-seeking (Moriceau et al., 2010; Raineki et al., 2010; Bisaz and Sullivan, 2012; Perry et al., 2016; Opendak et al., 2017). This open attachment system permits the infant to attach to multiple caregivers, including non-biological caregivers, within the context of diverse rearing conditions. Strikingly, this proximity-seeking characteristic of the attachment system is maintained even when the caregiver is the source of the threat, as occurs in maltreatment in a wide variety of species, including humans (Bowlby, 1982; Tottenham and Sheridan, 2009; Sanchez et al., 2015; Drury et al., 2016; Howell et al., 2017; Zajac et al., 2019).

A less well-known feature of the attachment figure is his or her ability to suppress or block fear/threat responding during early life, also referred to as social buffering (Hostinar et al., 2014; Gunnar et al., 2015; Hostinar and Gunnar, 2015; Callaghan et al., 2019). This fear reduction system was first characterized within Bowlby's Attachment Theory (Bowlby, 1969, 1978) and is critical for the infant to approach the caregiver (safe base) for protection when threatened, rather than showing adult-like threat response behaviors (e.g., freezing, attacking or hiding; Coss, 2016). This phenomenon of social buffering of threat by the parent was first demonstrated in infant rats when the presence of the mother reduced the young infants' responses to shock and blocked stress hormone release. This system is strongly phylogenetically represented and has been shown in rodents (Stanton and Levine, 1985; Levine et al., 1988; Suchecki et al., 1993; Hennessy et al., 2006, 2009, 2015; Gunnar et al., 2015; Sullivan and Perry, 2015; Al Aïn et al., 2017; Opendak et al., 2019), nonhuman primates and children (Coe et al., 1978; Wiener et al., 1987; Nachmias et al., 1996; Hennessy et al., 2009; Tottenham et al., 2012, accepted; Gee et al., 2013a; Sanchez et al., 2015; Howell et al., 2017). This social buffering supports the role of the attachment figure as a regulator of the immature infant (Bowlby, 1982; Hofer, 1994; Sroufe, 2005; Blair and Raver, 2015; Chambers, 2017; Feldman, 2017; Perry et al., 2017).

We have some understanding of the neural network supporting infant social buffering. This system involves caregiver suppression of the paraventricular nucleus (PVN) of the hypothalamus to block engagement of the stress axis (Shionoya et al., 2007) and attenuation of the amygdala and ventral tegmental response to threat (Hennessy et al., 2006, 2009; Moriceau and Sullivan, 2006; Moriceau et al., 2006, 2009; Opendak et al., 2019). This network analysis has, in part, been replicated in children (Gee et al., 2014; Tottenham et al., accepted), and nonhuman primates (Gunnar et al., 2015; Sanchez et al., 2015; Howell et al., 2017). Importantly, the literature across these species suggests that social buffering by maternal presence is disrupted in mother-infant dyads with poor quality attachment (Nachmias et al., 1996; Gunnar and Quevedo, 2007; Hostinar et al., 2014; Gunnar et al., 2015; Sanchez et al., 2015; Gunnar and Sullivan, 2017; Opendak et al., 2019). Yet, the neurobiology of this compromised social buffering system has received little attention.

Social buffering wanes with maturation, although this effect can still be seen in adults of many species. While there appears to be some overlap in the neural mechanisms across development, the late-developing prefrontal cortex (PFC) appears critical in adult social buffering (Hennessy et al., 2006, 2015, 2018; Kiyokawa et al., 2007, 2012; Taylor et al., 2008; Upton and Sullivan, 2010; Inagaki and Eisenberger, 2012; Tottenham et al., 2012; Hostinar et al., 2015; Hornstein et al., 2016; Harrison et al., 2017; Hornstein and Eisenberger, 2017). Here, we focus on the PFC and its evolving role in social buffering of the threat response, targeting a developmental transition from dependence on the mother (postnatal day [PN] 18) to independence in preadolescent rats (PN28) weaned from the mother. To further probe the dynamics of this developing circuit, we perturbed the system by exposing half of the animals to maternal maltreatment in early infancy. Overall, our results suggest that the neurobehavioral substrates of maternal social buffering and its perturbation are distinct during sensitive periods in development.

MATERIALS AND METHODS

Subjects

A total of 322 Long Evans rats (178 PN18 ±1 day, 144 PN28 ±1 day), with approximately equal males and females, were bred and reared in our animal facility with *ad libitum* food and water. Animals were reared with an abusive mother or control mother from PN8-PN12–an age range documented to induce neurobehavioral deficits. Animals were tested at PN18 while still living with the mother or PN28 when pups live independently of the mother (all animal only tested once). Animals were always housed in an enclosure with solid floors, with both breeding and rearing occurring in a private animal room within the lab. Two weeks before giving birth, pregnant

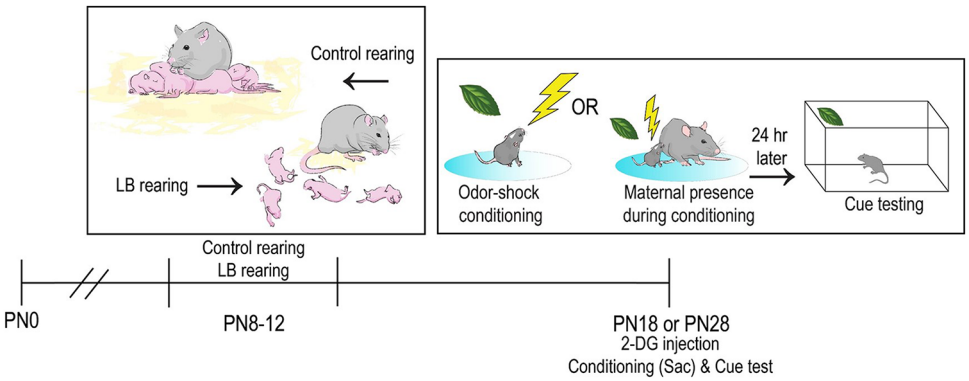


FIGURE 1 | Schematic of methodology and experimental timeline. In infancy, pups received either Scarcity-Adversity Model of Low Bedding (LB) rearing or control rearing from the mother (ages PN8–12). LB rearing involved providing the mother with insufficient bedding for nest building, which produces maltreatment of pups but growth indistinguishable from controls. Pups are odor-shock conditioned in the mother's presence or absence at one of two ages, with the goal of better understanding the neural mechanisms involved in social suppression of threat. A portion of the pups had the brain removed immediately after conditioning, while the other half were tested the next day (Cue test involving odor only presentations). The younger subjects were PN18, an age when pups are still with the mother but only for about 5 days before weaning. The other age tested was PN28, when pups have been independent for about 5 days.

females were moved from large breeding cages to standard cages for birth and pup rearing (34 long × 29 wide × 17 high cm). General health and births were checked twice daily with the day of birth designated PN0. Litters were culled to 12 pups (approximately equal males and females) at PN1. Cages were cleaned twice a week except for the nest, which was saved and placed back with the mother and pups. All procedures were approved by the Institutional Animal Care and Use Committee in accordance with guidelines from the National Institutes of Health.

Scarcity-Adversity Model of Low Bedding (LB; PN8–12)

Early-life trauma was modeled in rats using a well-established Scarcity-Adversity Model previously utilized by our lab and others (Sullivan et al., 2000; Raineki et al., 2010; Opendak and Sullivan, 2016; Opendak et al., 2017; Walker et al., 2017; Yan et al., 2017). As illustrated in **Figure 1**, the low bedding (LB) rearing takes place from PN8–12 and included the following manipulations: nest hutch removal, bedding material reduced from 4,000 mL to 100 mL and solid floor cage cleaned daily with bedding replaced to reduce odor and maintain a clean cage environment. As illustrated in **Table 1**, this procedure increases instances of maternal maltreatment of the pups (e.g., reduced time with pups, rough handling pups) and results in neurobehavioral dysfunction, including depressive-like behavior, disrupted social behavior and dysregulation of fear expression in pups, although major neurobehavioral effects show significant emergence at weaning age (Perry and Sullivan, 2014; Al Aïn et al., 2017; Opendak et al., 2017). Age-matched control litters were reared concurrently but with abundant bedding and nest-building materials. Pups were videotaped three times a week and data analyzed using Ethovision (Noldus Information Technologies Inc., Leesburg, VA, USA). Maternal behavior and infant-mother interactions were hand-scored using BORIS (Life Sciences and Systems Biology) behavioral coding software to validate abusive and non-abusive care.

TABLE 1 | The Scarcity-Adversity Model of Low Bedding (LB) is a validated procedure of inducing abuse by providing the mother with insufficient nest building material.

Maternal Behavior	Control % observations ± SEM	LB % observations ± SEM
Nursing	62.5 ± 23.8	76.7 ± 7.9
In nest	87.5 ± 10.2	91.1 ± 4.8
Step on pups	8.3 ± 8.3	50.0 ± 23.6
Drag pups	0 ± 0	27.8 ± 11.8
Pups vocalize	16.7 ± 9.6	64.4 ± 6.5

Convergent with previous studies (Roth and Sullivan, 2005; Walker et al., 2017; Santiago et al., 2018) we observed increased rough handling of pups and increased pup vocalizations during a greater percentage of observations in the LB groups.

Odor-Shock Conditioning (Dependent on Mother PN18 or Independent PN28)

Conditioning took place in standard mouse fear conditioning (Coulbourn Instruments) apparatus within a sound attenuation chamber (Med Associates) with Coulbourn FreezeFrame software controlling stimuli delivery and video recording. Animals received a 20 min habituation session in the conditioning chambers a day prior to conditioning. On conditioning day, animals were given a 10 min adaptation period to the conditioning chamber before the start of conditioning. The conditioned stimulus (CS) was a 30 s peppermint odor (McCormick Pure Peppermint; 2 L/min; 1:10 peppermint vapor to air) controlled with a solenoid valve that minimized pressure changes by diverting airflow from the clean air to the peppermint air stream. To ventilate the chamber and ensure removal of odor

CS, a standard attenuating chamber fan provided a constant stream of deodorized air flow through the chambers (2 L/min). The unconditioned stimulus (US) was a 1 s 0.6 mA foot shock delivered through a grid floor. The Paired experimental animals received a total of seven CS-US presentations administered at a 4 min inter-trial interval (ITI) and co-terminated with the 1 s footshock during the last second of the odor. Unpaired (behavioral control) animals received the same number of odor and shock presentations, however, the stimuli were separated by a 2 min inter-stimulus interval (ISI). Animals in the Odor-only condition also received the seven odor presentations but no shocks. Half of the experimental animals were conditioned in the presence of a urethane-anesthetized dam placed directly adjacent to the conditioning chamber where her odor was perceptible but she was not visible. Following conditioning, animals were either sacrificed and brains assessed for regional activity or retained for behavioral cue testing the next day to assess learning. PN18 and PN28 animals were only used at one age. These procedures were done according to published laboratory protocols (Boulanger Bertolus et al., 2014; Debiec and Sullivan, 2014; Tallot et al., 2016).

Neural Assessment

Animals used for neural assessment were injected with ^{14}C-labeled 2-deoxyglucose (2-DG; 20 μCi/100 g, i.p.) just prior to being placed in the conditioning chamber and brains removed after conditioning (45 min after injection). Brains were stored in a −80°C freezer before being sectioned in a cryostat (20 μm) at −20°C. Through the region of interest (ROI), every third slice was collected onto a coverslip and slices along with ^{14}C standards (10 × 0.02 mCi, American Radiolabeled Chemicals Inc., St. Louis, MO, USA) were exposed to X-ray film (Kodak) for 5 days. The autoradiograph was then digitally scanned and prepared for analysis. All procedures occurred according to published lab protocols (Perry et al., 2016; Opendak et al., 2019).

PFC Analysis

Autoradiographs were analyzed using ImageJ software (National Institutes of Health) for quantitative optical densitometry with an increase in autoradiographic density indicating increased 2-DG metabolism. Using Paxinos and Watson (2013) as a guide, two medial prefrontal regions were identified and analyzed for regional activity: Prelimbic (PL) and Infralimbic (IL), each of which was subdivided into additional subregions. At least three sections from the rostro-caudal extent were analyzed for each brain area.

Regional engagement levels were expressed as 2-DG uptake relative to that observed in white matter tracts (e.g., the anterior commissure or forceps minor) to control for differences in exposure levels or section thickness (Sullivan et al., 2000). Autoradiographic density was measured in both hemispheres of the brain for each region of interest and then averaged across both hemispheres, as no statistical difference was found between hemispheres.

Cue Test

Twenty-four hours following conditioning, learning was assessed using a cue test in a new context: novel room, placed in a 5,000 mL glass beaker inside a sound attenuating chamber (Coulbourn) with the fan placed outside the attenuating box. Context was further changed by cleaning the attenuating chamber with Windex (SC Johnson) 5 min before animals were placed within the beaker. For cue testing, animals were placed in the beaker and given a 5 min acclimation period prior to the first odor onset. Five 30 s presentations of the peppermint odor were presented using a 4-min ITI, as described for conditioning. Learning was measured by total time (in seconds) freezing during the odor with freezing defined as the cessation of all body movements with the exception of that minimally required for breathing. Freezing was scored automatically by FreezeFrame, although all freezing was checked by a blind scorer to determine freezing vs. inactivity. All animals were videotaped using two cameras, a side view and a top view to ensure accurate behavioral scoring.

Statistical Analysis

All behavior data were separated by age and rearing condition and analyzed using a two-way analysis of variance (ANOVA) with repeated measures [maternal presence (alone vs. with mom) × cue presentation (cue #1–5)] for training day data and two-way ANOVA [learning condition (paired, unpaired, odor only) × maternal presence (alone vs. with mom)] for cue test data, followed by Bonferroni-corrected pairwise tests. Planned comparisons were used when justified by a priori hypotheses (see Results section below). No sex effects or interactions were found in freezing behavior at either PN18 or PN28 and therefore data were collapsed across sex for analysis of maternal presence effects on behavior and 2-DG uptake. 2-DG uptake data were analyzed separately for each age using two-way ANOVA (rearing × maternal presence), followed by Bonferroni-corrected pairwise tests. All differences were considered significant when $p < 0.05$. All data analysis was performed by an experimenter blind to the experimental conditions.

RESULTS

Mother-Infant Response to Scarcity-Adversity Model

Offline, blinded observations of videos of mother-infant interactions during control and LB Adversity-Rearing (PN8–12) indicated that the LB pups received more rough handling by the mother than controls (see **Table 1** for further details).

Odor-Shock Conditioning Acquisition Curves

Assessment of paired animals with and without maternal presence during conditioning revealed significantly higher freezing in animals conditioned with the mom relative to animals conditioned alone during later trials except in PN28 control animals (**Figure 2**). For PN18 controls (**Figure 2A**), there was no main effect of maternal presence ($F_{(1,14)} = 2.601$, $p = 0.129$) but there was a main effect of cue presentation ($F_{(6,84)} = 37.90$, $p < 0.001$) and a cue presentation by maternal presence interaction ($F_{(6,84)} = 4.567$, $p = 0.0005$). *Post hoc* tests showed that during the sixth ($p = 0.016$) and seventh ($p = 0.001$)

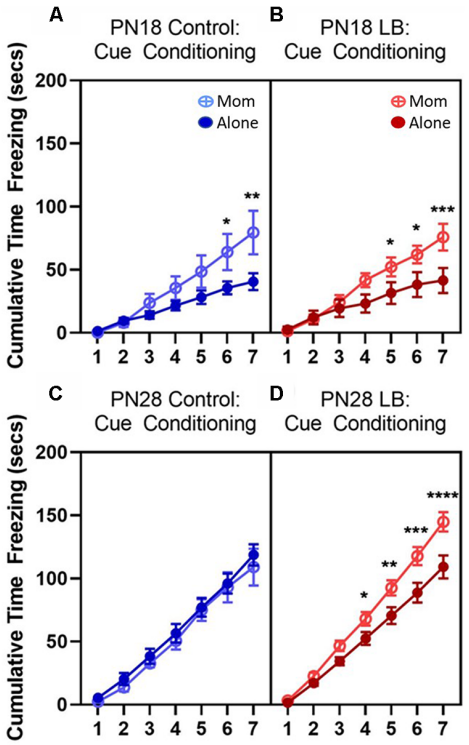


FIGURE 2 | Odor-shock cue conditioning increases freezing to odor during training. Total cumulative (seconds) freezing (±SEM) during paired odor-shock cue conditioning at **(A,B)** PN18 (Control: Alone $n = 8$; Mom $n = 8$; LB: Alone $n = 8$; Mom $n = 8$) and **(C,D)** PN28 (Control: Alone $n = 9$; Mom $n = 8$; LB: Alone $n = 14$; Mom $n = 15$). Cue conditioning increased freezing at both ages in both control and low bedding (LB) rearing conditions however increased freezing was observed in animals conditioned with the mom (except in PN28 Control group) relative to animals conditioned alone. Open circle = conditioned with the mom; filled circles = conditioned alone; blue = controls; red = LB. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

odor presentations animals conditioned with the mother showed higher freezing relative to animals conditioned alone. For the PN18 LB group (**Figure 2B**), there also was no main effect of maternal presence ($F_{(1,14)} = 2.885$, $p = 0.112$) but there was a main effect of cue presentation ($F_{(6,84)} = 50.66$, $p < 0.001$) and a cue presentation by maternal presence interaction ($F_{(6,84)} = 5.563$, $p < 0.001$). Similar to the control animals, during later cue presentations [fifth ($p = 0.040$), sixth ($p = 0.019$) and seventh ($p < 0.001$)] animals conditioned with the mother showed higher freezing relative to animals conditioned alone.

At PN28, similar effects were observed in the LB group although there were fewer differences observed in the control animals (**Figure 2C**). For controls, there was no main effect of maternal presence ($F_{(1,15)} = 0.331$, $p = 0.574$) or cue presentation by maternal presence interaction ($F_{(6,90)} = 0.177$, $p = 0.983$), but there was a main effect of cue presentation ($F_{(6,90)} = 167.0$, $p < 0.001$). The increase in freezing over time did not differ between animals conditioned alone or with the mom. In contrast, in the PN28 LB group (**Figure 2D**) there was a main effect of maternal presence ($F_{(1,27)} = 6.810$, $p = 0.015$), cue presentation ($F_{(6,162)} = 410.9$, $p < 0.001$) and a cue presentation by maternal presence interaction ($F_{(6,162)} = 7.722$, $p < 0.001$). During the fourth ($p = 0.046$), fifth ($p = 0.006$), sixth ($p < 0.001$) and seventh ($p = <0.001$) odor presentations, animals conditioned with the mother showed higher freezing relative to animals conditioned alone.

Cue Test

Overall, all paired animals at both ages and in both rearing conditions showed increased freezing to the CS relative to controls, indicating retention of the learned association between the odor and the shock (**Figure 3**; Johansen et al., 2011). For PN18 Controls (**Figure 3A**), there was a main effect of learning condition ($F_{(2,66)} = 49.07$, $p < 0.001$), maternal presence ($F_{(1,66)} = 7.27$ $p = 0.009$) and a trending interaction ($F_{(2,66)} = 2.784$, $p = 0.069$). *Post hoc* tests revealed that freezing in Paired groups with and without mom was significantly higher than control groups (all p's < 0.05) and maternal presence increased paired group freezing relative to paired animals conditioned alone ($p < 0.001$). For the PN18 LB group (**Figure 3B**), there was a main effect of learning condition ($F_{(2,65)} = 60.00$, $p < 0.001$), no effect of maternal presence ($F_{(1,65)} = 1.27$, $p = 0.264$) nor an interaction effect ($F_{(2,65)} = 0.22$, $p = 0.80$). *Post hoc* tests revealed that paired group freezing with and without mom was significantly higher than control groups (all p's < 0.05) and no significant difference between the two paired groups with and without the mother ($p = 0.359$) suggesting the mother did not suppress learning.

At PN28, similar effects were found for both controls and LB: only paired animals learned, although both rearing conditions showed attenuated learning with maternal presence. Specifically, for controls (**Figure 3C**) there were significant main effects of learning ($F_{(2,45)} = 36.93$, $p < 0.001$), maternal presence ($F_{(1,45)} = 4.872$, $p = 0.032$) and an interaction ($F_{(2,45)} = 6.363$, $p = 0.004$). *Post hoc* tests revealed that both paired freezing with and without the mom was significantly higher than all control groups (p's < 0.05) and there was a significant difference between the two paired groups (with mother freezing increased relative to without the mother, $p < 0.01$). A similar behavioral pattern was found in LB-reared animals (**Figure 3D**); there was a main effect of learning condition ($F_{(2,54)} = 39.81$, $p < 0.001$), no effect for maternal presence ($F_{(1,54)} = 0.311$, $p = 0.579$) nor was there an interaction ($F_{(2,54)} = 2.215$, $p = 0.119$). *Post hoc* tests revealed that the paired groups with and without mom were significantly higher than all control groups (p's < 0.001) and maternal presence increased paired group freezing (with mother vs. without the mother, $p = 0.026$).

Neural Analysis of Prefrontal Cortex (PFC)

Overall, we found significant evidence that PFC activation in several subregions at PN28 varied as a function of rearing condition (Control and LB) and whether the mother was present during conditioning. In contrast, no such PFC activation patterns at age PN18 were observed.

Infralimbic Prefrontal Cortex (IL)

The PFC showed significant differences across the dorsal-ventral axis at PN28, but not at PN18. Specifically for PN28 animals

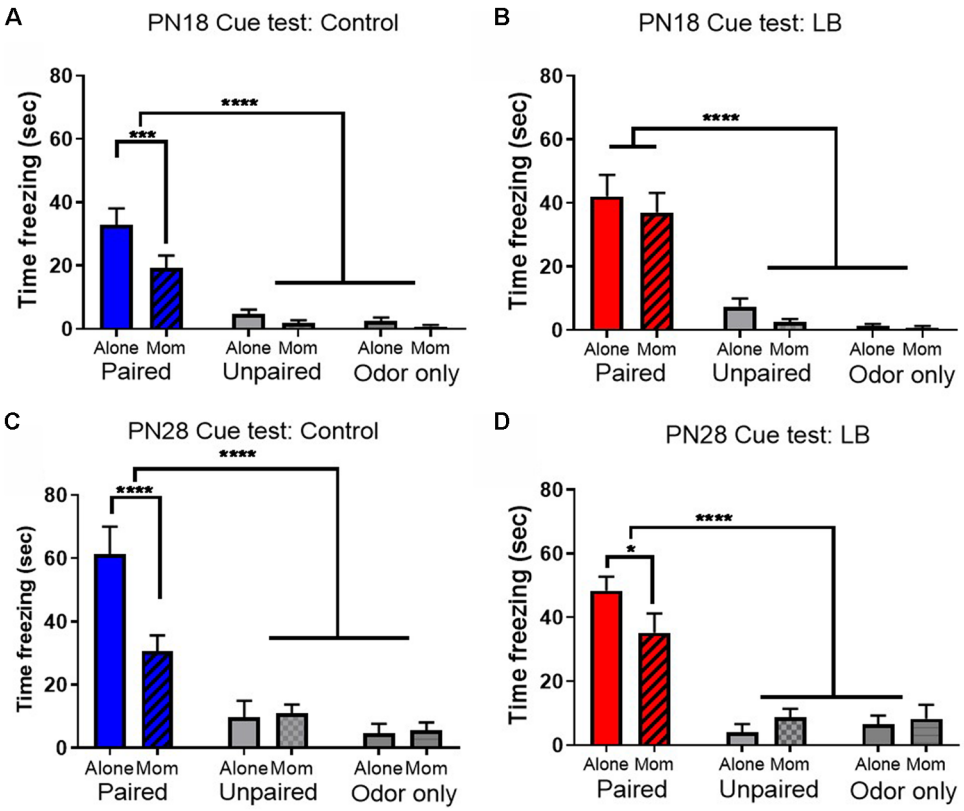


FIGURE 3 | Early abuse modulates maternal buffering of odor-shock conditioning. Total (seconds) freezing (±SEM) to a conditioned stimulus (CS) was higher in Paired odor-shock conditions than Unpaired and Odor only conditions. Maternal presence during conditioning attenuated learning at both **(A,B)** PN18 Control (Paired: Alone $n = 12$; Mom $n = 12$; Unpaired: Alone $n = 12$; Mom $n = 12$; odor Only: Alone $n = 12$; Mom $n = 12$) and LB (Paired: Alone $n = 11$; Mom $n = 12$; Unpaired: Alone $n = 12$; Mom $n = 12$; odor Only: Alone $n = 12$; Mom $n = 12$) and **(C,D)** PN28 Control (Paired: Alone $n = 9$; Mom $n = 10$; Unpaired: Alone $n = 8$; Mom $n = 8$; odor Only: Alone $n = 8$; Mom $n = 8$) and LB (Paired: Alone $n = 14$; Mom $n = 14$; Unpaired: Alone $n = 8$; Mom $n = 8$; odor Only: Alone $n = 8$; Mom $n = 8$), although this maternal presence effect was not present following early life PN18 LB maltreatment and present but attenuated following early life PN28 LB maltreatment. $^{*}p < 0.05$, $^{****}p < 0.0001$.

(**Figure 4B**), IL 2-DG uptake was higher when pups received paired CS-US conditioning with the mother vs. conditioned alone, while abused pups failed to show this effect [two-way ANOVA (rearing × maternal presence): main effect of rearing ($F_{(1,117)} = 30.77$, $p < 0.0001$), main effect of maternal presence ($F_{(1,117)} = 6.754$, $p = 0.011$), and a trending interaction ($F_{(1,117)} = 2.965$, $p = 0.088$)]. *Post hoc* tests showed that maternal presence during paired odor-shock conditioning was associated with increased 2-DG uptake in IL in controls, but not LB-reared PN28 pups (control alone vs. control with mom, $t_{(117)} = 3.041$, $p = 0.003$; LB alone vs. LB with mom, $t_{(117)} = 0.623$, $p = 0.535$).

At PN18 (**Figure 4A**), we failed to observe an effect of maternal presence on 2-DG uptake, though a main effect of rearing was observed [two-way ANOVA (rearing × maternal presence), main effect of rearing ($F_{(1,136)} = 4.705$, $p = 0.032$); no main effect of maternal presence ($F_{(1,136)} = 1.127$, $p = 0.293$); no interaction ($F_{(1,136)} = 1.557$, $p = 0.214$)]. *Post hoc* tests showed that LS-reared pups exhibited lower 2-DG uptake levels compared to controls (LS with mom vs. control with mom, $t_{(136)} = 2.44$, $p = 0.016$; LB with mom vs. control alone, $t_{(136)} = 2.26$, $p = 0.025$).

Prelimbic Prefrontal Cortex (PL)

We observed that in PN28 pups (**Figure 4D**), the ventral region of the PL showed significant changes in 2-DG metabolism depending on rearing condition (Control vs. LS) as well as maternal presence [two-way ANOVA (rearing × maternal presence), main effect of rearing ($F_{(1,128)} = 9.127$, $p = 0.003$), main effect of maternal presence ($F_{(1,128)} = 12.13$, $p = 0.001$), no interaction ($F_{(1,128)} = 1.902$, $p = 0.170$)]. *Post hoc* tests showed that maternal presence increased activity in Control pups conditioned with the mom but not LB (control alone vs. control with mom, $t_{(128)} = 3.39$, $p = 0.001$; LB alone vs. LB with mom ($t_{(128)} = 1.51$, $p = 0.134$). In the dorsal PL, only a main effect of rearing was observed ($F_{(1,95)} = 9.045$, $p = 0.003$) with no main effect of maternal presence ($F_{(1,95)} = 1.288$, $p = 0.259$) or interaction ($F_{(1,95)} = 1.869$, $p = 0.175$). 2-DG uptake was decreased in all LS-reared groups compared to controls (LS with mom vs. control with mom, $t_{(95)} = 3.138$, $p = 0.002$; LB alone

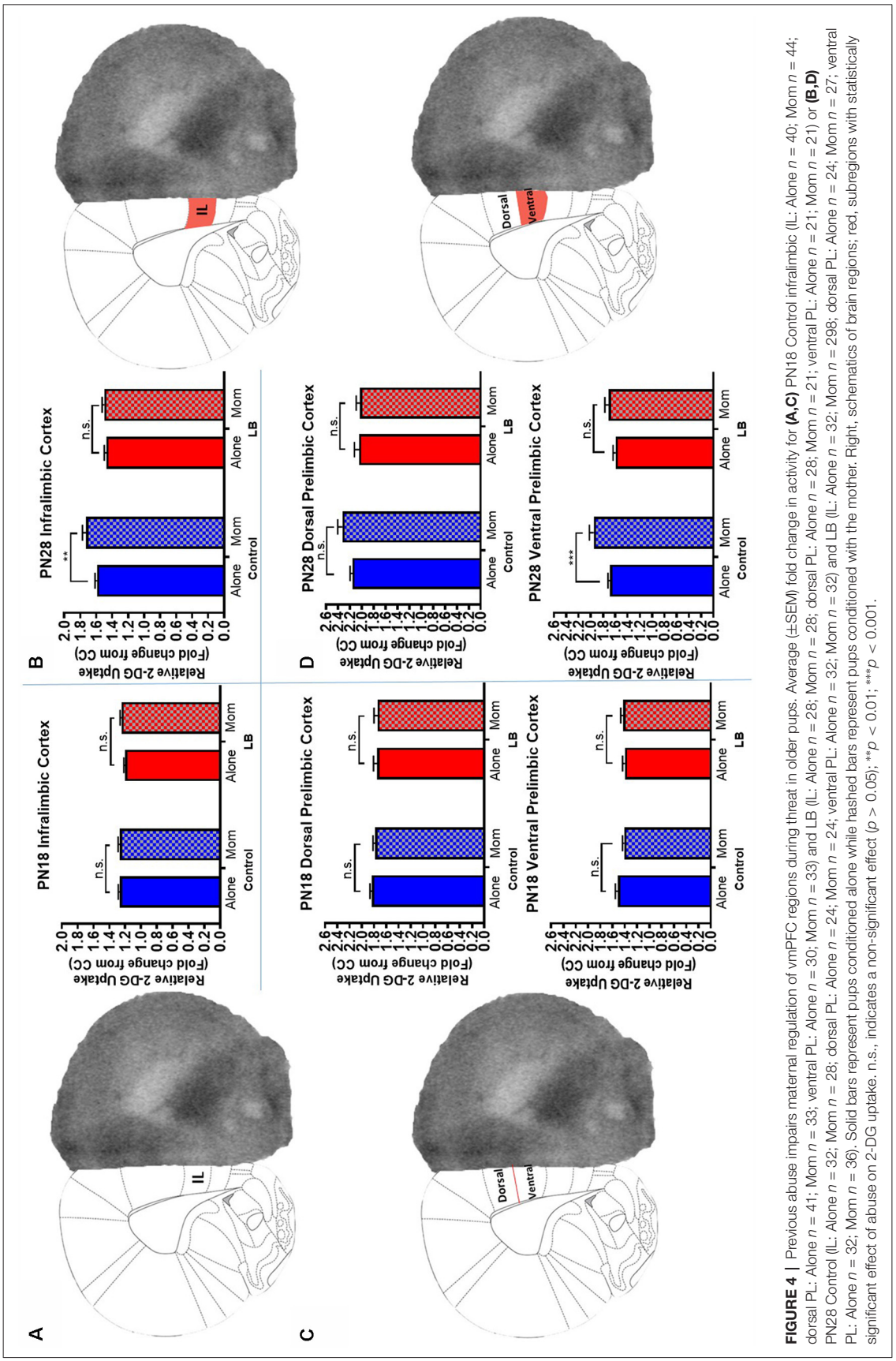


FIGURE 4 | Previous abuse impairs maternal regulation of vmPFC regions during threat in older pups. Average (±SEM) fold change in activity for **(A,C)** PN18 Control infralimbic (IL: Alone $n = 40$; Mom $n = 44$; dorsal PL: Alone $n = 41$; Mom $n = 33$; ventral PL: Alone $n = 30$; Mom $n = 33$) and LB (IL: Alone $n = 28$; Mom $n = 28$; dorsal PL: Alone $n = 28$; Mom $n = 21$; ventral PL: Alone $n = 21$; Mom $n = 21$) or **(B,D)** PN28 Control (IL: Alone $n = 32$; Mom $n = 28$; dorsal PL: Alone $n = 24$; Mom $n = 24$; ventral PL: Alone $n = 32$; Mom $n = 32$) and LB (IL: Alone $n = 32$; Mom $n = 298$; dorsal PL: Alone $n = 24$; Mom $n = 24$; ventral PL: Alone $n = 32$; Mom $n = 27$; ventral PL: Alone $n = 32$; Mom $n = 36$). Solid bars represent pups conditioned alone while hashed bars represent pups conditioned with the mother. Right, schematics of brain regions; red, subregions with statistically significant effect of abuse on 2-DG uptake. n.s., indicates a non-significant effect ($p > 0.05$); $^{**}p < 0.01$; $^{***}p < 0.001$.

vs. control mom, $t_{(95)} = 2.888$, $p = 0.005$). At PN18 (**Figure 4C**), dorsal PL had no effects of maternal presence, rearing, or an interaction observed in the ventral ($F_{(1,101)} = 1.066$, $p = 0.304$, $F_{(1,101)} = 1.764$, $p = 0.1871$, and $F_{(1,101)} = 3.199$, $p = 0.076$, respectively) or dorsal ($F_{(1,119)} = 0.480$, $p = 0.490$, $F_{(1,119)} = 1.831$, $p = 0.1785$, $F_{(1,119)} = 0.243$, $p = 0.623$, respectively).

DISCUSSION

Here, we assessed the neurobiology of social buffering of threat learning in typical and perturbed development. We focused on a developmental transition from dependence on the mother (PN18) to independence in preadolescent rats (PN28) weaned from the mother. Overall, our results show that social buffering of threat occurs across the lifespan, although the underlying neural circuit diverges, with the present results suggesting a late emerging role for the PFC after weaning from the mother. We summarize these results and integrate them into the existing social buffering literature in **Figure 5**: maternal presence blocks fear learning in early development, but switches to attenuation of threat responding, which behaviorally appears similar from PN16 into adulthood. This system is disrupted by early life trauma: PN18 maltreated pups were not socially buffered by the mother, but social buffering of threat emerged again by PN28. Most surprisingly, expression of social buffering in maltreated preadolescents did not require PFC engagement. Taken together, these results suggest that social buffering is a dynamic process that is sensitive to developmental events in an age-dependent manner.

Using an age range when the PFC and its connectivity with the amygdala are maturing (Bouwmeester et al., 2002; Cressman et al., 2010; Willing and Juraska, 2015; Arruda-Carvalho et al., 2017), we asked if the PFC is involved in maternal suppression of fear learning in infant rats during a developmentally significant transitional period. In humans, the late-developing PFC shows a switch from positive to negative connectivity with the amygdala as children develop into adolescents and amygdala-prefrontal circuitry is associated with increased behavioral modulation of children by their mothers (Gee et al., 2013b, 2014). Furthermore, early life trauma is associated with dysregulated cortico-limbic network connectivity through adolescence, impaired stress responding, and cortico-limbic hyperactivity in response to negative social cues (Andersen and Teicher, 2008; Suzuki et al., 2014; Teicher et al., 2014, 2016; Kaiser et al., 2018). Together with the current results, these reports suggest that prefrontal modulation of interacting fear and social systems contributes to the developmental profile of maternal fear regulation and this system can be disrupted following early life trauma. However, further investigation is needed to confirm this hypothesis.

Typical Rearing: Social Buffering of Threat Occurs at Both PN18 and PN28, but the PFC Is Only Engaged in Newly Independent PN28 Pups

The similar social buffering effects on the behavioral level at PN18 and PN28 appear to be supported by different neural networks; the ventromedial (vm)PFC IL and PL subregions were only modulated by the mother in the PN28 animals. The PFC is a late-developing structure (Gee et al., 2013b; Schubert et al., 2015; Hennessy et al., 2018) and the older infant/child and adult literature validates the important role of the amygdala and vmPFC for social buffering in humans (Lungwitz et al., 2014; Hornstein et al., 2016; Hornstein and Eisenberger, 2017; van Rooij et al., 2017), nonhuman primates (Winslow et al., 2003; Suomi et al., 2008; Sanchez et al., 2015; Howell et al., 2017) and rodents (Hennessy et al., 2015; Penha Farias et al., 2019). The absence of a PFC effect in the youngest pups is consistent with the literature as well. These reports suggest that the rodent vmPFC is not engaged by simple maternal presence, simple innate threat presentation, or learning about threat until around weaning age (∼PN23; Kim et al., 2009; Chan et al., 2011; Ball and Slane, 2012; Li et al., 2012; Shechner et al., 2014; Takahashi, 2014; Almada et al., 2015; Perry et al., 2016; Heroux et al., 2017; Robinson-Drummer et al., 2018). It should be noted that the PFC appears to be involved in the appetitive system in PN18 pups (Lilliquist et al., 1999; Nair et al., 2001a,b), suggesting a staggered developmental functional onset for various PFC functions.

The newly emerging role of the vmPFC by PN28 to support social buffering of threat is consistent with vmPFC importance in adult fear conditioning social presence literature in humans and rodents. For example, in adult rats, the presence of a cage mate significantly attenuates fear learning, compared to those conditioned alone and engages the vmPFC (Kiyokawa et al., 2014, 2007; Penha Farias et al., 2019). This effect also occurs in humans and involves the vmPFC; in adults, the presence of an important social partner (i.e., mother, romantic partner, cage mate) or a stimulus that provokes the memory of an individual (i.e., odor, photo) dampens fear through amygdala-vmPFC to block adult fear learning across species (Guzmán et al., 2009; Fuzzo et al., 2015; Hornstein et al., 2016; Hornstein and Eisenberger, 2017; van Rooij et al., 2017; Toumbelekis et al., 2018). Our results also overlap with the literature involving non-social cues predicting safety within a threatening situation: conditioned inhibitors/safety signals use a similar network of PFC input suppressing the amygdala (Rogan et al., 2005; Pollak et al., 2008; Christianson et al., 2012; Harrison et al., 2017; Levin et al., 2017). The specific connection between the vmPFC and amygdala has not been documented within the social buffering of threat literature, although our general understanding of vmPFC-amygdala functional connectivity suggests the PFC is required to modulate the amygdala's output response to threat (Phelps et al., 2004; Corcoran and Quirk, 2007; Marek et al., 2013). In general, the IL appears to reduce fear (Quirk et al., 2000; Sotres-Bayon et al., 2004; Do-Monte et al., 2015), and this is consistent with our findings; the largest maternal response in the PFC was found in the IL. In contrast, the PL is generally associated with enhanced amygdala responding and enhanced amygdala-dependent response to threat (Sharpe and Killcross, 2015a,b, 2018; Ye et al., 2017) although prelimbic-infralimbic projections have been shown to contribute to reductions in fear expression (Marek et al., 2018). The dorso-ventral gradient

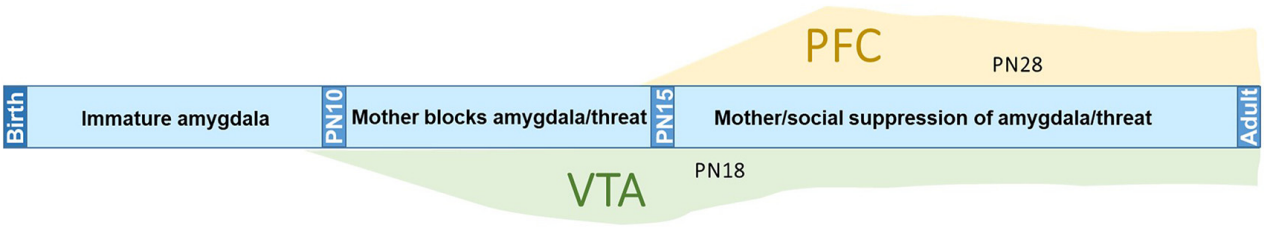


FIGURE 5 | Developmental transitions in amygdala inputs regulating social suppression of threat. The neural circuit supporting infant fear learning and its maternal presence blockade (≤PN15) or attenuation (≥PN16) undergoes developmental changes. Social buffering in early infancy is supported by VTA-amygdala connectivity (≤PN15), while in older pups (PN28) and adults social attenuation of fear is supported by vmPFC-amygdala connectivity. This system is disrupted following early life abusive rearing. At PN18, the ability of the mother to block fear learning is abolished and VTA showed compromised suppression of the amygdala. Early life maltreatment leaves social suppression of fear learning intact at PN28, although it is effectiveness is reduced and social modulation of vmPFC engagement is significantly reduced.

of activity observed at PN28 support a role for a subset of PL contributing to fear reduction with ventral regions sharing function with the IL cortex; a finding not surprising due to their close anatomical proximity.

As we consider the functional significance of late PFC engagement by social buffering of threat during early life, we suggest that as pups leave the nest they encounter a far more complicated environment where higher order brain areas (such as the vmPFC) are required for processing complex threat and safety cues. Indeed, outside the nest an animal must use changing, context- and time-dependent safety/threat cues to choose appropriate approach/avoidance responses in environments with complex social hierarchy (Cunningham et al., 2002; Holland and Gallagher, 2004; Taylor et al., 2008; Maren et al., 2013; Opendak et al., 2017). Development of functional connectivity between the vmPFC, threat and social circuits would allow necessary integration of these cues thereby facilitating proper social interactions and threat evaluation.

Maltreatment Rearing Blocked Social Buffering of Threat at PN18, but Returns at PN28 Without PFC Engagement

One of the more intriguing aspects of the present data is the effect of rearing on social buffering at across development; early life maltreatment transiently suppressed social buffering at PN18 (replicating effects observed in Opendak et al., 2019) and social buffering returned at PN28. Our experiments do not suggest a mechanism for this transition, although the evidence points to the slow decline of the infant VTA social buffering system and the protracted emergence of the adult-like, PFC-dependent, social buffering system (see **Figure 5**). Specifically, our previous work suggests this PN18 maltreatment effect is due to disruption of the infant VTA dopaminergic input to the basolateral amygdala, the mechanism supporting social blockade and suppression of fear learning in younger pups (Barr et al., 2009; Opendak et al., 2019). In further support of this framework, in typically-reared PN28 pups, social buffering was associated with PFC engagement, which was not observed at PN18.

Another striking feature of these data is the dissociation between PFC and social buffering following maltreatment in preadolescents. Specifically, buffering was still observed at PN28 following maltreatment, though we failed to observe the engagement of the PFC documented in control-reared pups. We should note that early maltreatment seemed to reduce the effect of maternal presence on fear learning; LB pups showed a smaller difference in freezing between paired conditioning alone and with mom groups although this result requires replication and direct comparison in a future study. However this complements existing literature on the impact of early life stress on the infant PFC and infant learning (Callaghan and Richardson, 2012; Pattwell et al., 2012; Fareri et al., 2017; Peña et al., 2017; Bath, 2018; Callaghan et al., 2019; Junod et al., provisionally accepted) and extends these results to include reduced social reduction of fear.

While it is abundantly clear that early life stress disrupts pups' neurobehavioral development (Barbosa Neto et al., 2012; Tang et al., 2014; Doherty and Roth, 2016; Pattwell and Bath, 2017; Walker et al., 2017), including PFC development (Braun and Bock, 2011; Kunzler et al., 2015; Schubert et al., 2015; Hanson et al., 2018; VanTieghem and Tottenham, 2018), we speculate that a critical feature of this effect is that the ability of the mother to impact pups' brains has failed to acquire the strength or value it has in typically reared pups. Indeed, our previous assessment of the value of maternal odor in control-reared vs. maltreatment-reared pups shows a slight yet significant decrease in approach to the maternal odor and decreased activation of amygdala and PFC in response to a maternal odor presentation without threat (Perry et al., 2016). It should be noted that the maltreatment-associated maternal odor *increases* in value across development. Indeed, adults reared with maltreatment have greater reduction of threat by maternal odor compared to controls, as evidenced by suppression of amygdala, attenuated fear conditioning and normalization of depressive-like behaviors (Sevelinges et al., 2011; Rincón-Cortés et al., 2015). This phenomenon may contribute to the transient effect of LB on behavior between PN18 and 28; as weaned animals approach

adulthood, the weakened maternal cue naturally regains value and is able to reduce fear behavior. This would suggest that modulation of LB fear behavior is redirected through other circuit nodes (e.g., the VTA) when maternal presence fails to modulate vmPFC activity at this age. Thus, in addition to the social buffering network changing during development, the social signal processing within a larger social brain network may contribute to maltreatment-associated effects on social buffering.

CONCLUSION

As we consider the implications of these results for infant neurobehavioral development and integration with the broader human development work, this work may inform our understanding of attachment. Within Attachment Theory, the mother is considered a "safe haven" or a source of safety, wherein the infant approaches the caregiver for safety and the caregiver reduces fear (Kerns et al., 2015; Hornstein et al., 2016). Here, using a fear conditioning paradigm, we show that maltreatment diminishes the mother's ability to serve as a "safe haven" and social buffering of threat takes on a nonlinear effect across development.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of National Institutes of Health. The protocol was approved by the Institutional Animal Care and Use Committees.

AUTHOR CONTRIBUTIONS

RS, MO and PR-D designed the experiments. PR-D, KW, MO and RS conducted the research/analyzed behavior. MO and AB made illustrations. ST, AB, PR-D, MO, SC, EF, CS, AS, DC, CD and ST analyzed the IA data. KW, LJ and GK performed histology and autoradiography. RS, PR-D, MO and AB wrote the manuscript. PR-D, MO, AB and RS performed and were consulted on data analysis and statistics.

FUNDING

This research was funded by Foundation for the National Institutes of Health (NIH) F32MH112232, BBRF NARSAD Young Investigator Award T32MH019524 (MO), Gålö-stiftelsen (AB), NYU undergraduate DURF award (SC, ST, CD), Fulbright Fellowship (GK), and R37HD083217 (RS).

ACKNOWLEDGMENTS

We thank Joyce Woo for the contribution of her drawings to use as illustrations in **Figure 1** and **Table 1**.

REFERENCES

Al Aïn, S., Perry, R. E., Nuñez, B., Kayser, K., Hochman, C., Brehman, E., et al. (2017). Neurobehavioral assessment of maternal odor in developing rat pups: implications for social buffering. *Soc. Neurosci.* 12, 32–49. doi: 10.1080/17470919.2016.1159605

Almada, R. C., Coimbra, N. C., and Brandão, M. L. (2015). Medial prefrontal cortex serotonergic and GABAergic mechanisms modulate the expression of contextual fear: intratelencephalic pathways and differential involvement of cortical subregions. *Neuroscience* 284, 988–997. doi: 10.1016/j.neuroscience.2014.11.001

Andersen, S. L., and Teicher, M. H. (2008). Stress, sensitive periods and maturational events in adolescent depression. *Trends Neurosci.* 31, 183–191. doi: 10.1016/j.tins.2008.01.004

Arruda-Carvalho, M., Wu, W. C., Cummings, K. A., and Clem, R. L. (2017). Optogenetic examination of prefrontal-amygdala synaptic development. *J. Neurosci.* 37, 2976–2985. doi: 10.1523/JNEUROSCI.3097-16.2017

Ball, K. T., and Slane, M. (2012). Differential involvement of prelimbic and infralimbic medial prefrontal cortex in discrete cue-induced reinstatement of 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) seeking in rats. *Psychopharmacology* 224, 377–385. doi: 10.1007/s00213-012-2762-5

Barbosa Neto, J. B., Tiba, P. A., Faturi, C. B., de Castro-Neto, E. F., da Graca Naffah-Mazacoratti, M., de Jesus Mari, J., et al. (2012). Stress during development alters anxiety-like behavior and hippocampal neurotransmission in male and female rats. *Neuropharmacology* 62, 518–526. doi: 10.1016/j.neuropharm.2011.09.011

Barr, G. A., Moriceau, S., Shionoya, K., Muzny, K., Gao, P., Wang, S., et al. (2009). Transitions in infant learning are modulated by dopamine in the amygdala. *Nat. Neurosci.* 12, 1367–1369. doi: 10.1038/nn.2403

Bath, K. G. (2018). "Early life stress is associated with precocious amygdala development and an unexpected dip in threat-associated freezing," in *Paper Presented at the International Society for Developmental Psychobiology*, San Diego, CA.

Bisaz, R., and Sullivan, R. M. (2012). Developmental neurobiology of the rat attachment system and its modulation by stress. *Behav. Sci.* 2, 79–102. doi: 10.3390/bs2020079

Blair, C., and Raver, C. C. (2015). School readiness and self-regulation: a developmental psychobiological approach. *Annu. Rev. Psychol.* 66, 711–731. doi: 10.1146/annurev-psych-010814-015221

Boulanger Bertolus, J., Hegoburu, C., Ahers, J. L., Londen, E., Rousselot, J., Szyba, K., et al. (2014). Infant rats can learn time intervals before the maturation of the striatum: evidence from odor fear conditioning. *Front. Behav. Neurosci.* 8:176. doi: 10.3389/fnbeh.2014.00176

Bouwmeester, H., Smits, K., and Van Ree, J. M. (2002). Neonatal development of projections to the basolateral amygdala from prefrontal and thalamic structures in rat. *J. Comp. Neurol.* 450, 241–255. doi: 10.1002/cne.10321

Bowlby, J. (1969). *Attachment and Loss*. New York, NY: Basic Books.

Bowlby, J. (1978). Attachment theory and its therapeutic implications. *Adolesc. Psychiatry* 6, 5–33.

Bowlby, J. (1982). Attachment and loss: retrospect and prospect. *Am. J. Orthopsychiatry* 52, 664–678. doi: 10.1111/j.1939-0025.1982.tb01456.x

Braun, K., and Bock, J. (2011). The experience-dependent maturation of prefronto-limbic circuits and the origin of developmental psychopathology: implications for the pathogenesis and therapy of behavioural disorders. *Dev. Med. Child Neurol.* 53, 14–18. doi: 10.1111/j.1469-8749.2011.04056.x

Callaghan, B. L., and Richardson, R. (2012). Early-life stress affects extinction during critical periods of development: an analysis of the effects of maternal separation on extinction in adolescent rats. *Stress* 15, 671–679. doi: 10.3109/10253890.2012.667463

Callaghan, B. L., Meyer, H., Opendak, M., Van Tieghem, M. R., Li, A., Harmon, C., et al. (2019). The developmental ecology of fear neurobiology: scaffolding

by caregiving. *Annu. Rev. Clin. Psychol.* 15, 345–369. doi: 10.1146/annurev-clinpsy-050718-095727

Chambers, J. (2017). The neurobiology of attachment: from infancy to clinical outcomes. *Psychodyn. Psychiatry* 45, 542–563. doi: 10.1521/pdps.2017.45.4.542

Chan, T., Kyere, K., Davis, B. R., Shemyakin, A., Kabitzke, P. A., Shair, H. N., et al. (2011). The role of the medial prefrontal cortex in innate fear regulation in infants, juveniles and adolescents. *J. Neurosci.* 31, 4991–4999. doi: 10.1523/JNEUROSCI.5216-10.2011

Christianson, J. P., Fernando, A. B., Kazama, A. M., Jovanovic, T., Ostroff, L. E., and Sangha, S. (2012). Inhibition of fear by learned safety signals: a mini-symposium review. *J. Neurosci.* 32, 14118–14124. doi: 10.1523/JNEUROSCI.3340-12.2012

Coe, C. L., Mendoza, S. P., Smotherman, W. P., and Levine, S. (1978). Mother-infant attachment in the squirrel monkey: adrenal response to separation. *Behav. Biol.* 22, 256–263. doi: 10.1016/s0091-6773(78)92305-2

Corcoran, K. A., and Quirk, G. J. (2007). Recalling safety: cooperative functions of the ventromedial prefrontal cortex and the hippocampus in extinction. *CNS Spectr.* 12, 200–206. doi: 10.1017/s1092852900020915

Coss, R. G. (2016). Sex difference in choice of concealed or exposed refuge sites by preschool children viewing a model leopard in a playground simulation of antipredator behavior. *Int. J. Psychol. Res.* 9, 8–19. doi: 10.21500/20112084.2325

Cressman, V. L., Balaban, J., Steinfeld, S., Shemyakin, A., Graham, P., Parisot, N., et al. (2010). Prefrontal cortical inputs to the basal amygdala undergo pruning during late adolescence in the rat. *J. Comp. Neurol.* 518, 2693–2709. doi: 10.1002/cne.22359

Cunningham, M. G., Bhattacharyya, S., and Benes, F. M. (2002). Amygdalo-cortical sprouting continues into early adulthood: implications for the development of normal and abnormal function during adolescence. *J. Comp. Neurol.* 453, 116–130. doi: 10.1002/cne.10376

Debiec, J., and Sullivan, R. M. (2014). Intergenerational transmission of emotional trauma through amygdala-dependent mother-to-infant transfer of specific fear. *Proc. Natl. Acad. Sci. U S A* 111, 12222–12227. doi: 10.1073/pnas.1316740111

Doherty, T. S., and Roth, T. L. (2016). Insight from animal models of environmentally driven epigenetic changes in the developing and adult brain. *Dev. Psychopathol.* 28, 1229–1243. doi: 10.1017/s095457941600081x

Do-Monte, F. H., Manzano-Nieves, G., Quiñones-Laracuente, K., Ramos-Medina, L., and Quirk, G. J. (2015). Revisiting the role of infralimbic cortex in fear extinction with optogenetics. *J. Neurosci.* 35, 3607–3615. doi: 10.1523/JNEUROSCI.3137-14.2015

Drury, S. S., Sánchez, M. M., and Gonzalez, A. (2016). When mothering goes awry: challenges and opportunities for utilizing evidence across rodent, nonhuman primate and human studies to better define the biological consequences of negative early caregiving. *Horm. Behav.* 77, 182–192. doi: 10.1016/j.yhbeh.2015.10.007

Fareri, D. S., Gabard-Durnam, L., Goff, B., Flannery, J., Gee, D. G., Lumian, D. S., et al. (2017). Altered ventral striatal-medial prefrontal cortex resting-state connectivity mediates adolescent social problems after early institutional care. *Dev. Psychopathol.* 29, 1865–1876. doi: 10.1017/s0954579417001456

Feldman, R. (2017). The neurobiology of human attachments. *Trends Cogn. Sci.* 21, 80–99. doi: 10.1016/j.tics.2016.11.007

Fuzzo, F., Matsumoto, J., Kiyokawa, Y., Takeuchi, Y., Ono, T., and Nishijo, H. (2015). Social buffering suppresses fear-associated activation of the lateral amygdala in male rats: behavioral and neurophysiological evidence. *Front. Neurosci.* 9:99. doi: 10.3389/fnins.2015.00099

Gee, D. G., Gabard-Durnam, L. J., Flannery, J., Goff, B., Humphreys, K. L., Telzer, E. H., et al. (2013a). Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. *Proc. Natl. Acad. Sci. U S A* 110, 15638–15643. doi: 10.1073/pnas.1307893110

Gee, D. G., Humphreys, K. L., Flannery, J., Goff, B., Telzer, E. H., Shapiro, M., et al. (2013b). A developmental shift from positive to negative connectivity in human amygdala-prefrontal circuitry. *J. Neurosci.* 33, 4584–4593. doi: 10.1523/JNEUROSCI.3446-12.2013

Gee, D. G., Gabard-Durnam, L., Telzer, E. H., Humphreys, K. L., Goff, B., Shapiro, M., et al. (2014). Maternal buffering of human amygdala-prefrontal circuitry during childhood but not during adolescence. *Psychol. Sci.* 25, 2067–2078. doi: 10.1177/0956797614550878

Gunnar, M. R., Hostinar, C. E., Sanchez, M. M., Tottenham, N., and Sullivan, R. M. (2015). Parental buffering of fear and stress neurobiology: reviewing parallels across rodent, monkey, and human models. *Soc. Neurosci.* 10, 474–478. doi: 10.1080/17470919.2015.1070198

Gunnar, M. R., and Sullivan, R. M. (2017). The neurodevelopment of social buffering and fear learning: integration and crosstalk. *Soc. Neurosci.* 12, 1–7. doi: 10.1080/17470919.2016.1151824

Gunnar, M. R., and Quevedo, K. M. (2007). Early care experiences and HPA axis regulation in children: a mechanism for later trauma vulnerability. *Prog. Brain Res.* 167, 137–149. doi: 10.1016/s0079-6123(07)67010-1

Guzmán, Y. F., Tronson, N. C., Guedea, A., Huh, K. H., Gao, C., and Radulovic, J. (2009). Social modeling of conditioned fear in mice by non-fearful conspecifics. *Behav. Brain Res.* 201, 173–178. doi: 10.1016/j.bbr.2009.02.024

Hanson, J. L., Knodt, A. R., Brigidi, B. D., and Hariri, A. R. (2018). Heightened connectivity between the ventral striatum and medial prefrontal cortex as a biomarker for stress-related psychopathology: understanding interactive effects of early and more recent stress. *Psychol. Med.* 48, 1835–1843. doi: 10.1017/s0033291717003348

Harrison, B. J., Fullana, M. A., Via, E., Soriano-Mas, C., Vervliet, B., Martinez-Zalacain, I., et al. (2017). Human ventromedial prefrontal cortex and the positive affective processing of safety signals. *Neuroimage* 152, 12–18. doi: 10.1016/j.neuroimage.2017.02.080

Hennessy, M. B., Hornschuh, G., Kaiser, S., and Sachser, N. (2006). Cortisol responses and social buffering: a study throughout the life span. *Horm. Behav.* 49, 383–390. doi: 10.1016/j.yhbeh.2005.08.006

Hennessy, M. B., Kaiser, S., and Sachser, N. (2009). Social buffering of the stress response: diversity, mechanisms, and functions. *Front. Neuroendocrinol.* 30, 470–482. doi: 10.1016/j.yfrne.2009.06.001

Hennessy, M. B., Schiml, P. A., Willen, R., Watanasriyakul, W., Johnson, J., and Garrett, T. (2015). Selective social buffering of behavioral and endocrine responses and Fos induction in the prelimbic cortex of infants exposed to a novel environment. *Dev. Psychobiol.* 57, 50–62. doi: 10.1002/dev.21256

Hennessy, M. B., Watanasriyakul, W. T., Price, B. C., Bertke, A. S., and Schiml, P. A. (2018). Adult males buffer the cortisol response of young guinea pigs: changes with age, mediation by behavior, and comparison with prefrontal activity. *Horm. Behav.* 98, 165–172. doi: 10.1016/j.yhbeh.2017.12.017

Heroux, N. A., Robinson-Drummer, P. A., Sanders, H. R., Rosen, J. B., and Stanton, M. E. (2017). Differential involvement of the medial prefrontal cortex across variants of contextual fear conditioning. *Learn. Mem.* 24, 322–330. doi: 10.1101/lm.045286.117

Hofer, M. A. (1994). Hidden regulators in attachment, separation, and loss. *Monogr. Soc. Res. Child Dev.* 59, 192–207. doi: 10.1111/j.1540-5834.1994.tb01285.x

Holland, P. C., and Gallagher, M. (2004). Amygdala-frontal interactions and reward expectancy. *Curr. Opin. Neurobiol.* 14, 148–155. doi: 10.1016/j.conb.2004.03.007

Hornstein, E. A., and Eisenberger, N. I. (2017). Unpacking the buffering effect of social support figures: social support attenuates fear acquisition. *PLoS One* 12:e0175891. doi: 10.1371/journal.pone.0175891

Hornstein, E. A., Fanselow, M. S., and Eisenberger, N. I. (2016). A safe haven: investigating social-support figures as prepared safety stimuli. *Psychol. Sci.* 27, 1051–1060. doi: 10.1177/0956797616646580

Hostinar, C. E., and Gunnar, M. R. (2015). Social support can buffer against stress and shape brain activity. *AJOB Neurosci.* 6, 34–42. doi: 10.1080/21507740.2015.1047054

Hostinar, C. E., Johnson, A. E., and Gunnar, M. R. (2015). Parent support is less effective in buffering cortisol stress reactivity for adolescents compared to children. *Dev. Sci.* 18, 281–297. doi: 10.1111/desc.12195

Hostinar, C. E., Sullivan, R. M., and Gunnar, M. R. (2014). Psychobiological mechanisms underlying the social buffering of the hypothalamic-pituitary-adrenocortical axis: a review of animal models and human studies across development. *Psychol. Bull.* 140, 256–282. doi: 10.1037/a0032671

Howell, B. R., McMurray, M. S., Guzman, D. B., Nair, G., Shi, Y., McCormack, K. M., et al. (2017). Maternal buffering beyond glucocorticoids: impact of early life stress on corticolimbic circuits that control infant responses to novelty. *Soc. Neurosci.* 12, 50–64. doi: 10.1080/17470919.2016.1200481

Inagaki, T. K., and Eisenberger, N. I. (2012). Neural correlates of giving support to a loved one. *Psychosom. Med.* 74, 3–7. doi: 10.1097/psy.0b013e3182359335

Johansen, J. P., Cain, C. K., Ostroff, L. E., and LeDoux, J. E. (2011). Molecular mechanisms of fear learning and memory. *Cell* 147, 509–524. doi: 10.1016/j.cell.2011.10.009

Junod, A., Opendak, M., LeDoux, J., and Sullivan, R. M. (provisionally accepted). Development of threat expression following infant maltreatment: infant and adult enhancement but adolescent attenuation. *Front. Behav. Neurosci.* doi: 10.3389/fnbeh.2019.00130

Kaiser, R. H., Clegg, R., Goer, F., Pechtel, P., Beltzer, M., Vitaliano, G., et al. (2018). Childhood stress, grown-up brain networks: corticolimbic correlates of threat-related early life stress and adult stress response. *Psychol. Med.* 48, 1157–1166. doi: 10.1017/s0033291717002628

Kerns, K. A., Mathews, B. L., Koehn, A. J., Williams, C. T., and Siener-Ciesla, S. (2015). Assessing both safe haven and secure base support in parent-child relationships. *Attach. Hum. Dev.* 17, 337–353. doi: 10.1080/14616734.2015.1042487

Kim, J. H., Hamlin, A. S., and Richardson, R. (2009). Fear extinction across development: the involvement of the medial prefrontal cortex as assessed by temporary inactivation and immunohistochemistry. *J. Neurosci.* 29, 10802–10808. doi: 10.1523/JNEUROSCI.0596-09.2009

Kiyokawa, Y., Hiroshima, S., Takeuchi, Y., and Mori, Y. (2014). Social buffering reduces male rats' behavioral and corticosterone responses to a conditioned stimulus. *Horm. Behav.* 65, 114–118. doi: 10.1016/j.yhbeh.2013.12.005

Kiyokawa, Y., Takeuchi, Y., and Mori, Y. (2007). Two types of social buffering differentially mitigate conditioned fear responses. *Eur. J. Neurosci.* 26, 3606–3613. doi: 10.1111/j.1460-9568.2007.05969.x

Kiyokawa, Y., Wakabayashi, Y., Takeuchi, Y., and Mori, Y. (2012). The neural pathway underlying social buffering of conditioned fear responses in male rats. *Eur. J. Neurosci.* 36, 3429–3437. doi: 10.1111/j.1460-9568.2012.08257.x

Kunzler, J., Braun, K., and Bock, J. (2015). Early life stress and sex-specific sensitivity of the catecholaminergic systems in prefrontal and limbic regions of Octodon degus. *Brain Struct. Funct.* 220, 861–868. doi: 10.1007/s00429-013-0688-2

Levin, N., Kritman, M., Maroun, M., and Akirav, I. (2017). Differential roles of the infralimbic and prelimbic areas of the prefrontal cortex in reconsolidation of a traumatic memory. *Eur. Neuropsychopharmacol.* 27, 900–912. doi: 10.1016/j.euroneuro.2017.06.007

Levine, S., Stanton, M. E., and Gutierrez, Y. R. (1988). Maternal modulation of pituitary-adrenal activity during ontogeny. *Adv. Exp. Med. Biol.* 245, 295–310. doi: 10.1007/978-1-4899-2064-5_24

Li, S., Kim, J. H., and Richardson, R. (2012). Differential involvement of the medial prefrontal cortex in the expression of learned fear across development. *Behav. Neurosci.* 126, 217–225. doi: 10.1037/a0027151

Lilliquist, M. W., Nair, H. P., Gonzalez-Lima, F., and Amsel, A. (1999). Extinction after regular and irregular reward schedules in the infant rat: influence of age and training duration. *Dev. Psychobiol.* 34, 57–70. doi: 10.1002/(sici)1098-2302(199901)34:1<57::aid-dev7>3.0.co;2-r

Lungwitz, E. A., Stuber, G. D., Johnson, P. L., Dietrich, A. D., Schartz, N., Hanrahan, B., et al. (2014). The role of the medial prefrontal cortex in regulating social familiarity-induced anxiolysis. *Neuropsychopharmacology* 39, 1009–1019. doi: 10.1038/npp.2013.302

Marek, R., Strobel, C., Bredy, T. W., and Sah, P. (2013). The amygdala and medial prefrontal cortex: partners in the fear circuit. *J. Physiol.* 591, 2381–2391. doi: 10.1113/jphysiol.2012.248575

Marek, R., Xu, L., Sullivan, R. K. P., and Sah, P. (2018). Excitatory connections between the prelimbic and infralimbic medial prefrontal cortex show a role for the prelimbic cortex in fear extinction. *Nat. Neurosci.* 21, 654–658. doi: 10.1038/s41593-018-0137-x

Maren, S., Phan, K. L., and Liberzon, I. (2013). The contextual brain: implications for fear conditioning, extinction and psychopathology. *Nat. Rev. Neurosci.* 14, 417–428. doi: 10.1038/nrn3492

Moriceau, S., and Sullivan, R. M. (2006). Maternal presence serves as a switch between learning fear and attraction in infancy. *Nat. Neurosci.* 9, 1004–1006. doi: 10.1038/nn1733

Moriceau, S., Roth, T. L., and Sullivan, R. M. (2010). Rodent model of infant attachment learning and stress. *Dev. Psychobiol.* 52, 651–660. doi: 10.1002/dev.20482

Moriceau, S., Shionoya, K., Jakubs, K., and Sullivan, R. M. (2009). Early-life stress disrupts attachment learning: the role of amygdala corticosterone, locus ceruleus corticotropin releasing hormone, and olfactory bulb norepinephrine. *J. Neurosci.* 29, 15745–15755. doi: 10.1523/JNEUROSCI.4106-09.2009

Moriceau, S., Wilson, D. A., Levine, S., and Sullivan, R. M. (2006). Dual circuitry for odor-shock conditioning during infancy: corticosterone switches between fear and attraction *via* amygdala. *J. Neurosci.* 26, 6737–6748. doi: 10.1523/JNEUROSCI.0499-06.2006

Nachmias, M., Gunnar, M., Mangelsdorf, S., Parritz, R. H., and Buss, K. (1996). Behavioral inhibition and stress reactivity: the moderating role of attachment security. *Child Dev.* 67, 508–522. doi: 10.2307/1131829

Nair, H. P., Berndt, J. D., Barrett, D., and Gonzalez-Lima, F. (2001a). Maturation of extinction behavior in infant rats: large-scale regional interactions with medial prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex. *J. Neurosci.* 21, 4400–4407. doi: 10.1523/JNEUROSCI.21-12-04400.2001

Nair, H. P., Berndt, J. D., Barrett, D., and Gonzalez-Lima, F. (2001b). Metabolic mapping of brain regions associated with behavioral extinction in preweanling rats. *Brain Res.* 903, 141–153. doi: 10.1016/s0006-8993(01)02469-6

Opendak, M., Gould, E., and Sullivan, R. (2017). Early life adversity during the infant sensitive period for attachment: programming of behavioral neurobiology of threat processing and social behavior. *Dev. Cogn. Neurosci.* 25, 145–159. doi: 10.1016/j.dcn.2017.02.002

Opendak, M., Robinson-Drummer, P., Blomkvist, A., Zanca, R. M., Wood, K., Jacobs, L., et al. (2019). Neurobiology of maternal regulation of infant fear: the role of mesolimbic dopamine and its disruption by maltreatment. *Neuropsychopharmacology* 44, 1247–1257. doi: 10.1038/s41386-019-0340-9

Opendak, M., and Sullivan, R. M. (2016). Unique neurobiology during the sensitive period for attachment produces distinctive infant trauma processing. *Eur. J. Psychotraumatol.* 7:31276. doi: 10.3402/ejpt.v7.31276

Pattwell, S. S., and Bath, K. G. (2017). Emotional learning, stress, and development: an ever-changing landscape shaped by early-life experience. *Neurobiol. Learn. Mem.* 143, 36–48. doi: 10.1016/j.nlm.2017.04.014

Pattwell, S. S., Duhoux, S., Hartley, C. A., Johnson, D. C., Jing, D., Elliott, M. D., et al. (2012). Altered fear learning across development in both mouse and human. *Proc. Natl. Acad. Sci. U S A* 109, 16318–16323. doi: 10.1073/pnas.1206834109

Paxinos, G., and Watson, C. (2013). *The Rat Brain in Stereotaxic Coordinates*. 7th Edn. Boston, MA: Academic Press.

Peña, C. J., Kronman, H. G., Walker, D. M., Cates, H. M., Bagot, R. C., Purushothaman, I., et al. (2017). Early life stress confers lifelong stress susceptibility in mice *via* ventral tegmental area OTX2. *Science* 356, 1185–1188. doi: 10.1126/science.aan4491

Penha Farias, C., Guerino Furini, C. R., Godfried Nachtigall, E., Kielbovicz Behling, J. A., Silva de Assis Brasil, E., Bühler, L., et al. (2019). Extinction learning with social support depends on protein synthesis in prefrontal cortex but not hippocampus. *Proc. Natl. Acad. Sci. U S A* 116, 1765–1769. doi: 10.1073/pnas.1815893116

Perry, R. E., Al Aïn, S., Raineki, C., Sullivan, R. M., and Wilson, D. A. (2016). Development of odor hedonics: experience-dependent ontogeny of circuits supporting maternal and predator odor responses in rats. *J. Neurosci.* 36, 6634–6650. doi: 10.1523/JNEUROSCI.0632-16.2016

Perry, R. E., Blair, C., and Sullivan, R. M. (2017). Neurobiology of infant attachment: attachment despite adversity and parental programming of emotionality. *Curr. Opin. Psychol.* 17, 1–6. doi: 10.1016/j.copsyc.2017.04.022

Perry, R. E., and Sullivan, R. M. (2014). Neurobiology of attachment to an abusive caregiver: short-term benefits and long-term costs. *Dev. Psychobiol.* 56, 1626–1634. doi: 10.1002/dev.21219

Phelps, E. A., Delgado, M. R., Nearing, K. I., and LeDoux, J. E. (2004). Extinction learning in humans: role of the amygdala and vmPFC. *Neuron* 43, 897–905. doi: 10.1016/j.neuron.2004.08.042

Pollak, D. D., Monje, F. J., Zuckerman, L., Denny, C. A., Drew, M. R., and Kandel, E. R. (2008). An animal model of a behavioral intervention for depression. *Neuron* 60, 149–161. doi: 10.1016/j.neuron.2008.07.041

Quirk, G. J., Russo, G. K., Barron, J. L., and Lebron, K. (2000). The role of ventromedial prefrontal cortex in the recovery of extinguished fear. *J. Neurosci.* 20, 6225–6231. doi: 10.1523/JNEUROSCI.20-16-06225.2000

Raineki, C., Moriceau, S., and Sullivan, R. M. (2010). Developing a neurobehavioral animal model of infant attachment to an abusive caregiver. *Biol. Psychiatry* 67, 1137–1145. doi: 10.1016/j.biopsych.2009.12.019

Rincón-Cortés, M., Barr, G. A., Mouly, A. M., Shionoya, K., Nuñez, B. S., and Sullivan, R. M. (2015). Enduring good memories of infant trauma: rescue of adult neurobehavioral deficits *via* amygdala serotonin and corticosterone interaction. *Proc. Natl. Acad. Sci. U S A* 112, 881–886. doi: 10.1073/pnas.1416065112

Robinson-Drummer, P. A., Chakraborty, T., Heroux, N. A., Rosen, J. B., and Stanton, M. E. (2018). Age and experience dependent changes in Egr-1 expression during the ontogeny of the context preexposure facilitation effect (CPFE). *Neurobiol. Learn. Mem.* 150, 1–12. doi: 10.1016/j.nlm.2018.02.008

Rogan, M. T., Leon, K. S., Perez, D. L., and Kandel, E. R. (2005). Distinct neural signatures for safety and danger in the amygdala and striatum of the mouse. *Neuron* 46, 309–320. doi: 10.1016/j.neuron.2005.02.017

Roth, T., and Sullivan, R. (2005). Memory of early maltreatment: neonatal behavioral and neural correlates of maternal maltreatment within the context of classical conditioning. *Biol. Psychiatry* 57, 823–831. doi: 10.1016/j.biopsych.2005.01.032

Sanchez, M. M., McCormack, K. M., and Howell, B. R. (2015). Social buffering of stress responses in nonhuman primates: maternal regulation of the development of emotional regulatory brain circuits. *Soc. Neurosci.* 10, 512–526. doi: 10.1080/17470919.2015.1087426

Santiago, A. N., Lim, K. Y., Opendak, M., Sullivan, R. M., and Aoki, C. (2018). Early life trauma increases threat response of peri-weaning rats, reduction of axo-somatic synapses formed by parvalbumin cells and perineuronal net in the basolateral nucleus of amygdala. *J. Comp. Neurol.* 526, 2647–2664. doi: 10.1002/cne.24522

Schubert, D., Martens, G. J., and Kolk, S. M. (2015). Molecular underpinnings of prefrontal cortex development in rodents provide insights into the etiology of neurodevelopmental disorders. *Mol. Psychiatry* 20, 795–809. doi: 10.1038/mp.2014.147

Sevelinges, Y., Mouly, A. M., Raineki, C., Moriceau, S., Forest, C., and Sullivan, R. M. (2011). Adult depression-like behavior, amygdala and olfactory cortex functions are restored by odor previously paired with shock during infant's sensitive period attachment learning. *Dev. Cogn. Neurosci.* 1, 77–87. doi: 10.1016/j.dcn.2010.07.005

Sharpe, M. J., and Killcross, S. (2015a). The prelimbic cortex uses higher-order cues to modulate both the acquisition and expression of conditioned fear. *Front. Syst. Neurosci.* 8:235. doi: 10.3389/fnsys.2014.00235

Sharpe, M. J., and Killcross, S. (2015b). The prelimbic cortex directs attention toward predictive cues during fear learning. *Learn. Mem.* 22, 289–293. doi: 10.1101/lm.038273.115

Sharpe, M. J., and Killcross, S. (2018). Modulation of attention and action in the medial prefrontal cortex of rats. *Psychol. Rev.* 125, 822–843. doi: 10.1037/rev0000118

Shechner, T., Hong, M., Britton, J. C., Pine, D. S., and Fox, N. A. (2014). Fear conditioning and extinction across development: evidence from human studies and animal models. *Biol. Psychol.* 100, 1–12. doi: 10.1016/j.biopsycho.2014.04.001

Shionoya, K., Moriceau, S., Bradstock, P., and Sullivan, R. M. (2007). Maternal attenuation of hypothalamic paraventricular nucleus norepinephrine switches avoidance learning to preference learning in preweanling rat pups. *Horm. Behav.* 52, 391–400. doi: 10.1016/j.yhbeh.2007.06.004

Sotres-Bayon, F., Bush, D. E., and LeDoux, J. E. (2004). Emotional perseveration: an update on prefrontal-amygdala interactions in fear extinction. *Learn. Mem.* 11, 525–535. doi: 10.1101/lm.79504

Sroufe, L. A. (2005). Attachment and development: a prospective, longitudinal study from birth to adulthood. *Attach. Hum. Dev.* 7, 349–367. doi: 10.1080/14616730500365928

Stanton, M. E., and Levine, S. (1985). Brief separation elevates cortisol in mother and infant squirrel monkeys. *Physiol. Behav.* 34, 1007–1008. doi: 10.1016/0031-9384(85)90029-0

Suchecki, D., Rosenfeld, P., and Levine, S. (1993). Maternal regulation of the hypothalamic-pituitary-adrenal axis in the infant rat: the roles of feeding and stroking. *Dev. Brain Res.* 75, 185–192. doi: 10.1016/0165-3806(93)90022-3

Sullivan, R. M., Landers, M., Yeaman, B., and Wilson, D. A. (2000). Good memories of bad events in infancy. *Nature* 407, 38–39. doi: 10.1038/35024156

Sullivan, R. M., and Perry, R. E. (2015). Mechanisms and functional implications of social buffering in infants: lessons from animal models. *Soc. Neurosci.* 10, 500–511. doi: 10.1080/17470919.2015.1087425

Suomi, S. J., van der Horst, F. C., and van der Veer, R. (2008). Rigorous experiments on monkey love: an account of Harry F. Harlow's role in the history of attachment theory. *Integr. Psychol. Behav. Sci.* 42, 354–369. doi: 10.1007/s12124-008-9072-9

Suzuki, H., Luby, J. L., Botteron, K. N., Dietrich, R., McAvoy, M. P., and Barch, D. M. (2014). Early life stress and trauma and enhanced limbic activation to emotionally valenced faces in depressed and healthy children. *J. Am. Acad. Child Adolesc. Psychiatry* 53, 800.e10–813.e10. doi: 10.1016/j.jaac.2014.04.013

Takahashi, L. K. (2014). Olfactory systems and neural circuits that modulate predator odor fear. *Front. Behav. Neurosci.* 8:72. doi: 10.3389/fnbeh.2014.00072

Tallot, L., Doyère, V., and Sullivan, R. M. (2016). Developmental emergence of fear/threat learning: neurobiology, associations and timing. *Genes Brain Behav.* 15, 144–154. doi: 10.1111/gbb.12261

Tang, A. C., Reeb-Sutherland, B. C., Romeo, R. D., and McEwen, B. S. (2014). On the causes of early life experience effects: evaluating the role of mom. *Front. Neuroendocrinol.* 35, 245–251. doi: 10.1016/j.yfrne.2013.11.002

Taylor, S. E., Burklund, L. J., Eisenberger, N. I., Lehman, B. J., Hilmert, C. J., and Lieberman, M. D. (2008). Neural bases of moderation of cortisol stress responses by psychosocial resources. *J. Pers. Soc. Psychol.* 95, 197–211. doi: 10.1037/0022-3514.95.1.197

Teicher, M. H., Anderson, C. M., Ohashi, K., and Polcari, A. (2014). Childhood maltreatment: altered network centrality of cingulate, precuneus, temporal pole and insula. *Biol. Psychiatry* 76, 297–305. doi: 10.1016/j.biopsych.2013.09.016

Teicher, M. H., Samson, J. A., Anderson, C. M., and Ohashi, K. (2016). The effects of childhood maltreatment on brain structure, function and connectivity. *Nat. Rev. Neurosci.* 17, 652–666. doi: 10.1038/nrn.2016.111

Tottenham, N., and Sheridan, M. A. (2009). A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. *Front. Hum. Neurosci.* 3:68. doi: 10.3389/neuro.09.068.2009

Tottenham, N., Shapiro, M., Flannery, J., Caldera, C., and Sullivan, R. (accepted). Parental presence switches avoidance to attraction learning in children. *Nature Hum. Beh.*

Tottenham, N., Shapiro, M., Telzer, E. H., and Humphreys, K. L. (2012). Amygdala response to mother. *Dev. Sci.* 15, 307–319. doi: 10.1111/j.1467-7687.2011.01128.x

Toumbelekis, M., Liddell, B. J., and Bryant, R. A. (2018). Thinking of attachment figures blocks differential fear conditioning. *Soc. Cogn. Affect. Neurosci.* 13, 989–994. doi: 10.1093/scan/nsy065

Upton, K. J., and Sullivan, R. M. (2010). Defining age limits of the sensitive period for attachment learning in rat pups. *Dev. Psychobiol.* 52, 453–464. doi: 10.1002/dev.20448

van Rooij, S. J., Cross, D., Stevens, J. S., Vance, L. A., Kim, Y. J., Bradley, B., et al. (2017). Maternal buffering of fear-potentiated startle in children and adolescents with trauma exposure. *Soc. Neurosci.* 12, 22–31. doi: 10.1080/17470919.2016.1164244

VanTieghem, M. R., and Tottenham, N. (2018). Neurobiological programming of early life stress: functional development of amygdala-prefrontal circuitry and vulnerability for stress-related psychopathology. *Curr. Top. Behav. Neurosci.* 38, 117–136. doi: 10.1007/7854_2016_42

Walker, C. D., Bath, K. G., Joels, M., Korosi, A., Larauche, M., Lucassen, P. J., et al. (2017). Chronic early life stress induced by limited bedding and nesting (LBN) material in rodents: critical considerations of methodology, outcomes and translational potential. *Stress* 20, 421–448. doi: 10.1080/10253890.2017.1343296

Wiener, S. G., Johnson, D. F., and Levine, S. (1987). Influence of postnatal rearing conditions on the response of squirrel monkey infants to brief perturbations in mother-infant relationships. *Physiol. Behav.* 39, 21–26. doi: 10.1016/0031-9384(87)90339-8

Willing, J., and Juraska, J. M. (2015). The timing of neuronal loss across adolescence in the medial prefrontal cortex of male and female rats. *Neuroscience* 301, 268–275. doi: 10.1016/j.neuroscience.2015.05.073

Winslow, J. T., Noble, P. L., Lyons, C. K., Sterk, S. M., and Insel, T. R. (2003). Rearing effects on cerebrospinal fluid oxytocin concentration and social buffering in rhesus monkeys. *Neuropsychopharmacology* 28, 910–918. doi: 10.1038/sj.npp.1300128

Yan, C. G., Rincón-Cortés, M., Raineki, C., Sarro, E., Colcombe, S., Guilfoyle, D. N., et al. (2017). Aberrant development of intrinsic brain activity in a rat model of caregiver maltreatment of offspring. *Transl. Psychiatry* 7:e1005. doi: 10.1038/tp.2016.276

Ye, X., Kapeller-Libermann, D., Travaglia, A., Inda, M. C., and Alberini, C. M. (2017). Direct dorsal hippocampal-prelimbic cortex connections strengthen fear memories. *Nat. Neurosci.* 20, 52–61. doi: 10.1038/nn.4443

Zajac, L., Raby, K. L., and Dozier, M. (2019). Attachment state of mind and childhood experiences of maltreatment as predictors of sensitive care from infancy through middle childhood: results from a longitudinal study of parents involved with Child Protective Services. *Dev. Psychopathol.* 31, 113–125. doi: 10.1017/s0954579418001554

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 02 July 2019
doi: 10.3389/fnbeh.2019.00142

Vicarious Rewards Modulate the Drift Rate of Evidence Accumulation From the Drift Diffusion Model

*Laure Bottemanne and Jean-Claude Dreher**

Neuroeconomics, Reward and Decision-Making Team, Institut des Sciences Cognitives Marc Jeannerod, Centre National de la Recherche Scientifique, Bron, France

Taking other people's interests into account is a fundamental ability allowing humans to maintain relationships. Yet, the mechanisms by which monetary incentives for close others influence perceptual decision-making processes remain elusive. Here, we compared perceptual decisions motivated by payoffs for oneself or a close relative. According to drift diffusion models (DDMs), perceptual decisions are made when sensory evidence accumulated over time – with a given drift rate – reaches one of the decision boundaries. We used these computational models to identify whether the drift rate of evidence accumulation or the decision boundary is affected by these two sources of motivation. Reaction times and sensitivity were modulated by three factors: the Difficulty (motion coherence of the moving dots), the Payoff associated with, and the Beneficiary of the decision. Reaction times (RTs) were faster for easy compared to difficult trials and faster for high payoffs as compared to low payoffs. More interestingly, RTs were also faster for self than for other-affecting decisions. Finally, using DDM, we found that these faster RTs were linked to a higher drift rate of the decision variable. This study offers a mechanistic understanding of how incentives for others and motion coherence influence decision-making processes.

Keywords: social cognition, motivation, decision making, drift diffusion models, drift rate, vicarious reward

OPEN ACCESS

Edited by:
Johanna M. Jarcho,
Temple University, United States

Reviewed by:
Manuela Sellitto,
Heinrich Heine University Düsseldorf, Germany
Andrés Antonio González-Garrido,
Universidad de Guadalajara, Mexico
Joseph W. Kable,
University of Pennsylvania, United States

***Correspondence:**
Jean-Claude Dreher
dreher@isc.cnrs.fr

Received: *15 January 2019*
Accepted: *11 June 2019*
Published: *02 July 2019*

Citation:
Bottemanne L and Dreher J-C (2019) Vicarious Rewards Modulate the Drift Rate of Evidence Accumulation From the Drift Diffusion Model. Front. Behav. Neurosci. 13:142. doi: 10.3389/fnbeh.2019.00142

INTRODUCTION

When playing at a shooting range in a fairground, we accumulate sensory evidence (about target movement) until we can shoot accurately, and win the prize. Now, if such decisions are made so that the prize goes to a close friend, will we process and use information in the exact same way? More precisely, how does motivational incentives for someone else influence the mechanisms engaged in making simple perceptual choices as compared to the same decisions associated with the same incentives, but for you?

In the last decades, the framework of sequential-sampling models, such as drift diffusion models (DDMs), has proven to be a powerful approach to explain the process of making a decision (Vandekerckhove and Tuerlinckx, 2007; Ratcliff and McKoon, 2008; Leite and Ratcliff, 2010; Summerfield and Tsetsos, 2012; Forstmann et al., 2016; Ratcliff et al., 2016). DDMs successfully capture the complex relationship between choice and reaction times (RTs) by decomposing these behavioral data into internal cognitive components of decision processing. In this framework, a decision reflects a decision variable drifting with a given rate (v), from an intermediate starting

point (z) toward one of the decision boundaries at hands. Each boundary is separated from the starting point (z) of a given distance (a) and acts as a decision threshold for an option, so that the response of a decision is initiated when the decision variable reaches one of the boundaries. In the example of the shooting range, the decision variable would accumulate information about the position of the moving ducks over time, and when (relative) certainty about their position is reached, the decision of pulling the target is made.

Sensory encoding of information basically relies on the quality of the available evidence (Ratcliff and McKoon, 2008). A foggy weather would slow the rate at which the decision variable rises, as compared to clear climate conditions. Reliability of the decision depends on the distance between the starting point of the decision variable and the decision boundary; the decision rules are set by the read-out mechanisms (Brainard, 1997; Summerfield and Tsetsos, 2012; Oppenheimer and Kelso, 2015; Forstmann et al., 2016). Reaching higher decision boundaries requires more evidence to be accumulated, thus leading to a better accuracy, but takes a longer time. Which of the evidence accumulation stage (drift of the decision variable) or the read-out mechanisms (distance between the starting point and the decision boundaries) would be adjusted differently based on vicarious information (the beneficiary of the decision)? How is the perceptual decision process modulated when the source of motivation concerns a close relative rather than oneself?

Here, we designed a new paradigm, enabling the use of DDMs to investigate the influence of the payoff associated with and the person affected by a perceptual decision (**Figure 1**). The participants performed a random dots task (left/right direction categorization) to win low or high payoffs, for themselves or for a close relative. We tested which of the DDM parameters are modified between other-affecting and self-affecting decisions: the drift rate of the decision variable (encoding) or the decision boundary (read-out; **Figure 2**)? Changes in the distance between the starting point and the decision boundary (a) would mean that people integrate beneficiary-related motivation through the read-out mechanisms, setting the decision rules prior to starting the evidence integration itself. Alternatively, a direct influence of self/other motivation on the decisional process could affect the drift rate of the decision variable, which is an index of the quality of evidence used for the decision. This would suggest that sources of motivation (payoff for self/payoff for other) are integrated together with the evidence for the choice alternatives into a single source of evidence during the accumulation process. Finally, a variation in the non-decision time would indicate that the beneficiary-related motivation acts on cognitive mechanisms outside of the decision process itself, such as primary encoding of the stimuli and motor execution.

MATERIALS AND METHODS

Participants

Forty healthy subjects were recruited by advertisements in the Lyon 1 Claude Bernard University students' mailing list. Subjects were screened using self-reports to exclude any psychiatric or neurological history, and current or previous substance abuse (except nicotine and festive alcohol consumptions). All participants gave written informed consent and received 20€ for their participation. This study was approved by the local research ethics committee (Comité de Protection des Personnes Sud-Est III); all methods were performed in accordance with the relevant guidelines and regulations. Two subjects were excluded, one for chance level performances and the other for technical problems, leaving 38 subjects for further analyses (15 females; mean age = 21.84, range = 18–34).

Stimuli

Random dots kinematograms (RDKs) were programmed using the MATLAB® Psychtoolbox (Brainard, 1997; Pelli, 1997). The mask stimulus was a drifting random dots display of 2000 ms duration. Dots were white on a black background, with each frame composed of 50 white Gaussian blobs with a diameter of 2.85 mm. The stationary dots began to move with a speed of 2.7°/s from their original locations, and each dot had a life duration of 500 ms. The motion of the dots was made by replotting dots corresponding to the previous ones at a determined spatial offset in the same direction so that all the dots moved in their directions at the same speed. During the experiment, RDKs appeared in a square centered on the screen (Dell, 19″, screen resolution set to 1,280 × 1,050, vertical refresh rate of 60 Hz), taking 30.8% of the screen, with participants at a distance of 60 cm.

Procedure

Before going to the laboratory, the volunteers were asked to choose a close relative for who they would be willing to play for, on half of the experiment. At their arrival, the participants sat in the experimental room, were informed, and gave their written consent. Their relationship with the chosen person was asked [seven participants chose one of their parents (mother or father), seven chose a sibling, eight chose their lover, three chose a friend, and two chose their roommate]. A few demonstration trials were shown, for them to see how the condition cue (Payoff and Beneficiary) was displayed. Subjects were trained and then finally completed the task. It lasted approximately 64 min, in four blocks of 16 min each. All were debriefed when the task was over.

Training

Before the task, subjects were trained to be familiarized with the design and timing. The training was composed of 10 trials of 15% coherently moving dots, which is the easy level of the task. To ensure that participants did not respond randomly, a sensitivity (d') criterion was set at d = 0.6 (i.e., 60% correct, which is higher than chance level). If subjects were below this criterion in the training session, they performed a second identical training. All of the included subjects eventually reached the criteria and subsequently performed the task.

Instructions

Participants were explained that they would perform a game in order to win money, either for themselves of for the close relative they chose. They were told that they would earn 10€

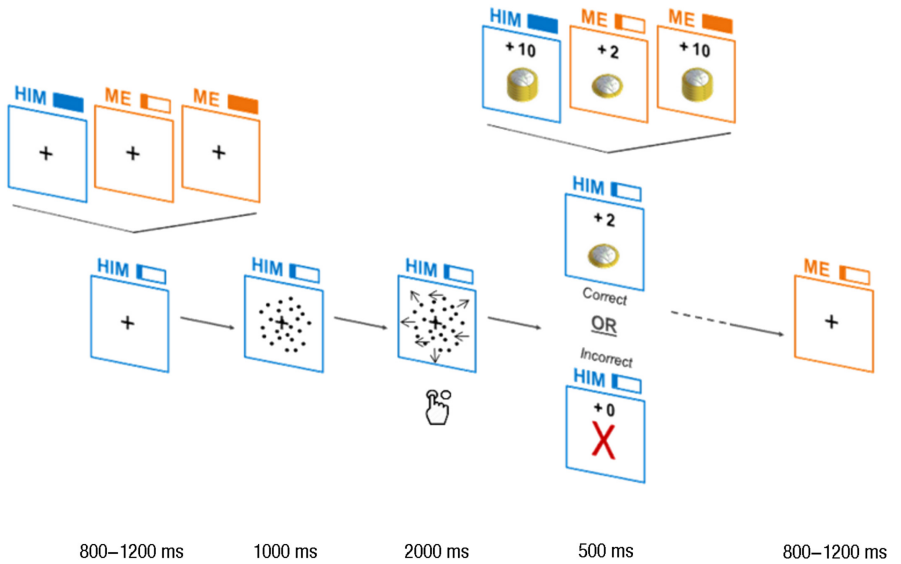


FIGURE 1 | Trials design. Each trial began with a cue, showing "me" or "him" (for self- and other-affecting decisions, respectively) and a full filled rectangle (high payoff) or a one-fifth filled rectangle (low payoff) on top of a square. The cue and the square were depicted in yellow or in blue, according to the beneficiary. Then, the first frame of the random dots kinematogram (RDK; stationary dots) appeared in the square for 1,000 ms. Following this, the moving dots were presented for 2,000 ms and the subject had to respond while the dots were moving. At the end of the 2,000 ms of dots motion, the payoff was presented. If the response was correct, a pile of coins proportional to the payoff was shown together with the value of payoff itself ("+2," "+10") above it. For incorrect responses and misses, a red-colored cross was displayed together with "+0" on top of it. Then, a new trial began and the cue of the upcoming trial was shown.

for doing the experiment and could win 2€ or 10€ more for themselves and also 2€ or 10€ for their relatives. The participants were asked to discriminate the left/right direction of coherently moving dots. They were instructed that they had to give one, and only one, response during the dots motion: if they gave more than one response or did not respond (miss), the program would consider it as incorrect. Money was not accumulated over trials, nor was such accumulation shown to the participants. They were told that one trial of each of the beneficiary condition (self and other) would be randomly selected (by a computer program) to determine their final payoffs. The payoff associated with the trial would be won by the beneficiary, if it was a correct trial. Participants were told (and believed) that the payoff for the other (as well as for themselves) would be sent after completing the experiment. In reality, the close relative received nothing and all participants received 20€ (as if the selected trial was won for himself and associated with a high payoff). This procedure (i) ensured that participants treated all decisions as equally relevant, both for themselves and their close relative; (ii) avoided any competition effects to arise between self and other interests. Also, accuracy was implicitly emphasized by telling the participants that, although they would have to adapt to the given 2 s to answer, time should not be a problem since the duration of the stimuli was chosen based on previous experimental results (pilot study).

Task Design

A square was always present in the middle of the screen. On top of this square appeared the cue, which indicated the beneficiary and payoff conditions of the forthcoming trial. The dots were displayed inside the area defined by the square. The square and the cue were colored yellow or blue, according to the beneficiary of the payoff associated with the trial. The color was used to emphasize the beneficiary of the trial and was counterbalanced between subjects.

Each trial began with the cue, which had a jittered duration from 800 to 1,200 ms and was used as inter-trial interval (ITI). The cue consisted in a word announcing the beneficiary of the decision ("him" for others-affecting decisions, "me" for self-affecting decisions) to the left of a rectangle filled proportionally to the payoff associated with the decision (full filled rectangle for 10€, one-fifth filled rectangle for 2€). This cue remained on the screen during the entire subsequent trial. After the cue, the first frame of the RDK to come (a picture of stationary dots) was shown for 1,000 ms. Then, dots motion began and lasted for 2,000 ms, during which the subject had to respond. Motion coherence was either 13% (difficult) of 15% (easy), for all participants. At the end of the 2,000 ms of dots motion, the feedback illustrated the payoff for 500 ms. If the response was correct, a pile of coins proportional to the payoff (2 or 10€), was shown together with the value of payoff itself ("+2," "+10"). For incorrect responses and misses, a red-colored cross was displayed together with "+0" above it. At the end of the trial, a new ITI was displayed, showing the cue for the trial to come.

A total of 104 trials per Beneficiary*Payoff*Difficulty condition were performed, leading to 832 trials per subject. The task was composed of 4 blocks, of 208 trials each. Each block included 26 trials of each of the 8 conditions. Difficulty levels, Payoffs, Beneficiaries, and dots direction were pseudo-randomized within each block and across participants. Randomization of dots direction was designed to avoid a bias

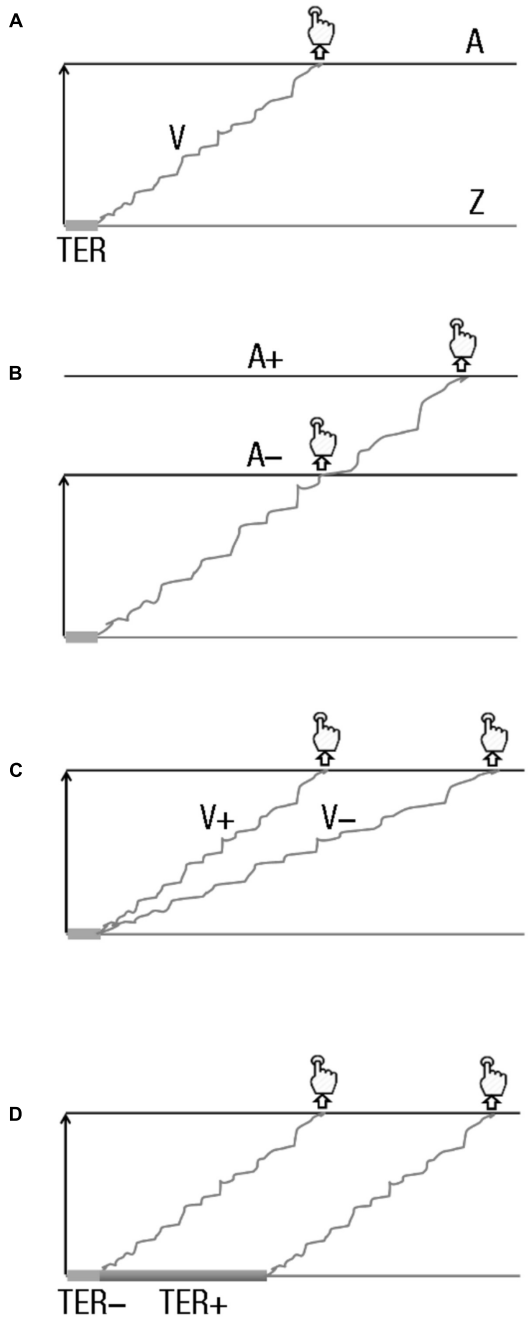


FIGURE 2 | Drift diffusion models (DDMs) and hypotheses. **(A)** DDM main parameters. DDM assumes that two-choice decisions are made by a noisy process that accumulates information, with a given drift rate (*v*), over time. This process goes from the starting point (*z*) toward the decision boundary. When the boundary is reached, a response is initiated (with a button press, in usual experimental setups). The starting point and the boundary are separated by the distance (*A*). **(B–D)** Effects of boundary modulation, drift-rate changes, and non-decision time variation on response initiation. **(B)** Boundary modulation. A boundary increase (*A*+) leads decisions that require more sensory evidence, and thus a longer time, than when a lower boundary is set up (*A*–). **(C)** Drift-rate change. A drift rate increase (*V*+) produces faster sensory evidence accumulation than a lower one (*V*–), producing faster reaction times. **(D)** Non-decision time variation. A longer non-decision time (TER+) leads to slower decisions than a shorter one (TER–).

toward one of the two (left or right) alternatives, constraining it to no more than three consecutive trials of the same dots direction.

It is to be noted that we actually ran a first experiment using another anonymous, randomly selected, participant as "the other." However, there was no main effect of the beneficiary on RT or on *d*' (**Supplementary Table 1**). Since we were aiming to characterize how others are taken into account into the perceptual decision-making process, and based on the literature showing that familiarity increase vicarious effects (Mobbs et al., 2009; Kawamichi et al., 2013), we adapted our task with a close relative.

Statistical Analysis

Reaction times for corrects and RTs for errors were analyzed separately, and RTs were logarithmically transformed. logRT and sensitivity (*d*') normality distribution was ensured using Lilliefors tests. logRT and *d*' were then analyzed using three-way repeated-measures analyses of variances (rmANOVAs). The factors were as follows: "Beneficiary" (two levels: other vs. self), "Payoff" [two levels: high (10€) vs. low (2€)], and "Difficulty" [two levels: 13% motion coherence (difficult) vs. 15% coherence (easy)]. Beneficiary and Payoffs were overt factors, indicated by cues on each trial, but difficulty was not explicitly given to participants. During debriefing, we asked participants during debriefing how many difficulty levels they perceived. Most of them perceived two levels; only two of them thought there were more and one did not conscientiously perceived any. All *post hoc* analyses were performed using LSD Fisher tests. There was no effect of gender on behavior (**Supplementary Table 2**). Although there could be effects of sex hormone variations on decision making in young women, we did not record the phase of the menstrual cycle in our sample. All statistical analyses were performed using Statistica (STATISTICA®, Dell Inc., 2015), except for normality tests and DDM fitting, performed on MATLAB®.

Fitting the DDM to the Data

The DDM assumes that two-choice decisions are made by a noisy process that accumulates information over time from a starting point (z) toward one of two choice criteria or boundaries (here, corresponding to left and right response decision, respectively; **Figure 2A**). When one of the boundaries is reached, a response is initiated. The starting point and the decision boundaries are separated by distance (*a*). The evidence that drives the accumulation process, the drift rate (*v*), is derived from the representation of the stimulus. The better the quality of the evidence, the larger the drift rate toward the appropriate decision boundary, and the faster and more accurate the response (**Figure 2C**). The components of processing acting outside the decision process itself, such as encoding and response output, are combined in a single parameter: the non-decision time parameter (Ter). RT being the result of non-decision time added to the time it takes for accumulated evidence to reach one of the boundaries, and sensitivity coming from the reached boundary that determines which response is given, the model extracts the components of the decision process (values of drift rate, non-decision processes, and boundaries) from RT distribution and sensitivity data simultaneously.

For fitting the diffusion model to the data (Ratcliff and Tuerlinckx, 2002; Vandekerckhove and Tuerlinckx, 2007), we used the MATLAB Diffusion Model Analysis Toolbox [DMAT (Vandekerckhove and Tuerlinckx, 2008)]. The DMAT extracts the components of the decision process and their variability from RT distribution and sensitivity data from all trials for each condition. All trials, correct and error, are thus included in the DMAT parameter estimation. Parameters are estimated by maximizing a multinomial likelihood function. Left and right trials being equally distributed across the experiment (50% of trials for each direction, within each block), the underlying diffusion processes are supposed to be symmetric and no bias toward the left or right answer should arise. We ran a model where the starting point (z) was estimated independently from the decision boundary for the left and the right button presses separately. We then checked that z was not different between left and right responses using a one-way rmANOVA with response direction as factor. The analyses showed no effect of response direction ($F_{1,37}$ = 0.001; p = 0.971), ensuring that no bias emerged toward either the left or the right response. Consequently, we applied in all our models a starting point equal to half the distance between the left and right decision criteria (z = ½ a). Each model was fitted to the data separately for each participant.

The first model we ran allowed all three parameters to vary [the boundary (a), the drift (v), and the non-decision time (Ter)]. The estimated parameter values did not follow a normal distribution; we thus used a decimal logarithmic transformation and ensured it normalized their distribution using Lilliefors tests (**Supplementary Table 3**) before we applied the three-way rmANOVA. The three factors were the Beneficiary of the decision, the Payoff associated with the decision and the Difficulty (dots coherence). The boundary (a) and the non-decision time (Ter) showed no effect of any factor. We thus ran a model where only the drift (v) was free to vary across conditions. Once again, we analyzed log(v) using the same three-way rmANOVA. In order to compare the goodness of fit of our models, we also ran the intermediate models (either the drift and the boundary or the drift and the non-decision time were allowed to vary) and compared the sum of the individual Bayesian Information Criterion (BIC) of the models.

Data Availability

The data used in the present paper will be available to any reader after publication. The datasets generated and/or analyzed during the current study will be available in the repository, on a permanent free-access web link.

RESULTS

Participants performed a random dots (left/right direction categorization) task to win low or high payoffs, for themselves or for a close relative. RTs and sensitivity (d') were collected and analyzed using three-way rmANOVAs, with "Beneficiary" (two levels: Other vs. Self), "Payoff" (two levels: High vs. Low), and "Difficulty" (two levels: Difficult vs. Easy) as factors.

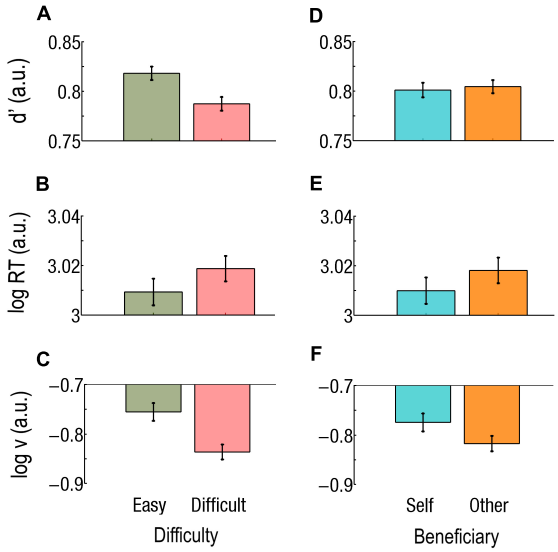


FIGURE 3 | (A–C) Main effect of difficulty. Easy trials are green and on the left, Difficult trials are red and on the right. **(A)** Sensitivity (d') is worse, **(B)** reaction times (RTs) are longer, and **(C)** drift rate (v) is lower during Difficult trials than during Easy trials. **(D–F)** Main effects of beneficiary. Self-affecting trials are cyan and on the left; other-affecting trials are orange and on the right. **(D)** Sensitivity did not differ but there was **(E)** a faster RT and **(F)** a higher drift rate (v) for Self than for Others. Log RT, d', and log v are expressed in arbitrary units (a.u.). Bars represent the standard errors of the mean (SEM).

Sensitivity (d')

Participants missed only one trial in the experiment. A main effect of task Difficulty was found; d' was better during Easy trials than during Difficult trials (d'_{Easy} = 0.82; $d'_{\text{Difficult}}$ = 0.79; $F_{1,37}$ = 57.4; p = 0.0000001; Cohen's d = 0.362; **Figure 3A**). All interaction effects also reached significance, including the triple interaction effect ($F_{1,37}$ = 16.8; p = 0.000220). We consequently ran two-ways rmANOVAs for each difficulty level, keeping Beneficiary and Payoff as factors.

During Easy trials, d' was better for Self than for Other (d'_{Self} = 0.83; d'_{Other} = 0.80; $F_{1,37}$ = 16.2; p = 0.000276; Cohen's d = 0.305; **Figure 4A**) and better for Low than for High Payoffs (d'_{Low} = 0.83; d'_{High} = 0.81; $F_{1,37}$ = 11.5; p = 0.001683; Cohen's d = 0.266; **Figure 4D**). During Difficult trials, both Beneficiary (d'_{Self} = 0.77; d'_{Other} = 0.80; $F_{1,37}$ = 24.7; p = 0.000015; Cohen's d = 0.375) and Payoff (d'_{Low} = 0.77; d'_{High} = 0.81; $F_{1,37}$ = 30.0; p = 0.000003; Cohen's d = 0.465) were significant. The Beneficiary*Payoff interaction also reached significance ($F_{1,37}$ = 19.9; p = 0.000072). Sensitivity for Self-affecting decisions associated with a Low Payoff was lower than for Other-affecting ones (d'_{Self} = 0.74; d'_{Other} = 0.80; p < 0.000001; Cohen's d = 0.780) and lower than when associated with a High Payoff (Self: d'_{High} = 0.80; Other: d'_{High} = 0.81; p < 0.000001; Cohen's d = 0.816; **Figure 5A**).

Reaction Times

The results presented here come from analyses performed on logarithmically transformed RTs (decimal logarithm), for correct

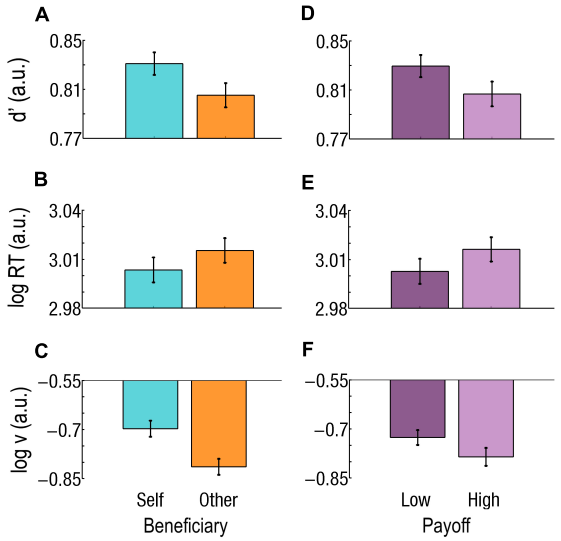


FIGURE 4 | Effect of beneficiary and payoff for easy trials only. **(A–C)** Beneficiary. Self-affecting trials are cyan and on the left; Other-affecting trials are orange and on the right. During Easy trials, **(A)** sensitivity (d') is better, **(B)** RTs are faster, and (C) drift rate (v) is higher for Self than for Other. **(D–F)** Effect of payoff. Low Payoffs are in deep purple and on the left; High Payoffs are in light purple and on the right. **(D)** Sensitivity (d') is better, **(E)** RT is faster, and **(F)** v is higher for Low than for High Payoffs. Log RT, d', and log v are expressed in arbitrary units (a.u.). Bars represent the standard errors of the mean (SEM).

and error trials separately. For intelligibility, the mean values in the following paragraph are given as non-transformed RT, in milliseconds (ms). Difficulty had an effect on log RT from errors, with subjects being slower during Difficult than during Easy trials ($RT_{Difficult}$ = 1146 ms; RT_{Easy} = 1110 ms; $F_{1,37}$ = 6.6; p = 0.0146; Cohen's d = 0.209). This was the only effect on RT from errors.

All the following results concern correct responses. We found a main effect of task Difficulty (**Figure 3B**) and a main effect of Beneficiary (**Figure 3E**) on log RT (for correct responses). That is, RTs were slower during Difficult than during Easy trials ($RT_{Difficult}$ = 1055 ms; RT_{Easy} = 1033 ms; $F_{1,37}$ = 36.56; $p < 0.001$; Cohen's d = 0.144) and slower for Other than for Self (RT_{Other} = 1054 ms; RT_{Self} = 1035 ms; $F_{1,37}$ = 18.86; $p < 0.001$; Cohen's d = 0.125). The triple interaction effect was not significant ($F_{1,37}$ = 0.22; p = 0.645). However, both the Beneficiary*Difficulty and the Payoff*Difficulty interaction effects reached significance ($F_{1,37}$ = 37.10; $p < 0.000001$ and $F_{1,37}$ = 4.26; p = 0.0461, respectively). Given the main effect of Difficulty, we then ran separate two-way rmANOVA at each Difficulty levels, keeping Beneficiary and Payoff as factors.

RTs were slower for Other than for Self, during Easy trials only (RT_{Other} = 1047 ms, RT_{Self} = 1020 ms, $F_{1,37}$ = 32.6; p = 0.000002; Cohen's d = 0.180; **Figure 4B**). Payoff had an effect at both Difficulty level, but with opposite direction. During Easy trials, RTs were slower for High than for Low Payoffs (RT_{High} = 1049 ms, RT_{Low} = 1017 ms, $F_{1,37}$ = 23.5; p = 0.000022; Cohen's d = 0.203; **Figure 4E**), while during Difficult trials, they were faster for High than for Low Payoffs (RT_{High} = 1045 ms, RT_{Low} = 1065 ms, $F_{1,37}$ = 21.53; p = 0.000043; Cohen's d = 0.142).

DDM Parameters

We started with the selection of the best-fitting model. The first model we ran allowed all three parameters [the boundary (a), the drift (v), and the non-decision time (Ter)] to vary. In this model ("full model"), the boundary (a) and the non-decision time (Ter) showed no effect of any of the three factors (Beneficiary, Payoff, and Difficulty). We thus applied a model where only the drift (v) was free to vary across conditions ("v free"). In order to compare the goodness of fit of our models, we also ran the intermediate models (either the drift and the boundary, "v free–a free," or the drift and the non-decision time, "v free–Ter free," were allowed to vary) and compared the sums of the individual BIC of the models. The model where only the drift (v) was allowed to vary showed a lower BIC than all other models (BIC sums: full model: 7.62×10^4, v free: 7.30×10^4; v free–a free: 7.46×10^4; v free–Ter free: 7.45×10^4). To ensure that this reflected individual fits, we also compared the BICs of the models within each individual. Thirty-six of 38 subjects were best fitted with the model where only the drift is allowed to vary ("v free"); the two other subjects were best fitted with the addition of modulations of the boundary a ("v free–a free"). Furthermore, we ran the simulations of the data predicted by the model using the estimated parameter, for each subject (**Supplementary Figure 1**).

We subsequently applied a three-way (Beneficiary, Payoff, and Difficulty) rmANOVAs on the drift parameter (v) from the "v free" model. Note that log(v) values are negative, so that higher absolute values of log(v) actually mean lower drift rates (v) of the decision variables. Difficulty had a main effect on the drift rate (v), which was higher during Easy than during Difficult trials [$\log(v)_{Easy} = -0.76$; $\log(v)_{Difficult} = -0.84$; $F_{1,37}$ = 35.9; p = 0.000001; Cohen's d = 0.503; **Figure 3D**]. Beneficiary also had a main effect, v being higher during Self- than during Other-affecting decisions [$\log(v)_{Self} = -0.78$; $\log(v)_{Other} = -0.82$; F = 4.42; p = 0.0423; Cohen's d = 0.273; **Figure 3F**]. The Beneficiary*Payoff interaction also reached significance ($F_{1,37}$ = 6.28; p = 0.01673). For decision associated with a High Payoff, v was higher for Self than for Other [$\log(v)_{Self} = -0.76$; $\log(v)_{Other} = -0.83$; p = 0.000078; Cohen's d = 0.385]. The Beneficiary*Difficulty and the Payoff*Difficulty interactions were significant ($F_{1,37}$ = 29.5; p = 0.0000004 and $F_{1,37}$ = 13.3; p = 0.000801, respectively). We consequently ran two-way rmANOVAs at each Difficulty level, keeping Beneficiary and Payoff as factors.

During Difficult trials, Payoff had a main effect [$\log(v)_{High} = -0.81$, $\log(v)_{Low} = -0.87$, $F_{1,37}$ = 9.28; p = 0.004265; Cohen's d = 0.409; **Figure 5C**], but the Beneficiary*Payoff interaction was also significant ($F_{1,37}$ = 8.80; p = 0.005251). Payoff actually had an effect only for Self-affecting decisions, with a higher drift (v) for High than for Low Payoffs [$\log(v)_{High} = -0.80$, $\log(v)_{Low} = -0.91$; p = 0.000045; Cohen's d = 0.592].

During Easy trials, both Beneficiary and Payoff had a main effect: the drift (v) was higher for Self than for Other [$\log(v)_{Self} = -0.70$; $\log(v)_{Other} = -0.81$; $F_{1,37}$ = 19.8; p = 0.000076; Cohen's d = 0.587] and higher for Low than for High Payoffs

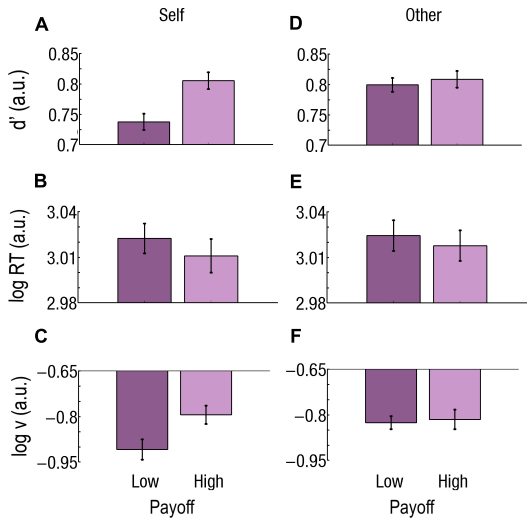


FIGURE 5 | Effect of payoff for difficult trials for self and close relative (other). **(A–C)** Effect of payoff for Self. **(A)** Sensitivity (*d'*) is lower, **(B)** reaction times (RTs) are slower, and **(C)** drift rate (*v*) is lower for Low Payoffs than for High Payoffs. **(D–F)** Effect of payoff for Other. There is no difference in **(D)** sensitivity (*d'*), **(E)** RT, or **(F)** *v* between Low and High Payoffs. Log RT, *d'*, and log *v* are expressed in arbitrary units (a.u.). Bars represent the standard errors of the mean (SEM).

$[\log(v)_{High} = -0.79, \log(v)_{\text{Low}} = -0.73, F = 6.18; p = 0.017588;$ Cohen's $d = 0.179]$.

DISCUSSION

Taking advantage of the DDM and the perceptual decision-making framework, we provided a mechanistic explanation of how others are integrated into the decisional process. Our results indicate that the beneficiary of the incentive associated with a decision modifies how decisions are performed. Decisions were faster for self than for others. As explained by the DDM, this was related to a higher drift rate (v) of the decision variable. In the present experiment, better sensitivity and faster RT were mirrored by higher drift rates. Higher drift rates have been found to explain shorter RT in tactile discrimination as well (Mulder and van Maanen, 2013). A change in the drift rate of the decision variable indicates a modification of the integration process itself, as branding does for economic value-based choices (Philiastides and Ratcliff, 2013). Our result indicates that sensory evidence is integrated faster for self than for others. In the example of the shooting range, if we aim to reach a target to win a price for a close relative, the decision process would not differ in the amount of evidence we would accumulate before making the decision to shoot, but rather in the efficiency of accumulation of the sensory evidence.

It may be that participants tried to imagine their relative receiving the payoff, although not instructed to do so. This would have required higher cognitive demands and redirect part of the attentional load and neuronal energy from the evidence accumulation process. Using the Game Theory and Public Good Games, studies show that taking into account another person into a decision engages the processes of *mentalizing* (or the Theory of Minds) (Frith and Singer, 2008; Stallen and Sanfey, 2013). It could also be that, when performing a self-affecting decision, more attentional resources are spent on the task (because of a higher motivation, due to direct self-benefit), thereby increasing the efficiency of evidence accumulation. In a study on value-based decision making combined with DDM, it has been suggested that, when choosing on behalf of another, a dual process takes place. Stimulus value integration, reflected in the drift rate (v), would be firstly computed based on self-preferences and then adjusted to the other's inferred preferences (Harris et al., 2018). For others with similar preferences, RTs were longer and linked to a change in drift rate. Analogous mechanisms could have occurred during our experiment as well. The importance accorded to the evidence, reflected in the drift rate (v) of the decision variable, could have been initially lower during other-affecting decisions, or it could have been re-adjusted during the time of the decision. Alternatively, RTs for dissimilar others were also longer but associated with a higher decision boundary (a), which could have been implemented to overcompensate for an increased uncertainty about their preferences (Harris et al., 2018).

Payoffs for others could have been integrated into the perceptual decision process through a change in the decision rules, outside of the mechanism of sensory evidence accumulation and change the distance between the starting point of the decision variable and the decision boundary. Other researchers also suggested that payoff can modify both stages, evidence accumulation and decision boundary. It postulates two processes, one for payoffs and another for stimulus information, and that on a given trial, attention is directed toward one of these information, never both (Diederich and Busemeyer, 2006; Diederich, 2008). Sequential-sampling models have previously been used to account for the effects of payoffs in a perceptual decision task with time constraints. These studies have reported changes in the distance from the starting point to the decision boundaries, a bias in the starting point of the decision variable, induced either by prior probabilities of being correct (Leite and Ratcliff, 2010; Mulder et al., 2012) or by asymmetrical payoffs associated with the possible response alternatives (Simen et al., 2009; Mulder et al., 2012). These changes were characterized by a shift of the starting point of the decision variable closer to the decision boundary associated with the alternative having the higher probability or associated with the higher payoff. The starting point is then further from the other boundary (for the other alternative at hand) and the decision variable is less likely to reach it, establishing a bias and a change in response proportion.

In contrast, our experimental setup was designed to avoid response probability manipulations toward one of the (left or right) alternatives, in terms of probability (through trials randomization) and in terms of payoff (by assigning the same payoff to both response alternatives). We aimed to compare identical decisions made by the participants, either for themselves or for another person. It would be interesting to adapt our paradigm to asymmetrical alternatives, with the

payoff going to one of the beneficiaries depending on the correct answer. Following our results, it could be expected that a bias toward the response associated with self-payoff would emerge. Finally, a variation in the non-decision time (Ter) would have indicated that the beneficiary-related motivation acts on cognitive mechanisms that are outside of the decision process itself, such as primary encoding of the stimuli and motor execution. Non-decision time is usually referred to as reflecting the early encoding of the stimulus of interest and the execution of the motor response, once the decision process is completed (Brainard, 1997; Frith and Singer, 2008; Ratcliff and McKoon, 2008; Philiastides and Ratcliff, 2013; Stallen and Sanfey, 2013), both external to the visuo-motor decision process in itself. Moreover, the non-decision time is thought to be necessary to account for speed–accuracy trade-offs (Mulder and van Maanen, 2013), and it has been shown that speed–accuracy instructions also modulate the non-decision time (Zhang and Rowe, 2014). Variation in the non-decision time can mean that different strategies are applied (Schuch, 2016) and could include other components that influence the decision-making processes. However, the DDM cannot distinguish between different mechanisms within the non-decision time.

This study is a first step toward a better comprehension of how others influence decision-making processes. Altogether, our results suggest that the beneficiary affected by the decision is integrated together with the sensory evidence into the decision variable and affect the efficiency of the accumulation process during perceptual decision making. The present work provides further evidence of the strength of sequential-sampling models in a unified theory of choices (Summerfield and Tsetsos, 2012; Polanía et al., 2014, 2015), with outcomes that are self-interested or vicarious. However, while the main effect of beneficiary was significant on RT and drift rate (v), when analyzing difficulty levels separately, the effect was not present during difficult trials. This may be attributed to the fact that sensory evidence was too low for the drift to be modulated. Although the study of payoff *per se* was not our main goal, it is puzzling to observe that its effect was reversed between the easy and difficult level. Further studies are needed to confirm both results. A future direction would also be to specify how social distance to others changes perceptual decisions, as previously investigated using economic games where participants chose between selfish and generous alternatives (Strombach et al., 2015).

ETHICS STATEMENT

All participants gave written informed consent and received 20€ for their participation. This study was approved by the local research ethics committee (Comité de Protection des Personnes Sud-Est III), all methods were performed in accordance with the relevant guidelines and regulations.

AUTHOR CONTRIBUTIONS

J-CD and LB designed the study and wrote the manuscript. LB collected the data and conducted the data analysis.

FUNDING

This research has benefited from the financial support of IDEXLYON from the Université de Lyon (project INDEPTH) within the program Investissements d'Avenir (ANR-16-IDEX-0005) and of the LABEX CORTEX (ANR-11-LABX-0042) of the Université de Lyon, within the program Investissements d'Avenir (ANR-11-IDEX-007) operated by the French National Research Agency. This work was carried out within the framework of the LABEX ANR-11-LABEX-0042 of the Université de Lyon, within the program "Investissements d'Avenir" (ANR-11-IDEX-0007) operated by the French National Research Agency (ANR). This work was also supported by grants from the Agence Nationale de la Recherche (ANR "Brain Choice" n°14-CE13-0006 and ANR "Social-POMDP" n°16-NEUC-0003-01) to J-CD.

ACKNOWLEDGMENTS

We thank Dr. Caroline Demily for medical screening of the participants.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2019.00142/full#supplementary-material

REFERENCES

Brainard, D. H. (1997). The psychophysics toolbox. *Spat. Vis.* 10, 433–436.

Diederich, A. (2008). A further test of sequential-sampling models that account for payoff effects on response bias in perceptual decision tasks. *Percept. Psychophys.* 70, 229–256.

Diederich, A., and Busemeyer, J. R. (2006). Modeling the effects of payoff on response bias in a perceptual discrimination task: bound-change, drift-rate-change, or two-stage-processing hypothesis. *Percept. Psychophys.* 68, 194–207.

Forstmann, B. U., Ratcliff, R., and Wagenmakers, E.-J. (2016). Sequential sampling models in cognitive neuroscience: advantages, applications, and extensions. *Annu. Rev. Psychol.* 67, 641–666. doi: 10.1146/annurev-psych-122414-033645

Frith, C. D., and Singer, T. (2008). The role of social cognition in decision making. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 363, 3875–3886. doi: 10.1098/rstb.2008.0156

Harris, A., Clithero, J. A., and Hutcherson, C. A. (2018). Accounting for taste: a multi-attribute neurocomputational model explains the neural dynamics of choices for self and others. *J. Neurosci.* 38, 7952–7968. doi: 10.1523/JNEUROSCI.3327-17.2018

Kawamichi, H., Tanabe, H. C., Takahashi, H. K., and Sadato, N. (2013). Activation of the reward system during sympathetic concern is mediated by two types of empathy in a familiarity-dependent manner. *Soc. Neurosci.* 8, 90–100. doi: 10.1080/17470919.2012.744349

Leite, F. P., and Ratcliff, R. (2010). Modeling reaction time and accuracy of multiple-alternative decisions. *Atten. Percept. Psychophys.* 72, 246–273. doi: 10.3758/APP.72.1.246

Mobbs, D., Yu, R., Meyer, M., Passamonti, L., Seymour, B., Calder, A. J., et al. (2009). A key role for similarity in vicarious reward. *Science* 324:900. doi: 10.1126/science.1170539

Mulder, M. J., and van Maanen, L. (2013). Are accuracy and reaction time affected via different processes? *PLoS One* 8:e80222. doi: 10.1371/journal.pone.0080222

Mulder, M. J., Wagenmakers, E.-J., Ratcliff, R., Boekel, W., and Forstmann, B. U. (2012). Bias in the brain: a diffusion model analysis of prior probability and potential payoff. *J. Neurosci.* 32, 2335–2343. doi: 10.1523/JNEUROSCI.4156-11.2012

Oppenheimer, D. M., and Kelso, E. (2015). Information processing as a paradigm for decision making. *Annu. Rev. Psychol.* 66, 277–294. doi: 10.1146/annurev-psych-010814-015148

Pelli, D. G. (1997). The videotoolbox software for visual psychophysics: transforming numbers into movies. *Spat. Vis.* 10, 437–442.

Philiastides, M. G., and Ratcliff, R. (2013). Influence of branding on preference-based decision making. *Psychol. Sci.* 24, 1208–1215. doi: 10.1177/0956797612470701

Polanía, R., Krajbich, I., Grueschow, M., and Ruff, C. C. (2014). Neural oscillations and synchronization differentially support evidence accumulation in perceptual and value-based decision making. *Neuron* 82, 709–720. doi: 10.1016/j.neuron.2014.03.014

Polanía, R., Moisa, M., Opitz, A., Grueschow, M., and Ruff, C. C. (2015). The precision of value-based choices depends causally on fronto-parietal phase coupling. *Nat. Commun.* 6:8090. doi: 10.1038/ncomms9090

Ratcliff, R., and McKoon, G. (2008). The diffusion decision model: theory and data for two-choice decision tasks. *Neural Comput.* 20, 873–922. doi: 10.1162/neco.2008.12-06-420

Ratcliff, R., Smith, P. L., Brown, S. D., and McKoon, G. (2016). Diffusion decision model: current issues and history. *Trends. Cogn. Sci.* 20, 260–281. doi: 10.1016/j.tics.2016.01.007

Ratcliff, R., and Tuerlinckx, F. (2002). Estimating parameters of the diffusion model: approaches to dealing with contaminant reaction times and parameter variability. *Psychon. Bull. Rev.* 9, 438–481.

Schuch, S. (2016). Task inhibition and response inhibition in older vs. younger adults: a diffusion model analysis. *Front. Psychol.* 7:1722. doi: 10.3389/fpsyg.2016.01722

Simen, P., Contreras, D., Buck, C., Hu, P., Holmes, P., and Cohen, J. (2009). Reward rate optimization in two-alternative decision making: empirical tests of theoretical predictions. *J. Exp. Psychol. Hum. Percept. Perform.* 35, 1865–1897. doi: 10.1037/a0016926

Stallen, M., and Sanfey, A. G. (2013). The cooperative brain. *Neuroscientist* 19, 292–303. doi: 10.1177/1073858412469728

Strombach, T., Weber, B., Hangebrauk, Z., Kenning, P., Karipidis, I. I., Tobler, P. N., et al. (2015). Social discounting involves modulation of neural value signals by temporoparietal junction. *Proc. Natl. Acad. Sci. U.S.A.* 112, 1619–1624. doi: 10.1073/pnas.1414715112

Summerfield, C., and Tsetsos, K. (2012). Building bridges between perceptual and economic decision-making: neural and computational mechanisms. *Decis. Neurosci.* 6:70. doi: 10.3389/fnins.2012.00070

Vandekerckhove, J., and Tuerlinckx, F. (2007). Fitting the ratcliff diffusion model to experimental data. *Psychon. Bull. Rev.* 14, 1011–1026. doi: 10.3758/BF03193087

Vandekerckhove, J., and Tuerlinckx, F. (2008). Diffusion model analysis with MATLAB: a DMAT primer. *Behav. Res. Methods* 40, 61–72.

Zhang, J., and Rowe, J. B. (2014). Dissociable mechanisms of speed-accuracy tradeoff during visual perceptual learning are revealed by a hierarchical drift-diffusion model. *Front. Neurosci.* 8:69. doi: 10.3389/fnins.2014.00069

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 02 July 2019
doi: 10.3389/fnbeh.2019.00147

Changes in Magnitude and Variability of Corticospinal Excitability During Rewarded Time-Sensitive Behavior

Makoto Suzuki[1], Takako Suzuki[2], Yin-Jung Wang[1] and Toyohiro Hamaguchi[2]*

[1]Faculty of Health Sciences, Tokyo Kasei University, Saitama, Japan, [2]School of Health Sciences, Saitama Prefectural University, Saitama, Japan

Reward expectation and time estimation are important for behavior and affect corticospinal excitability. This study investigated changes in corticospinal excitability during rewarded time-sensitive behavioral tasks. The rewarded time-sensitive task comprised three fixed-ratio (FR) schedules: FR_A contained a reward stimulus after every response, FR_B after every two responses, and FR_C after every four responses. The participants were instructed to press a left button with the index finger as quickly as possible in response to the appearance of a red circle. Just after the left button press, the word "10-yen" (approximately $0.1) or "no pay" was presented as feedback. Then, the participant had to mentally estimate/wait for 2.5 s from pressing the left button to pressing the right button. One second after the reward stimulus, transcranial magnetic stimulation (TMS) was delivered to the primary motor cortex at the hotspot of the first dorsal interosseous (FDI) muscle. Each participant received items corresponding to the total monetary reward accumulated at the end of the experiment. The variability of motor evoked potential (MEP) amplitudes transformed from a random process during the resting state into an autoregressive process during the rewarded time-sensitive behavioral task. Additionally, the random variation of MEP amplitudes in the FR_C, FR_B, and FR_A schedules increased in a stepwise fashion. However, the magnitude of MEP amplitudes significantly increased for the FR_B and FR_C schedules compared to the FR_A schedule. The time estimation lag was negative for the three FR schedules but there was no difference among the three FR schedules. The magnitude of corticospinal excitability increased in low reward probability, whereas the variability of corticospinal excitability transformed into an autoregressive process in high reward probability. These results imply that the magnitude and variability of expectation-related corticospinal excitabilities can be differentially altered by reward probability.

Keywords: reward, corticospinal excitability, behavior, schedule, magnetic stimulation

OPEN ACCESS

Edited by:
Jason M. Chein,
Temple University, United States

Reviewed by:
Anh Hai Tran,
Vietnam Military Medical University, Vietnam
Cedric L. Williams,
University of Virginia, United States

****Correspondence:***
Makoto Suzuki
maksuzu@gmail.com

Received: *26 January 2019*
Accepted: *18 June 2019*
Published: *02 July 2019*

Citation:
Suzuki M, Suzuki T, Wang Y-J and Hamaguchi T (2019) Changes in Magnitude and Variability of Corticospinal Excitability During Rewarded Time-Sensitive Behavior. Front. Behav. Neurosci. 13:147. doi: 10.3389/fnbeh.2019.00147

Abbreviations: FDI, first dorsal interosseous; FR, fixed ratio; MEP, motor evoked potential; RMT, resting motor threshold; TMS, transcranial magnetic stimulation.

INTRODUCTION

The interaction between time estimation and reward perception is crucial to execute behaviors in everyday life. The saying "time flies when we are having fun" refers to how reward influences brain activity during time-sensitive behavior. Previous studies have shown that time estimation and reward perception act by utilizing partially overlapping processing routes (Apaydin et al., 2018). Several brain areas are specialized in temporal processing including the striatum, supplementary motor area, and prefrontal cortex (Bueti et al., 2008; Coull et al., 2011; Üstün et al., 2017; Apaydin et al., 2018), and these brain areas influence M1 activity to execute time-sensitive behavior. Recent studies have indicated that dopamine regulates corticostriatal circuits, and dopamine signaling could modulate time estimation and time-sensitive behaviors (Wiener et al., 2014; Tomasi et al., 2015; Soares et al., 2016).

In human studies, because the corticospinal tract can be activated by transcranial magnetic stimulation (TMS), it has been suggested that the changes in the magnitude and variability of motor evoked potentials (MEPs) depend on M1 activity (Rösler, 2001). Monetary rewards increase MEP amplitudes for the rewarded behavior (Gupta and Aron, 2011; Kapogiannis et al., 2011; Thabit et al., 2011; Borgomaneri et al., 2014; Pisoni et al., 2014; Suzuki et al., 2014), but deprivation of reward as a penalty also increases MEP amplitudes (Suzuki et al., 2018). These observations suggest that reward probability is functionally related to the effectiveness of a reward stimulus, and reward-related signals modulate M1 motor output and MEPs. Especially, a previous study (Nosik and Carr, 2015) indicated that reward probability could momentarily change the value of a consequential reward stimulus, and this phenomenon is termed the "establishing operation." A previous study on the change in corticospinal excitability during reward tasks indicated that MEP amplitudes before reward stimuli were higher for low reward probability and suggested that this might be related to reward expectation (Suzuki et al., 2014). However, previous studies did not assess the variability of MEP amplitudes but only assessed the magnitude of corticospinal excitability. In addition, previous studies used observational settings without specific behavioral tasks (Kapogiannis et al., 2011; Pisoni et al., 2014) or behavioral tasks unrelated to time perception (Gupta and Aron, 2011; Thabit et al., 2011; Suzuki et al., 2014, 2018). Therefore, it is impossible to know whether expecting a reward or non-reward, based on reward probability, affects the magnitude and variability of corticospinal excitability during time-sensitive behavioral tasks and whether the observed reward-related corticospinal excitability changes are associated with time-sensitive behavioral changes. Therefore, although corticospinal excitability changes are associated with reward expectations, it remains unclear whether reward probabilities affect the magnitude and variability of expectation-related M1 excitability in the context of time-sensitive behavior. These are serious lacunae to elucidate the relationship between reward probability and MEP amplitude changes during time-sensitive behavioral tasks. In addition to expanding on previous findings, exploring how reward probabilities during time-sensitive behavioral tasks affect expectation-related corticospinal excitability may have interesting implications for behavioral science and neuroscience.

Because the temporal resolution of TMS is adequate for observing changes in corticospinal excitability during the rewarded time-sensitive behavioral tasks, we considered that changes in the magnitude and variability of MEPs would be observed using this technique during rewarded time-sensitive behavioral tasks. Therefore, we designed a paradigm involving high and low reward probabilities for time-sensitive behaviors. This paradigm facilitates the investigation of the magnitude and variability of M1 excitability in the context of reward expectation and time estimation. If corticospinal excitability and time estimation change in line with the "establishing operation," high reward probability contains low reward stimulus value, despite the amount of rewards being large, because high reward probability momentarily decreases the value of a consequential reward stimulus (Nosik and Carr, 2015). In contrast, low reward probability contains high reward stimulus value, despite the amount of rewards being small, because low reward probability momentarily increases the value of a consequential reward stimulus. This raises the question of whether the magnitude and variability of corticospinal excitability related to reward perception reflect the value or the amount of rewards during time-sensitive behavioral tasks. We predicted that if reward amount and value differentially affect M1 excitability, then reward probability should differentially alter the magnitude and variability of MEP amplitudes from the view point of the amount and value of the reward during time-sensitive behavioral tasks. We, therefore, used TMS to investigate expectation-related corticospinal excitation during time-sensitive behavioral tasks with high and low reward probability and to clarify how the magnitude and variability of corticospinal excitations would be altered by reward probability.

MATERIALS AND METHODS

Participants

We recruited 12 healthy participants [eight women and four men, aged 20–21 years, mean ± standard deviation (SD): 20.8 ± 0.4 years] for the behavioral and MEP amplitude measurements. Two participants only took part in the resting state experiments, four participants only in the behavioral experiments, and six participants in both the resting and behavioral experiments described below. No participant had risks of adverse events from TMS (Rossi et al., 2009) or used medication or had any psychiatric or neurological diseases. The Ethics Committee of the Saitama Prefectural University approved the experimental procedures, and the experiments were performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Electromyographic (EMG) Recordings

The skin above the first dorsal interosseous (FDI) muscle was cleaned with alcohol to reduce its electrical resistance.

Then, double differential surface electrodes (FAD-DEMG1, 4Assist, Tokyo, Japan) adhered on the skin for recording surface EMG activity from the FDI muscle in order to assess corticospinal excitability changes during the rewarded time-sensitive behavioral tasks. The EMG signals were amplified a hundredfold by a DL-140 amplifier (4Assist, Tokyo, Japan), bandpass filtered between 5 and 2,000 Hz and digitized at 10 kHz by a PowerLab system (ADInstruments, Dunedin, New Zealand), and stored on magnetic media.

TMS

A figure-eight coil (internal diameter of each wing: 70 mm) on the subject's scalp and a Magstim 200^2 stimulator (Magstim, Whitland, UK) delivered TMS to the scalp *via* the coil. The coil handle was held approximately 45° to the midline and tangentially to the scalp, thereby a current was induced from the posterolateral to the anteromedial left brain. We determined the appropriate coil position to elicit MEPs in the FDI muscle, and this position was termed the "hotspot" by moving the coil on the left side of the scalp. Then, the hotspot was marked by a soft-tipped pen. The coil was fixed at the hotspot throughout this experiment. The resting motor threshold (RMT) at the hotspot of the relaxed FDI muscle was determined to elicit a MEP of at least 0.05 mV in 5 out of 10 consecutive trials.

Resting State Experiment

Following excitation of cortical neurons by TMS over the M1, multiple descending volleys are temporally and spatially summated in corticospinal neurons (Rösler, 2001). A previous study (Kiers et al., 1993) noted that MEP amplitudes, shapes, and sizes randomly fluctuated between stimuli. We, therefore, conducted a resting state experiment to confirm the fluctuation of MEP amplitudes. Each participant sat comfortably with their right hand resting on the table throughout the resting state experiment. The MEPs for the FDI muscle were evoked by 20 TMS of 120% of the RMT at the hotspot (the interstimulus interval was 5 s).

Behavioral Experiment

The behavioral experiment was carried out on a different day from the resting state experiment. Previous experiments using reward tasks (Gupta and Aron, 2011; Thabit et al., 2011; Suzuki et al., 2014, 2018) carried out 18–100 trials per condition. Therefore, the time-sensitive reward task comprised three fixed-ratio (FR) schedules of 50 trials per schedule; the 50 trials of the FR_A schedule contained a reward stimulus delivered after every response, the 50 trials of the FR_B schedule contained a reward stimulus delivered after every two responses, and the 50 trials of the FR_C schedule contained a reward stimulus delivered after every four responses. The order of the three FR schedules was randomized for counterbalancing purposes. The participants were not aware of the reward probabilities and the order of the schedules. The reward probabilities were predetermined.

Each participant sat comfortably in front of a 27.5 × 31.0 cm screen located approximately (mean ± SD) 66.9 ± 6.5 cm from the face at 11.3 ± 4.7° downward from the eye level with the right palm and forearm resting on the test equipment with two buttons located 4.0 cm apart parallel to the coronal plane (**Figure 1A**). The left button was pressed with the index finger as quickly as possible after a red circle cue was presented. The red circle cues were presented on the screen at random intervals of 5–6 s (**Figure 1B**). The participant was instructed to press the left button with the index finger as quickly as possible in response to the appearance of the red circle. Just after the button press, the word "10-yen" or "no pay" was presented for 1 s as feedback. The word "10-yen" denoted 10 Japanese yen (approximately $0.1). In the FR_A schedule, the word "10-yen" or "no pay" would be presented in 100% (50 reward stimuli in 50 presses of the left button) and 0% (zero no-reward stimuli in 50 presses of the left button) of trials, respectively. In the FR_B schedule, the word "10-yen" or "no pay" would be presented in 50% (25 reward stimuli in 50 presses of the left button) and 50% (25 no-reward stimuli in 50 presses of the left button) of trials, respectively. In the FR_C schedule, the word "10-yen" or "no pay" would be presented in 26% (13 reward stimuli in 50 presses of the left button) and 74% (37 no-reward stimuli in 50 presses of the left button) of trials, respectively. Schultz (2007) noted that dopamine concentrations were greatest at 1 s after the presentation of a reward stimulus and returned to baseline after approximately 4 s. Borgomaneri et al. (2012) noted that corticospinal excitability increased at least 300 ms after the presentation of pictures representing negative emotion. Thabit et al. (2011) noted that corticospinal excitability increased 1 s after the presentation of a reward stimulus for 3- to 4-s intervals. We set the delivery time of TMS and inter-trial interval in our protocol in consideration of the previous studies' time courses and delivered TMS of 120% of the FDI's RMT 1 s after pressing the left button. Then, the participant had to mentally estimate/wait for 2.5 s from pressing the left button to pressing the right button. Therefore, 50 TMSs were delivered in each FR schedule because the participants pressed the left button iteratively 50 times after the reward or no-reward stimulus. This ensured that the magnitude and variability of corticospinal excitability reflected the expectation of reward or non-reward during time-sensitive behavioral tasks. Each participant received items corresponding to a total of 870 Japanese yen (approximately $8.7) as reward accumulated at the end of the experiment.

Data Analysis

To facilitate investigations of intraindividual MEP variability during the time-sensitive reward task, the MEP data were normalized by linear transformation. The normalized MEP data are expressed as Z scores. We predicted that TMS over the M1 would naturally induce a random fluctuation of MEP amplitudes and that time-oriented reward perception would transform activity of the M1 *via* corticospinal excitability from a random process into an autoregressive process because the autoregressive process could indicate that the MEP amplitude was affected not by random fluctuation but by the preceding MEP amplitudes related to reward or no-reward stimuli from the previous trials. Therefore, a state-changing model was

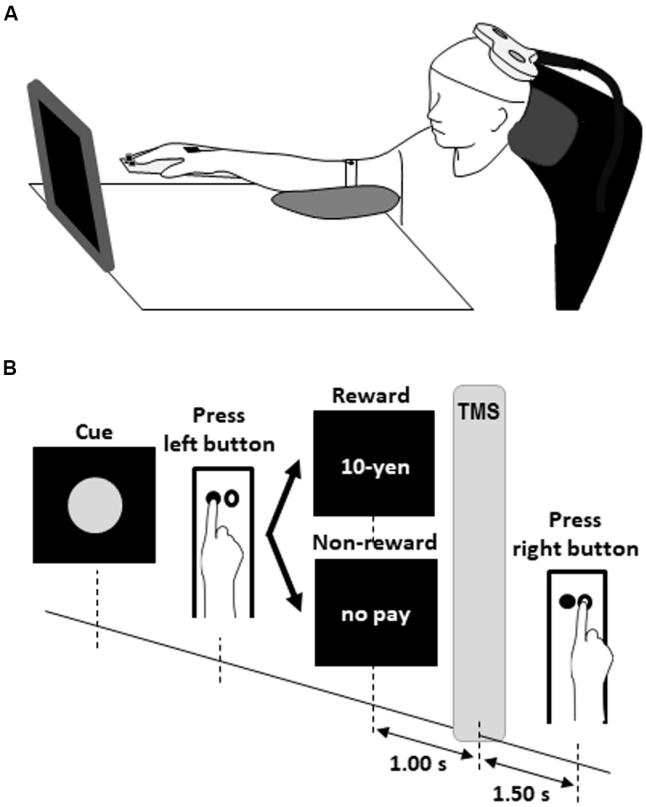


FIGURE 1 | Experimental design for the rewarded time-sensitive behavioral task. Each participant sat comfortably in front of a screen with the right palm and forearm resting on the test equipment with two buttons **(A)**. The left button was pressed with the index finger as quickly as possible after a red circle cue was presented **(B)**. Just after the left button press, the word "10-yen" or "no pay" was presented for 1 s as feedback. The word "10-yen" denoted 10 Japanese yen (approximately $0.1). Then, the participant had to mentally estimate/wait for 2.5 s from pressing the left button to pressing the right button. Single-pulse TMS of 120% of the FDI's RMT was delivered 1 s after pressing the left button. TMS, transcranial magnetic stimulation; FDI, first dorsal interosseous; RMT, resting motor threshold.

constructed, which included trend, autoregressive, and random fluctuation processes to distinguish between inherent MEP changes by the reward stimulus and MEP random fluctuation as follows:

$$f(t) = \alpha + \beta t + \sum_{i=1}^{p} \phi_i x_{t-i} + \varepsilon_t \quad (1)$$

where α is the y-intercept of the MEP amplitude, reflecting initial corticospinal excitability; β is the MEP amplitude slope, reflecting changes in corticospinal excitability; ϕ and x are the coefficient and previous reference MEP amplitudes of the autoregressive model, reflecting the temporal dependance structure of a time series; ε_t is the random variation, reflecting the inherent fluctuation of MEPs; i is the order of the model, and t is the number of TMS deliveries during the time-sensitive reward task. By the least-squares method, each participant's data were fitted to the model. If the model is applicable, the series of values of ε_t in Equation (1) should be uncorrelated to each other (i.e., independence). Therefore, we assessed the applicability of the model with the Ljung–Box test to measure the independence of ε_t as a white noise and residuals process. The following equation was used for the Ljung–Box test.

$$Q(h) = n(n+2)\sum_{i=1}^{h} \frac{\widehat{\rho_i}^2}{n-i} \quad (2)$$

where n is the sample size ($\widehat{\rho_i}$) is the sample autocorrelation at lag i, and h is the number of lags being tested. Thus, the data eliminate inherent fluctuations of MEPs, permitting the evaluation of whether reward probability affects corticospinal excitability during time-sensitive behavioral tasks. Differences in the MEP amplitudes eliminating inherent fluctuations between three FR schedules and 50 trials were compared by two-way repeated measures analysis of variance (ANOVA). *Post hoc* testing with Bonferroni correction was performed to compare differences in MEP amplitudes among the three FR schedules. We also compared the MEP amplitudes across trials following presentation of the word "10-yen" or "no-pay" to assess the effect of the immediately preceding reward or no-reward stimulus on expectation-related corticospinal excitability by unpaired *t*-test. Moreover, the permutated Brunner–Munzel test was performed to carefully assess intra- and inter-individual changes for small sample data because the asymptotic permutational

distribution of this test using the central limit theorem can deduce the standard normal distribution and accurate p-value (Fagerland et al., 2011). Response time was calculated as the elapsed time between the left and the right button presses. The time lag between the absolute target time (2.5 s) and subjective response time (the elapsed time between the left and right button presses) was calculated for each trial for each participant to predict change in the participant's time estimation. To assess group changes, we compared time estimation data based on the response time across the FR schedules using one-way ANOVA. In addition, we compared the time estimation lag across trials immediately preceding a reward ("10-yen") or no-reward ("no-pay") stimulus by unpaired t-test and the permutated Brunner–Munzel test. We defined statistical significance as $p < 0.05$. All statistical analyses were performed with R 3.4.0 software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

No participant had adverse TMS-related effects in any experiment.

Corticospinal Excitability During the Resting State

The mean ± standard errors of MEP amplitudes of the FDI muscle during the resting state was 0.94 ± 0.06 mV. **Figure 2A** shows the time course of changes in FDI MEP amplitudes in the resting state. **Figures 2B,C** show the random fluctuation of MEP amplitudes [ε_t value in Equation (1)] and the MEP amplitudes eliminating inherent random fluctuations, respectively. **Table 1** shows the α, β, p, and ϕ values in Equation (1) for the resting state. Two of eight (25.0%) participants' α values were positive, and six of eight (75.0%) participants' α values were negative. However, six of eight (75.0%) participants' β values were positive and two of eight (25.0%) participants' β values were negative. **Figure 2D** shows the time-series plots of the decomposed mean MEP amplitudes during the resting state. **Figure 2A** indicates that the raw MEP amplitude increases and decreases during trials, whereas **Figures 2C,D** indicate that the MEP amplitudes eliminating inherent fluctuations (ε_t) were generally stable. Based on the p parameter estimation of Equation (1), in seven of eight (87.5%) participants, the p-value of the model was 0, which indicates that the errors were uncorrelated across time. In one of eight (12.5%) participants, the p-value

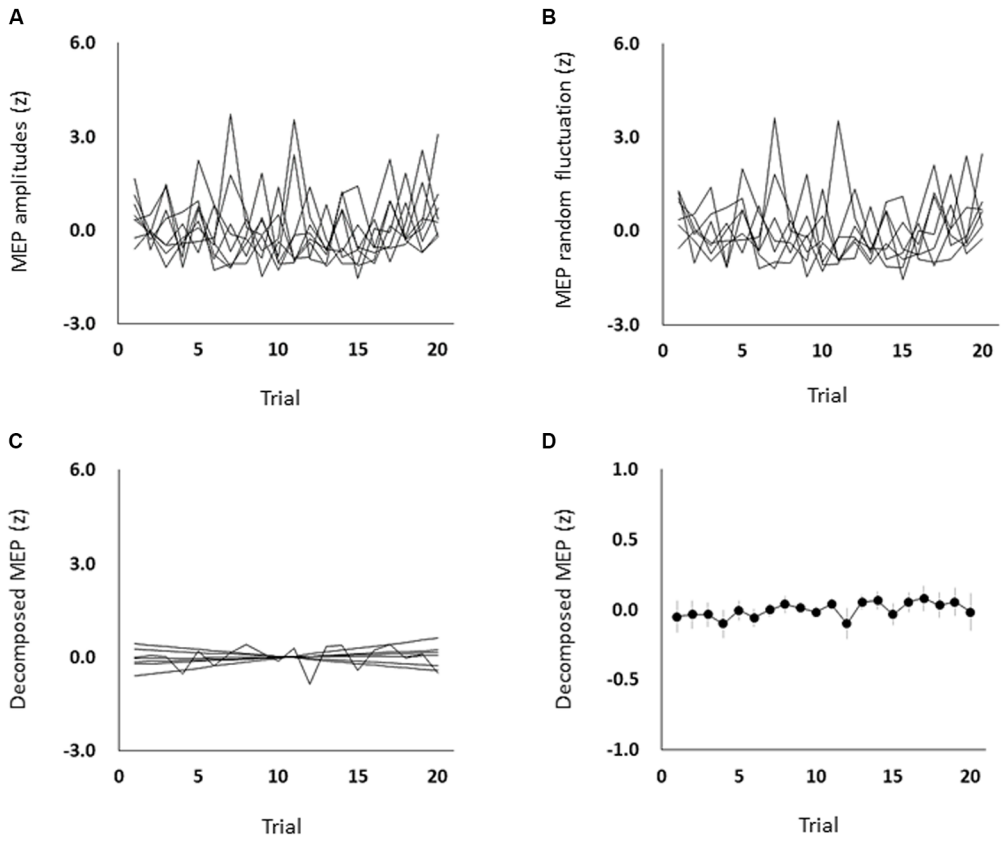


FIGURE 2 | The time course of changes in each participant's MEP amplitudes **(A)**, each participant's MEP random fluctuation **(B)**, each participant's MEP amplitudes eliminating random fluctuation **(C)**, and the mean MEP amplitudes eliminating random fluctuation **(D)** during the resting state. The symbols and error bars denote means and standard errors of the mean, respectively. Raw MEP amplitude changes across trials were jumbled, whereas MEP amplitudes eliminating random fluctuations were generally stable. MEP, motor-evoked potential.

TABLE 1 | Assessment of the model fit in the resting state experiment.

Participants	Trend term		AR term		Box-Ljung test	
	α	β	$p^{\#}$	ϕ	χ^2	p^*
1	−0.25	0.02	0	-	0.64	0.43
2	−0.67	0.06	0	-	0.18	0.67
3	−0.02	0.00	1	−0.3569	2.82	0.09
4	−0.17	0.02	0	-	0.08	0.77
5	0.29	−0.03	0	-	0.30	0.59
6	0.48	−0.05	0	-	0.41	0.52
7	−0.05	0.00	0	-	1.56	0.21
8	−0.05	0.00	0	-	0.34	0.56
Total	−0.13 ± 0.10	0.01 ± 0.01				

*MEP, motor evoked potential; FR, fixed-ratio; AR, autoregressive. #p value of the Equation (1). *p value of the Ljung-Box test.*

of the model was 1, indicating an autoregressive process with a 1-bin time lag and that previous corticospinal excitability affected the variability of corticospinal excitability. The Ljung–Box test showed that the series of ε_t of the model was independent in eight of eight (100%) participants, which indicates that the model was efficient.

Corticospinal Excitability During the Time-Sensitive Behavioral Tasks

All subjects completed all experimental conditions. Erroneous button presses did not occur during the experiments. **Table 2** shows the MEP amplitudes obtained from the FDI muscle during the three FR schedules. **Figure 3** shows the time courses of changes in FDI MEP amplitudes during the three FR schedules. **Table 3** shows the differences in α, β, p, and ϕ values for the three FR schedules. The α values were almost the same across the three FR schedules; 4 of 10 (40.0%) participants' α values were positive for the FR_A schedule, five of 10 (50.0%) participants' α values were positive for the FR_B schedule, and 4 of 10 (40.0%) participants' α values were positive for the FR_C schedule. However, the β values were higher for the FR_B and FR_C schedules than for the FR_A schedule; five of 10 (50.0%) participants' β values were positive for the FR_A schedule, seven of 10 (70.0%) participants' β values were positive for the FR_B schedule, and eight of 10 (80.0%) participants' β values were positive for the FR_C schedule. **Figure 4A** shows the time-series plots of the decomposed mean MEP amplitudes during the rewarded time-sensitive behavioral tasks. Two-way repeated measures ANOVA showed that there was no significant interaction effect in the three FR schedules and 50 trials (F = 0.267, p = 0.769). This allowed us to pool the MEP amplitudes measured from the FDI muscle in the three FR schedules. *Post hoc* Bonferroni correction showed that the MEP amplitudes obtained for the FDI muscle significantly increased for the FR_B and FR_C schedules compared to the FR_A schedule (FR_A vs. FR_B, $p < 0.0001$; FR_A vs. FR_C, $p < 0.0001$; FR_B vs. FR_C, p = 1.000; **Figure 4B**). In addition, the permutated Brunner–Munzel test also showed that the MEP amplitudes for the FDI muscle in the FR_B and FR_C schedules were significantly greater than those in the FR_A schedule (FR_A vs. FR_B, $p < 0.0001$; FR_A vs. FR_C, $p < 0.0001$), but no such difference was observed between the FR_B and FR_C schedules (p = 0.812; **Figure 4B**). However, unpaired t-tests showed that there were no significant differences in MEP amplitudes immediately preceding the reward ("10-yen") or no-reward ("no-pay") stimulus in any FR schedule (FR_A, p = 0.746; FR_B, p = 0.758; FR_C, p = 0.969; **Figures 4C–E**). The permutated Brunner–Munzel test also showed that there were no significant differences in MEP amplitudes immediately preceding the reward ("10-yen") or no-reward ("no-pay") stimulus in any FR schedule (FR_A, p = 0.925; FR_B, p = 0.617; FR_C, p = 0.986). Based on the p parameter estimation of Equation (1), a 0 p-value was more frequent in the FR schedules of lower reward probability; three of 10 (30.0%) participants' p-values were 0 in the FR_A schedule, 4 of 10 (40.0%) participants' p-values were 0 in the FR_B schedule, and seven of 10 (70.0%) participants' p-values were 0 in the FR_C schedule. The Ljung–Box test showed that the series of ε_t values in Equation (1) was independent in 10 of 10 (100%) participants for the three FR schedules.

TABLE 2 | MEP amplitudes corresponding to the FR schedules.

Subjects	MEP amplitudes (mV)		
	FR_A	FR_B	FR_C
1	1.51 ± 0.03	1.63 ± 0.04	1.63 ± 0.04
2	3.99 ± 0.20	2.80 ± 0.15	2.39 ± 0.00
3	5.30 ± 0.12	6.63 ± 0.19	4.47 ± 0.14
4	1.30 ± 0.05	0.74 ± 0.03	1.13 ± 0.04
5	3.07 ± 0.20	2.08 ± 0.13	2.84 ± 0.20
6	4.40 ± 0.15	2.88 ± 0.28	3.88 ± 0.27
7	1.00 ± 0.08	1.27 ± 0.09	1.14 ± 0.07
8	1.21 ± 0.07	0.66 ± 0.04	0.60 ± 0.04
9	3.03 ± 0.06	3.09 ± 0.07	2.11 ± 0.14
10	1.77 ± 0.11	2.29 ± 0.21	3.66 ± 0.18
Total	2.65 ± 0.08	2.41 ± 0.09	2.38 ± 0.07

Values are mean ± standard error of the mean. MEP, motor-evoked potential; FR, fixed-ratio

Time Estimation During the Time-Sensitive Behavioral Tasks

The time lag between absolute target time and subjective response time was −0.35 ± 0.02 ms for the FR_A schedule, −0.18 ± 0.03 ms for the FR_B schedule, and −0.32 ± 0.03 ms for the FR_C schedule. Although the time lag was negative in all three FR schedules, one-way ANOVA showed that there were no significant differences among the FR schedules (F = 0.458, p = 0.499; **Figures 5A,B**). Additionally, unpaired t-tests showed

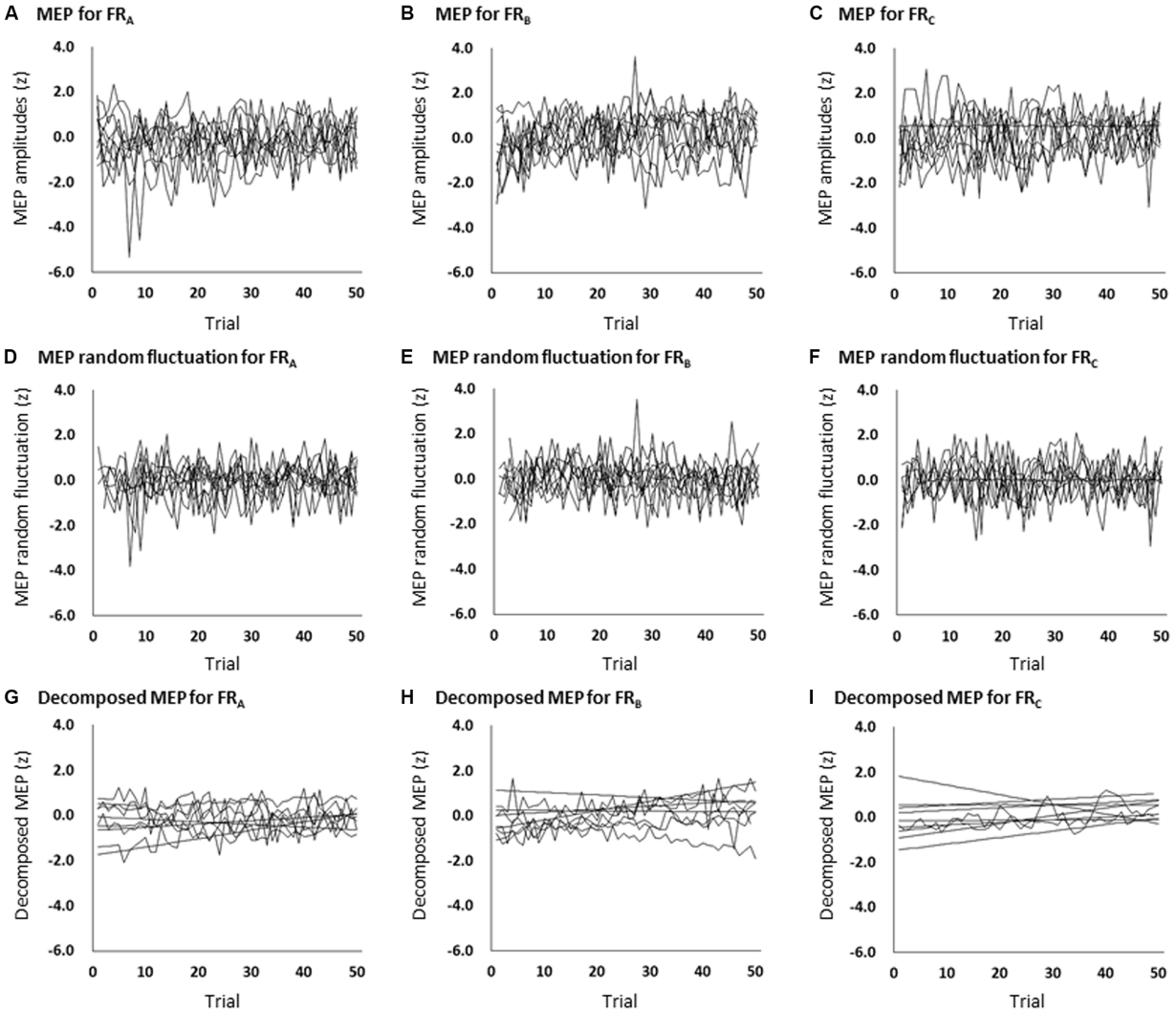


FIGURE 3 | The time course of changes in each participant's MEP amplitudes during the FR_A **(A)**, FR_B **(B)**, and FR_C **(C)** schedules; each participant's MEP random fluctuation during the FR_A **(D)**, FR_B **(E)**, and FR_C **(F)** schedules; and each participant's MEP amplitudes eliminating random fluctuation during the FR_A **(G)**, FR_B **(H)**, and FR_C **(I)** schedules. The slopes (β values) were higher for the FR_B and FR_C schedules than for the FR_A schedule. MEP, motor-evoked potential; FR, fixed-ratio.

that there were no significant differences in the time estimation lag immediately preceding the reward ("10-yen") or no-reward ("no-pay") stimulus in any FR schedule (FR_A, $p = 0.483$; FR_B, $p = 0.964$; FR_C, $p = 0.992$; **Figures 5C–E**). The permutated Brunner–Munzel test also showed that there were no significant differences in MEP amplitudes immediately preceding the reward ("10-yen") or no-reward ("no-pay") stimulus in any FR schedule (FR_A, $p = 0.384$; FR_B, $p = 0.982$; FR_C, $p = 0.894$).

DISCUSSION

To test the hypothesis that reward amount and value should differentially affect the magnitude and variability of corticospinal excitability, we measured changes in the magnitude and variability of the MEP amplitude related to reward expectation during a time-sensitive behavioral task. Our results showed that: (a) the variability of expectation-related MEP amplitudes transformed from a random process during the resting state into an autoregressive processes during the time-sensitive behavioral task; (b) the random variation of MEP amplitudes in the FR_C, FR_B, and FR_A schedules decreased in a stepwise fashion; (c) the magnitude of the MEP amplitudes increased for the FR_B and FR_C schedules compared to the FR_A schedule; and (d) the time estimation lag was negative for and similar among the three FR schedules. These observations show that reward probability modulated M1 motor output and MEPs. In fact, although the magnitude of the MEP amplitudes was higher in low reward probability (FR_C schedule) than in high reward probability (FR_A schedule), the variability of the MEP amplitudes was transformed into a time-varying autoregressive process by high reward probability (FR_A schedule) rather than by low reward probability (FR_C schedule).

TABLE 3 | Assessment of the model fit.

Subjects	Trend term		$p^{\#}$	AR term	Box-Ljung test	
	α	β		ϕ	χ^2	p^*
A. FR_A schedule						
1	0.76	−0.017	4	0.42, −0.32, 0.31, −0.28	3.85	0.050
2	−1.43	0.027	5	0.23, −0.08, −0.25, 0.33, −0.29	0.42	0.519
3	0.27	−0.006	2	−0.12, −0.36	0.40	0.527
4	−0.41	−0.010	1	0.28	0.04	0.850
5	−0.67	0.014	0	-	0.14	0.707
6	−0.49	0.005	8	−0.26, −0.19, −0.23, −0.19, 0.08, −0.15, −0.25, −0.32	0.75	0.388
7	0.53	−0.011	8	0.15, −0.11, 0.14, 0.37, 0.04, −0.14, −0.13, −0.32	2.85	0.091
8	−1.78	0.037	0	-	0.18	0.674
9	−0.06	−0.012	0	-	1.11	0.291
10	0.29	0.010	1	0.22	2.53	0.112
Total	−0.30 ± 0.26	0.00 ± 0.01				
B. FR_B schedule						
1	−0.50	0.013	2	0.19, 0.33	0.04	0.850
2	0.25	−0.002	0	-	0.20	0.654
3	0.00	−0.032	1	−0.23	2.92	0.087
4	1.15	−0.011	0	-	1.54	0.215
5	0.43	0.001	2	−0.15, 0.23	1.92	0.166
6	−0.60	0.042	0	-	0.78	0.378
7	−0.82	0.023	1	0.25	3.17	0.075
8	0.02	0.014	0	-	0.06	0.807
9	−0.63	0.008	2	−0.16, −0.33	0.69	0.405
10	−1.11	0.051	3	0.27, −0.31, 0.31	1.23	0.267
Total	−0.18 ± 0.21	0.01 ± 0.01				
C. FR_C schedule						
1	−0.47	0.012	0	-	0.65	0.420
2	0.55	−0.0002	5	0.04, 0.14, 0.16, −0.31, 0.20	0.24	0.626
3	0.40	0.013	0	-	0.70	0.404
4	−0.36	0.007	1	0.23	2.73	0.098
5	−0.15	0.0004	0	-	1.08	0.300
6	−0.94	0.034	0	-	0.12	0.725
7	−0.63	0.024	7	0.12, −0.03, −0.19, −0.27, −0.13, −0.15, −0.27	0.03	0.856
8	0.19	0.012	0	-	0.01	0.943
9	1.86	−0.043	0	-	0.57	0.449
10	−1.48	0.03	0	-	0.06	0.804
Total	−0.10 ± 0.29	0.01 ± 0.01				

*MEP: motor evoked potential; FR: fixed-ratio; AR: autoregressive. #p value of the Equation (1). *p value of the Ljung-Box test.*

This implies that reward probability does not equally affect the magnitude and variability of corticospinal excitability. To our knowledge, this is the first systematic study to report that reward probabilities change the magnitude and variability of expectation-related corticospinal excitabilities during time-sensitive behavior.

Many areas including the ventral tegmental area, striatum, supplementary motor area, and prefrontal cortex influence M1 activity in terms of reward processing (Wickens et al., 2003; Haruno et al., 2004; Campos et al., 2005; Ikemoto, 2007; Hikosaka et al., 2008). In addition, similar brain areas are also specialized in temporal processing including the striatum, supplementary motor area, and prefrontal cortex (Bueti et al., 2008; Macdonald et al., 2012; Failing and Theeuwes, 2016; Apaydin et al., 2018). Dopamine neurons connect to the striatum and prefrontal cortex (Haber and Knutson, 2010; Averbeck et al., 2014; Haber, 2016). In addition, the prefrontal cortex connects to the supplementary motor area (Goldman-Rakic, 1987); thus, prefrontal input is provided from dopamine neurons to the supplementary motor area, which in turn connects to the M1. Moreover, a retrograde tracing study found that approximately 70% of dopamine neurons in the midbrain projected to the M1 (Hosp et al., 2011). Previous studies have suggested that bursts of dopaminergic activity in the midbrain serve as time perception (Soares et al., 2016). These previous findings regarding neural networks and physiological mechanisms suggested that overall coactivation of the corticostriatal circuit including the ventral tegmental area, striatum, supplementary motor area, and prefrontal cortex might reveal the time perception and reward processing through direct and indirect projections of dopaminergic and glutamatergic neurons, and these circuits may influence corticospinal excitability *via* the M1. In our study, TMS was delivered 1 s after the presentation of reward or no-reward stimuli in accordance with the previous studies' time courses regarding dopamine concentration and corticospinal excitation by reward presentation (Schultz, 2007; Thabit et al., 2011).

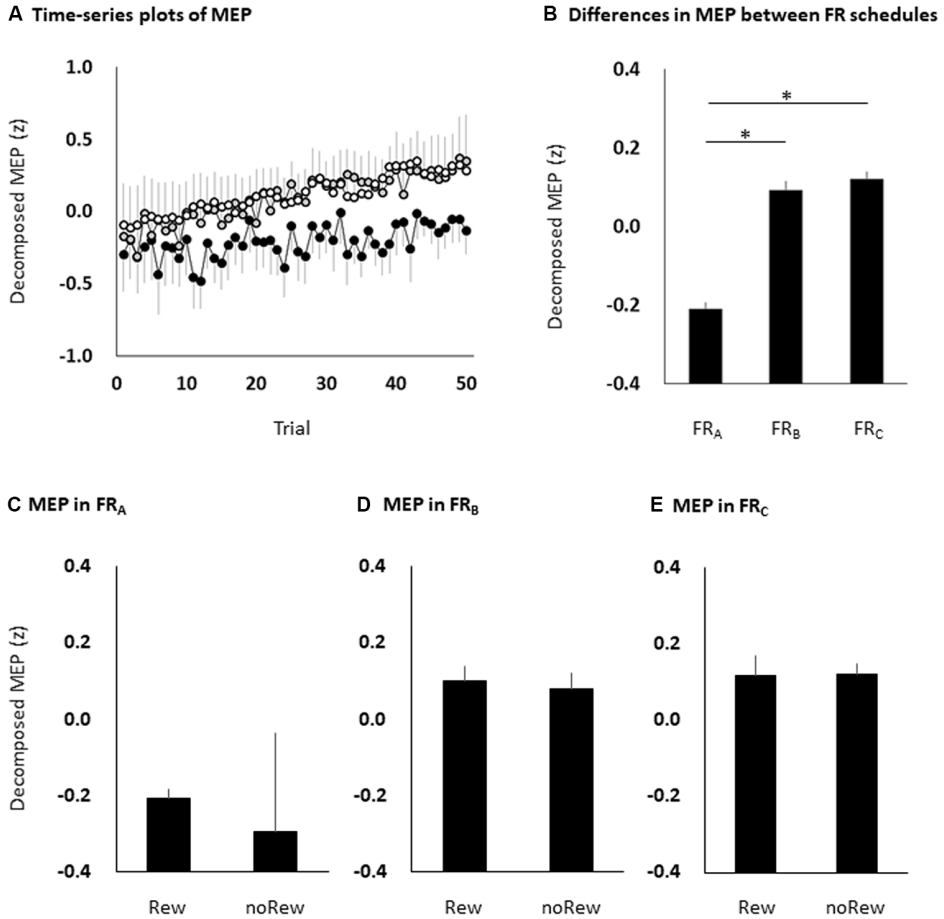


FIGURE 4 | The time course of changes in MEP amplitudes eliminating random fluctuation in the three FR schedules **(A)**, bar graphs of MEP amplitudes to pool the data for the three FR schedules **(B)**, and the MEP amplitudes of the immediately preceding reward or no-reward stimulus in the FR_A **(C)**, FR_B **(D)** and FR_C **(E)** schedules. The black (FR_A), grey (FR_B) and white (FR_C) symbols and error bars **(A)** denote means and standard errors of the mean, respectively. The columns and error bars **(B–E)** denote the means and standard errors of the mean, respectively. Two-way repeated measures ANOVA showed that there was no significant interaction effect in the three FR schedules and 50 trials ($F = 0.267$, $p = 0.769$). *Post hoc* Bonferroni correction showed that the MEP amplitudes obtained for the FDI muscle significantly increased for the FR_B and FR_C schedules compared to the FR_A schedule (FR_A vs. FR_B, $^*p < 0.0001$; FR_A vs. FR_C, $^*p < 0.0001$; FR_B vs. FR_C, $p = 1.000$; **B**). However, there were no significant differences in MEP amplitudes immediately preceding the reward or no-reward stimulus in any FR schedule (unpaired *t*-tests, FR_A, $p = 0.746$; FR_B, $p = 0.758$; FR_C, $p = 0.969$; **C–E**). MEP, motor-evoked potential; FR, fixed-ratio; ANOVA, analysis of variance; Rew: presentation of reward ("10-yen") in the immediately preceding trial; noRew: presentation of no-reward ("no-pay") in the immediately preceding trial.

This experimental setup allowed us to investigate changes in the magnitude and variability of MEPs during rewarded time-sensitive behavioral tasks. In our study, the magnitudes of the MEP amplitudes before reward presentation increased for low reward probability. This is the first novel observation of our study. Although the exact mechanism for high MEP amplitudes for low reward probability were not identified, we predict that M1 excitability during the time-sensitive behavioral task could have been influenced by reward probability. One possibility is that the activities of many brain regions, including the ventral tegmental area, striatum, supplementary motor area, and prefrontal cortex may affect M1 activity with different gains according to reward probability. Especially, recent research findings have suggested that low reward probability, rather than high reward probability, increases the number of behaviors (Derosa et al., 2015; Fisher et al., 2018). This phenomenon termed the "establishing operation" occurs as a result of low reward probability momentarily increasing the value of a consequential reward stimulus (Derosa et al., 2015; Nosik and Carr, 2015; Fisher et al., 2018). In addition, previous studies have suggested that low reward probabilities (Suzuki et al., 2014), upsetting images (Oliveri et al., 2003; Coelho et al., 2010; Borgomaneri et al., 2012), and unexpected penalties also increase corticospinal excitability (Suzuki et al., 2018). These may imply that M1 excitation may increase in line with the "establishing operation" or with no-reward in low reward probability. However, the MEP amplitudes immediately preceding the reward ("10-yen") or no-reward ("no-pay") stimulus did not differ in any of the three FR schedules. Therefore, changes in M1 excitability related to reward probability might be affected by the global reward signal throughout each FR schedule. To clarify this, further research is needed on the time course

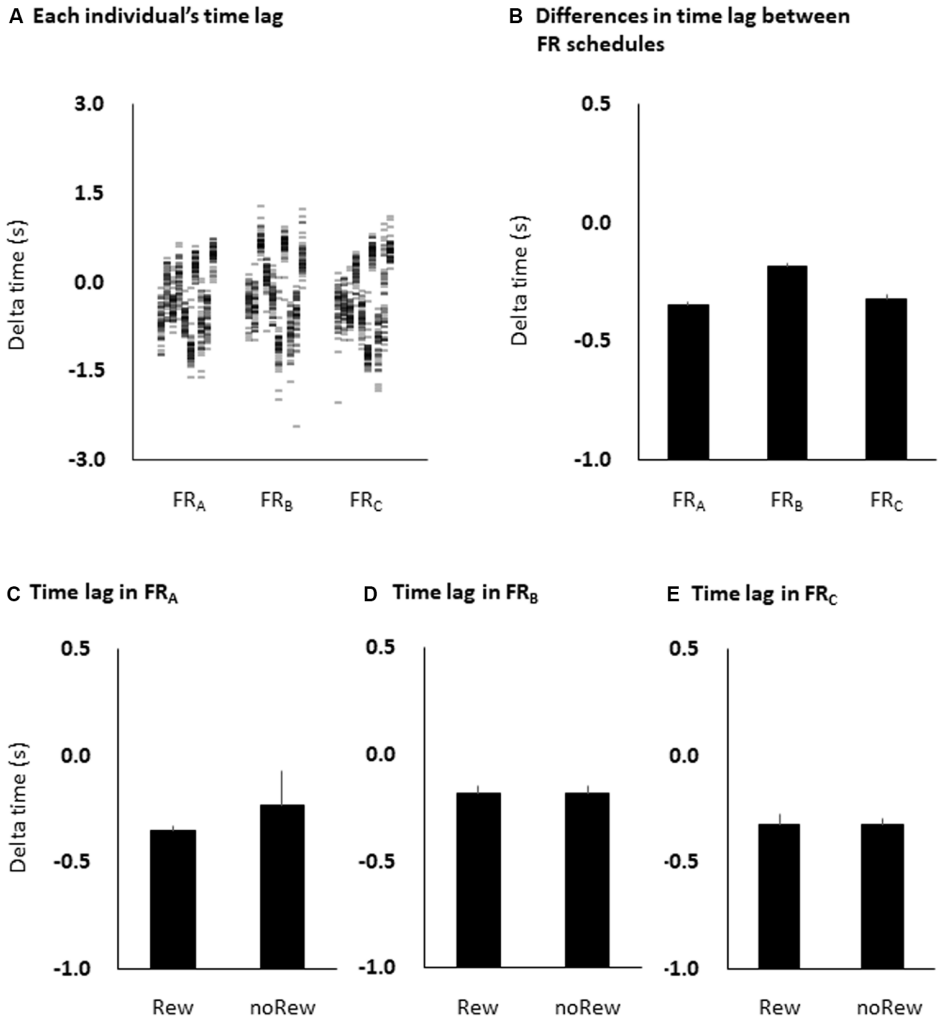


FIGURE 5 | Time estimation lags among the three FR schedules at the individual level **(A)** and the group level **(B)**, and among the immediately preceding reward or no-reward stimulus in the FR_A **(C)**, FR_B **(D)** and FR_C **(E)** schedules. The columns and error bars denote the means and standard errors of the mean, respectively. The difference between time estimation lags observed among the three FR schedules was small and non-significant (one-way ANOVA, $F = 0.458$, $p = 0.499$; **B**), although the time estimation lags were negative in all three FR schedules. Additionally, there were also no significant differences in time estimation lag immediately preceding the reward ("10-yen") or no-reward ("no-pay") stimulus in any FR schedule (unpaired *t*-tests, FR_A, $p = 0.483$; FR_B, $p = 0.964$; FR_C, $p = 0.992$; **C–E**). FR, fixed-ratio; ANOVA, analysis of variance.

of changes in M1 excitability in relation to various reward settings, including rewards and penalties, in fixed- and variable-ratio schedules.

Kiers et al. (1993) studied the variability of MEPs produced by TMS and noted that the variability in MEPs is essentially random in the resting state. In our study, the *p*-value of the model was 0 in most datasets during the resting state, which indicates that the variability of the MEP amplitudes was uncorrelated across time and a random process. However, TMS-evoked MEP amplitude variability was a time-varying autoregressive process during the time-sensitive behavioral task. In addition, the random variability of MEP amplitudes decreased from low reward probability (i.e., FR_C) to high reward probability (i.e., FR_A). This is the second novel observation of our study. It has been previously noted that the frontal network was engaged in time perception, reward perception, and working memory (Üstün et al., 2017; Apaydin et al., 2018). In our study, the participant waited for 5–6 s until seeing the next reward stimulus in the FR_A schedule, whereas the participant waited for 20–24 s until seeing the next reward stimulus in the FR_C schedule. This interval of reward presentation may affect the variability of corticospinal excitabilities during time-sensitive behavioral tasks from the standpoint of memory retention time. In fact, the red circle cue did not indicate reward signals and schedules but only preannounced reward appearance. Therefore, the subjects might expect the reward in reference to the history of reward appearances. Hence, our findings showed that high reward probability facilitates the variability of expectation-related M1 excitability in an autoregressive manner, which extends the

results of previous studies and supports the proposition that reward probability affects the variability of expectation-related corticospinal excitability.

In this study, the time estimation lag was negative in all three FR schedules. Soares et al. (2016) found that activation or inhibition of dopamine neurons contributed to decelerate or accelerate time estimation, respectively. Our result suggests that reward may decelerate time estimation and delay response time, and consequently, the time estimation lag became negative. However, there were no differences in the time estimation lag among the three FR schedules. Additionally, the time estimation lag immediately preceding the reward ("10-yen") or no-reward ("no-pay") stimulus did not differ in any of the three FR schedules. In previous reward tasks (Kapogiannis et al., 2008; Gupta and Aron, 2011; Thabit et al., 2011; Suzuki et al., 2014, 2018), 10–500 Japanese yen (approximately $0.1 to $5) were used as a monetary reward. However, in previous penalty tasks (Suzuki et al., 2018), the penalty stimulus indicated that the participant lost 100 Japanese yen (approximately $1.0). In our study, the reward stimulus was the word "10-yen," which had a rewarding value as it represented 10 actual Japanese yen. The non-reward stimulus was the word "no-pay," which did not have rewarding value. Therefore, the stimulus gap between "10-yen" and "no-pay" may be too small to clarify the changes in the time estimation lag among the three FR schedules. In the context of the gap between reward and no-reward, a higher reward may emphasize changes in the time estimation lag during time-sensitive behavioral tasks. In our study, the participant had to mentally estimate/wait for 2.5 s after TMS with suprathreshold intensity. Although previous studies suggested that TMS delays or shortens the reaction time according to the intensity of the stimuli (Pascual-Leone et al., 1992a,b), a 2.5 s waiting time is sufficiently long to reduce the effect of TMS on reaction time. Therefore, the effect on the time estimation lag of TMS in this study was considered minimal. However, the role of changes in corticospinal excitability during time-sensitive behavioral tasks for decelerating time estimation remains unclear. Further research is needed to investigate the relationship between the time estimation process and corticospinal excitability using higher reward stimuli.

A potential limitation of our study is the small sample size, although the permutated Brunner–Munzel test can deduce the standard normal distribution and accurate *p*-value in small sample data (Fagerland et al., 2011). In addition, corticostriatal neuronal activities related to midbrain dopaminergic neurons could not be directly observed. A previous study (Fiorillo et al., 2003) suggested that reward and penalty outcomes are related to the firing of dopaminergic neurons. A study by Koepp et al. (1998) found evidence that dopamine was released in the human striatum during a behavioral task. Another study (Zald et al., 2004) noted that rewards increased dopamine transmission. A larger number of participants will be needed in future studies, and additional detailed examination using both TMS and brain imaging methods should be conducted to identify the neuronal effects of reward probabilities.

In conclusion, we found that reward probabilities were associated with expectation-related corticospinal excitabilities during a time-sensitive behavioral task. In fact, the magnitude of corticospinal excitability increased in low reward probability, whereas the variability of corticospinal excitability transformed into an autoregressive process in high reward probability. These results imply that the magnitude and variability of corticospinal excitabilities can be differentially altered by reward probability. These findings have implications for the characteristics of corticospinal excitation including M1 changes during rewarded time-sensitive behavior.

ETHICS STATEMENT

The experimental procedures were approved by the Ethics Committee of the Saitama Prefectural University and performed in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent.

AUTHOR CONTRIBUTIONS

MS participated in the design of the study, carried out the experiment, performed the statistical analyses, and drafted the manuscript. TS conceived the study, participated in its design, carried out the experiment, and drafted the manuscript. Y-JW conceived the study, participated in its design, and helped with the experiment. TH conceived the study, participated in its design, and drafted the manuscript. All authors read and approved the final manuscript.

FUNDING

MS was supported by a Grant-in-Aid for Japan Society for the Promotion of Science (JSPS) KAKENHI 18H03133 and 18K19750.

REFERENCES

Apaydin, N., Üstün, S., Kale, E. H., Çelikağ, I., Özgüven, H. D., Baskak, B., et al. (2018). Neural mechanisms underlying time perception and reward anticipation. *Front. Hum. Neurosci.* 12:115. doi: 10.3389/fnhum.2018.00115

Averbeck, B. B., Lehman, J., Jacobson, M., and Haber, S. N. (2014). Estimates of projection overlap and zones of convergence within frontal-striatal circuits. *J. Neurosci.* 34, 9497–9505. doi: 10.1523/jneurosci.5806-12.2014

Borgomaneri, S., Gazzola, V., and Avenanti, A. (2012). Motor mapping of implied actions during perception of emotional body language. *Brain Stimul.* 5, 70–76. doi: 10.1016/j.brs.2012.03.011

Borgomaneri, S., Gazzola, V., and Avenanti, A. (2014). Temporal dynamics of motor cortex excitability during perception of natural emotional scenes. *Soc. Cogn. Affect. Neurosci.* 9, 1451–1457. doi: 10.1093/scan/nst139

Bueti, D., Bahrami, B., and Walsh, V. (2008). Sensory and association cortex in time perception. *J. Cogn. Neurosci.* 20, 1054–1062. doi: 10.1162/jocn.2008.20060

Campos, M., Breznen, B., Bernheim, K., and Andersen, R. A. (2005). Supplementary motor area encodes reward expectancy in eye-movement tasks. *J. Neurophysiol.* 94, 1325–1335. doi: 10.1152/jn.00022.2005

Coelho, C. M., Lipp, O. V., Marinovic, W., Wallis, G., and Riek, S. (2010). Increased corticospinal excitability induced by unpleasant visual stimuli. *Neurosci. Lett.* 481, 135–138. doi: 10.1016/j.neulet.2010.03.027

Coull, J. T., Cheng, R. K., and Meck, W. H. (2011). Neuroanatomical and neurochemical substrates of timing. *Neuropsychopharmacology* 36, 3–25. doi: 10.1038/npp.2010.113

Derosa, N. M., Fisher, W. W., and Steege, M. W. (2015). An evaluation of time in establishing operation on the effectiveness of functional communication training. *J. Appl. Behav. Anal.* 48, 115–130. doi: 10.1002/jaba.180

Fagerland, M. W., Sandvik, L., and Mowinckel, P. (2011). Parametric methods outperformed non-parametric methods in comparisons of discrete numerical variables. *BMC Med. Res. Methodol.* 11:44. doi: 10.1186/1471-2288-11-44

Failing, M., and Theeuwes, J. (2016). Reward alters the perception of time. *Cognition* 148, 19–26. doi: 10.1016/j.cognition.2015.12.005

Fiorillo, C. D., Tobler, P. N., and Schultz, W. (2003). Discrete coding of reward probability and uncertainty by dopamine neurons. *Science* 299, 1898–1902. doi: 10.1126/science.1077349

Fisher, W. W., Greer, B. D., Mitteer, D. R., Fuhrman, A. M., Romani, P. W., and Zangrillo, A. N. (2018). Further evaluation of differential exposure to establishing operations during functional communication training. *J. Appl. Behav. Anal.* 51, 360–373. doi: 10.1002/jaba.451

Goldman-Rakic, P. S. (1987). Motor control function of the prefrontal cortex. *Ciba Found. Symp.* 132, 187–200. doi: 10.1002/9780470513545.ch12

Gupta, N., and Aron, A. R. (2011). Urges for food and money spill over into motor system excitability before action is taken. *Eur. J. Neurosci.* 33, 183–188. doi: 10.1111/j.1460-9568.2010.07510.x

Haber, S. N. (2016). Corticostriatal circuitry. *Dialogues Clin. Neurosci.* 18, 7–21.

Haber, S. N., and Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* 35, 4–26. doi: 10.1038/npp.2009.129

Haruno, M., Kuroda, T., Doya, K., Toyama, K., Kimura, M., Samejima, K., et al. (2004). A neural correlate of reward-based behavioral learning in caudate nucleus: a functional magnetic resonance imaging study of a stochastic decision task. *J. Neurosci.* 24, 1660–1665. doi: 10.1523/jneurosci.3417-03.2004

Hikosaka, O., Bromberg-Martin, E., Hong, S., and Matsumoto, M. (2008). New insights on the subcortical representation of reward. *Curr. Opin. Neurobiol.* 18, 203–208. doi: 10.1016/j.conb.2008.07.002

Hosp, J. A., Pekanovic, A., Rioult-Pedotti, M. S., and Luft, A. R. (2011). Dopaminergic projections from midbrain to primary motor cortex mediate motor skill learning. *J. Neurosci.* 31, 2481–2487. doi: 10.1523/JNEUROSCI.5411-10.2011

Ikemoto, S. (2007). Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. *Brain Res. Rev.* 56, 27–78. doi: 10.1016/j.brainresrev.2007.05.004

Kapogiannis, D., Campion, P., Grafman, J., and Wassermann, E. M. (2008). Reward-related activity in the human motor cortex. *Eur. J. Neurosci.* 27, 1836–1842. doi: 10.1111/j.1460-9568.2008.06147.x

Kapogiannis, D., Mooshagian, E., Campion, P., Grafman, J., Zimmermann, T. J., Ladt, K. C., et al. (2011). Reward processing abnormalities in Parkinson's disease. *Mov. Disord.* 26, 1451–1457. doi: 10.1002/mds.23701

Kiers, L., Cros, D., Chiappa, K. H., and Fang, J. (1993). Variability of motor potentials evoked by transcranial magnetic stimulation. *Electroencephalogr. Clin. Neurophysiol.* 89, 415–423. doi: 10.1016/0168-5597(93)90115-6

Koepp, M. J., Gunn, R. N., Lawrence, A. D., Cunningham, V. J., Dagher, A., Jones, T., et al. (1998). Evidence for striatal dopamine release during a video game. *Nature* 393, 266–268. doi: 10.1038/30498

Macdonald, C. J., Cheng, R. K., and Meck, W. H. (2012). Acquisition of "Start" and "Stop" response thresholds in peak-interval timing is differentially sensitive to protein synthesis inhibition in the dorsal and ventral striatum. *Front. Integr. Neurosci.* 6:10. doi: 10.3389/fnint.2012.00010

Nosik, M. R., and Carr, J. E. (2015). On the distinction between the motivating operation and setting event concepts. *Behav. Anal.* 38, 219–223. doi: 10.1007/s40614-015-0042-5

Oliveri, M., Babiloni, C., Filippi, M. M., Caltagirone, C., Babiloni, F., Cicinelli, P., et al. (2003). Influence of the supplementary motor area on primary motor cortex excitability during movements triggered by neutral or emotionally unpleasant visual cues. *Exp. Brain Res.* 149, 214–221. doi: 10.1007/s00221-002-1346-8

Pascual-Leone, A., Brasil-Neto, J. P., Valls-Sole, J., Cohen, L. G., and Hallett, M. (1992a). Simple reaction time to focal transcranial magnetic stimulation. Comparison with reaction time to acoustic, visual and somatosensory stimuli. *Brain* 115, 109–122. doi: 10.1093/brain/115.1.109

Pascual-Leone, A., Valls-Sole, J., Wassermann, E. M., Brasil-Neto, J., Cohen, L. G., and Hallett, M. (1992b). Effects of focal transcranial magnetic stimulation on simple reaction time to acoustic, visual and somatosensory stimuli. *Brain* 115, 1045–1059. doi: 10.1093/brain/115.4.1045

Pisoni, A., Lo Gerfo, E., Ottone, S., Ponzano, F., Zarri, L., Vergallito, A., et al. (2014). Fair play doesn't matter: MEP modulation as a neurophysiological signature of status quo bias in economic interactions. *Neuroimage* 101, 150–158. doi: 10.1016/j.neuroimage.2014.06.056

Rösler, K. M. (2001). Transcranial magnetic brain stimulation: a tool to investigate central motor pathways. *News Physiol. Sci.* 16, 297–302. doi: 10.1152/physiologyonline.2001.16.6.297

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., and Safety of TMS Consensus Group (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin. Neurophysiol.* 120, 2008–2039. doi: 10.1016/j.clinph.2009.08.016

Schultz, W. (2007). Multiple dopamine functions at different time courses. *Annu. Rev. Neurosci.* 30, 259–288. doi: 10.1146/annurev.neuro.28.061604.135722

Soares, S., Atallah, B. V., and Paton, J. J. (2016). Midbrain dopamine neurons control judgment of time. *Science* 354, 1273–1277. doi: 10.1126/science.aah5234

Suzuki, M., Hamaguchi, T., and Matsunaga, A. (2018). Nonequivalent modulation of corticospinal excitability by positive and negative outcomes. *Brain Behav.* 8:e00862. doi: 10.1002/brb3.862

Suzuki, M., Kirimoto, H., Sugawara, K., Oyama, M., Yamada, S., Yamamoto, J., et al. (2014). Motor cortex-evoked activity in reciprocal muscles is modulated by reward probability. *PLoS One* 9:e90773. doi: 10.1371/journal.pone.0090773

Thabit, M. N., Nakatsuka, M., Koganemaru, S., Fawi, G., Fukuyama, H., and Mima, T. (2011). Momentary reward induce changes in excitability of primary motor cortex. *Clin. Neurophysiol.* 122, 1764–1770. doi: 10.1016/j.clinph.2011.02.021

Tomasi, D., Wang, G. J., Studentsova, Y., and Volkow, N. D. (2015). Dissecting neural responses to temporal prediction, attention, and memory: effects of reward learning and interoception on time perception. *Cereb. Cortex* 25, 3856–3867. doi: 10.1093/cercor/bhu269

Üstün, S., Kale, E. H., and Çiçek, M. (2017). Neural networks for time perception and working memory. *Front. Hum. Neurosci.* 11:83. doi: 10.3389/fnhum.2017.00083

Wickens, J. R., Reynolds, J. N., and Hyland, B. I. (2003). Neural mechanisms of reward-related motor learning. *Curr. Opin. Neurobiol.* 13, 685–690. doi: 10.1016/j.conb.2003.10.013

Wiener, M., Lee, Y. S., Lohoff, F. W., and Coslett, H. B. (2014). Individual differences in the morphometry and activation of time perception networks are influenced by dopamine genotype. *Neuroimage* 89, 10–22. doi: 10.1016/j.neuroimage.2013.11.019

Zald, D. H., Boileau, I., El-Dearedy, W., Gunn, R., Mcglone, F., Dichter, G. S., et al. (2004). Dopamine transmission in the human striatum during monetary reward tasks. *J. Neurosci.* 24, 4105–4112. doi: 10.1523/jneurosci.4643-03.2004

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 04 July 2019
doi: 10.3389/fnbeh.2019.00148

Social Housing Conditions Modulate the Long-Lasting Increase in Cocaine Reward Induced by Intermittent Social Defeat

*Carmen Ferrer-Pérez, Marina D. Reguilón, Carmen Manzanedo, José Miñarro and Marta Rodríguez-Arias**

Department of Psychobiology, Faculty of Psychology, Universitat de València, Valencia, Spain

Social defeat is considered the most representative animal model for studying the consequences of social stress. Intermittent social defeat (ISD) has proved to enhance the response to cocaine hedonic properties. In the present research, we evaluated if different social housing conditions, as housing with a familiar conspecific or with a female, exert a protective effect modulating the negative consequences of ISD as the increased sensitivity to cocaine and the induction of anxiety-like behavior. To achieve this objective, non-stressed or ISD OF1 male mice were divided into five different experimental groups according to their social environment: standard housing (four adult males per cage); male adolescent or adult in pairs (two males per cage); and adult males housed with a female for a short or long period (3 days vs. the whole duration of the study). Anxiety-like behavior was evaluated 19 days after the last episode of ISD using an elevated plus maze (EPM), and 24 h later the animals underwent a conditioned place preference paradigm (CPP) induced by a sub-threshold dose of cocaine (1 mg/kg). Following CPP, biological samples were taken to measure striatal levels of interleukin 6 (IL-6) and plasmatic levels of oxytocin (OT). Our results confirmed that ISD animals housed in standard condition displayed an anxious phenotype, developed CPP and had increased levels of IL-6 in the striatum. However, animals housed with a female or with a familiar male since adolescence did not develop CPP and were protected against the anxiogenic and neuroinflammatory potential of ISD stress. In the group of animals paired with a female throughout the experimental procedure, an increase in OT levels may have underlain this buffering effect, while the protective effect of being housed with a familiar male mouse seems to be related with a better resolution of the stress response. The present results expand our knowledge of the neurobiology of vulnerability to drug addiction and highlight the benefit of social support for recovery from the adverse effects of social stress.

Keywords: social defeat, oxytocin, cocaine, conditioned place preference, IL-6, social environment

OPEN ACCESS

Edited by:
Marijn Van Wingerden, Heinrich Heine University of Düsseldorf, Germany

Reviewed by:
Gina L. Forster, University of Otago, New Zealand
Akiko Shimamoto, Meharry Medical College, United States

****Correspondence:***
Marta Rodríguez-Arias
marta.rodriguez@uv.es

Received: *22 February 2019*
Accepted: *19 June 2019*
Published: *04 July 2019*

Citation:
Ferrer-Pérez C, Reguilón MD, Manzanedo C, Miñarro J and Rodríguez-Arias M (2019) Social Housing Conditions Modulate the Long-Lasting Increase in Cocaine Reward Induced by Intermittent Social Defeat. Front. Behav. Neurosci. 13:148. doi: 10.3389/fnbeh.2019.00148

INTRODUCTION

Drug addiction is a chronic disorder characterized by loss of control over the use of a substance and relapse during cessation attempts (Koob and Volkow, 2010; Volkow and Morales, 2015). The development of substance use disorder (SUD) is multifactorial, and the vulnerability to develop an addiction depends on a complex interplay between biological and environmental factors (Strickland and Smith, 2014).

Among environmental influences, social factors are powerful determinants of behavior and health status (Kessler et al., 2010; Ajonijebu et al., 2017). In this regard, there is a growing interest among researchers in studying the influence of social factors in addictive disorders (Neisewander et al., 2012). Although social stimuli can act as positive natural reinforcers that compete with drug reward, other social interactions can be highly challenging and become stressors (Heilig et al., 2016). For instance, social experiences with a negative affective valence (isolation or bulling in the workplace) are linked with higher rates of drug abuse and vulnerability to relapse after periods of detoxification (Sullivan et al., 2006; Niedhammer et al., 2010). On the other hand, positive social environments, such as strong family ties, involvement and attachment, are associated with lower rates of drug use and better prognosis during treatment (Stout et al., 2012; Litt et al., 2016).

Basic research with animal models using social and hierarchic status has highlighted the dual role of social factors in addiction. Animals living in social environments that provide access to socially rewarding experiences, such as sexual behaviors and pair bonding, are protected against drug-related behaviors (Beloate and Coolen, 2017; Rodríguez-Ortega and Cubero, 2018). For instance, a study carried out with socially housed rodents that acquired cocaine self-administration (SA) behavior and then experienced a forced period of abstinence showed a lower risk of displaying cue-elicited cocaine-seeking behavior than socially isolated animals that underwent the same experimental procedure (Thiel et al., 2010). Similarly, group-housed animals showed a lower risk of drug- or stress-induced reinstatement of cocaine conditioned place preference (CPP) in a former research carried out in our laboratory (Ribeiro Do Couto et al., 2009). On the other hand, social stressor experiences have repeatedly been reported to enhance the response to drugs, to escalate drug consumption and to promote relapse (see revision in Neisewander et al., 2012; Montagud-Romero et al., 2016). For example, early-life social stress experiences, like poor maternal care or maternal separation, have shown to increase ethanol and cocaine consumption in rats in different studies (Francis and Kuhar, 2008; Isengulova et al., 2009). Among all the paradigms that model social stress in rodents, such as social deprivation, social instability, and territorial and maternal aggression, social defeat is considered the most representative for studying the physiological and behavioral consequences (Neisewander et al., 2012; Hammels et al., 2015). This paradigm closely mimics the reality of subordinate vs. aggressor relations in humans (Björkqvist, 2001; Selten et al., 2013), and its ecological validity is widely demonstrated (Miczek et al., 2008). Also named the resident-intruder paradigm, it is based on the territorial attack of a resident male confronted with a conspecific intruder. In these agonistic encounters, residents and intruders demonstrate natural offensive and defensive behaviors, which allows researchers to study the short- and long-term behavioral and physiological consequences of social defeat stress. Overall, the scientific literature affirms that experiences of repeated or intermittent social defeat (ISD) enhance the unconditioned and conditioned rewarding responses to psychostimulant drugs and precipitate the reinstatement of drug seeking in the SA and CPP paradigms, while chronic social defeat produces the opposite effects, with animals displaying a decreased tendency to consume cocaine (see revision in Neisewander et al., 2012; Shimamoto, 2018).

Several neurobiological theories have been proposed to explain stress-induced vulnerability, including alterations of corticotrophin-releasing factor (CRF; Ferrer-Pérez et al., 2018b), dopamine neurotransmission system (Reguilón et al., 2017) and epigenetic forms of plasticity (Montagud-Romero et al., 2016; Ajonijebu et al., 2017). Recent studies suggest that inflammatory processes mediate the effect of ISD stress with regard to an enhanced drug response and anxiety-like behavior (Ferrer-Pérez et al., 2018a). Chronic social defeat and ISD promote the activation of the immune system and trigger a pro-inflammatory state characterized by increased levels of cytokines such as interleukin IL-1β or IL-6 (Wohleb et al., 2011, 2013, 2014; Hodes et al., 2014; Stankiewicz et al., 2015; Pfau and Russo, 2016; Ferrer-Pérez et al., 2018a), which has also been reported to compromise the integrity of the brain blood barrier (Rodríguez-Arias et al., 2017). Within the framework of this theory of neuroinflammation, some researchers have explored anti-inflammatory interventions as therapeutic targets in stress-related disorders, which have proven to be effective in reversing cognitive impairments, anxiety-like behavior and the enhancement in cocaine response induced by social stress (Pfau and Russo, 2016; Duque et al., 2017; Ferrer-Pérez et al., 2018a).

Positive social environments have been reported to have a protective effect on SUD development. Oxytocin (OT), is a neuropeptide that is released during physical contact and potentiates social behaviors (Carter, 2003). It might be central explaining the buffering effect of positive social environments as it has a direct effect reducing the activity of the hypothalamic-adrenal-axis (HPA) during stress response (Lee et al., 2009). Additionally, several studies have revealed anti-inflammatory and antioxidant properties of OT (Karelina et al., 2011; Yuan et al., 2016). In fact, it has shown to be effective in attenuating behavioral and physiological consequences of social stressors such as isolation, and has proven to be effective in reversing depressive and anxiety-like behaviors (Windle et al., 1997; Grippo et al., 2012). In the present research, we have analyzed if the long-lasting negative consequences of ISD on the anxiety-like phenotype and cocaine response can be reversed by different positive social housing conditions (e.g., pairing with a familiar conspecific or a female). Additionally, we aimed to determine if the

physiological mechanism that underlies this protective effect is linked to an anti-inflammatory effect of social intervention that could be mediated by the release of OT. Increasing our knowledge of how social context contributes to responses to drugs can lead to new avenues of drug prevention and treatment.

MATERIALS AND METHODS

Animals

A total number of 195 OF1 mice were supplied by Charles Rivers (France). The mice were divided into groups of 92 adults (42 days old) and 24 adolescents (21 days old). On arrival at the animal facility, the experimental mice were housed in groups of four in plastic cages (27 × 27 × 14 cm), with the exception of 48 animals (24 adults and 24 adolescents) that were housed in pairs. In addition to the experimental mice, 44 adult OF1 females were employed to provide female-paired housing. Finally, 35 adult male OF1 mice, to be used later as residents in the social defeat encounters, were housed individually in plastic cages (21 × 32 × 20 cm) for a month prior to the experiments in order to induce heightened aggression (Rodríguez-Arias et al., 1998).

Regardless of the experimental group to which they were assigned, all the animals were kept under the same conditions: constant temperature; a reversed light schedule (white light on 8:00–20:00 h); and food and water available ad libitum, except during behavioral tests. The experimental protocol was approved by an Institutional Review Committee for the use of animal subjects (Comité d'Ética d'Experimentació i Benestar Animal, number 2015/VSC/PEA/00168). Procedures involving mice and their care were conducted according to national, regional and local laws and regulations, which are in compliance with the Directive 2010/63/EU. Every effort was made to minimize the animals' suffering and reduce the number of animals used.

Drugs

For CPP conditioning, animals were injected intraperitoneally with a dose of 1 mg/kg of cocaine hydrochloride (Alcaliber Laboratory, Spain) dissolved in physiological saline (NaCl 0.9%) and adjusted to a volume of 0.01 ml/g of weight. This dose of cocaine was selected on the basis of previous CPP studies (Montagud-Romero et al., 2016; Ferrer-Pérez et al., 2018a,b) showing 1 mg/kg to be a sub-threshold dose for inducing CPP in adult animals without previous stress or drug experiences and housed in standard condition.

Experimental Groups and Experimental Design

Mice were divided into different experimental groups (depicted in **Figure 1**) based on housing conditions. Next, half of the animals in each housing condition underwent an ISD, while the other half underwent a similar manipulation procedure without the experience of social defeat (nonISD). Subsequently, 19 days after the last social defeat, anxiety was evaluated in the elevated plus maze (EPM) test. One day later, the CPP procedure was initiated. Biological samples were taken after the CPP protocol on PND >89.

Apparatus and Procedures

Intermittent Social Defeat (ISD) Procedure

The ISD protocol followed in this study has been widely validated as a social stressor (Hodes et al., 2014; Hammels et al., 2015) and has been described in detail in previously published research by our group (Ferrer-Pérez et al., 2018a,b). Five days prior to initiation of the ISD protocol, aggressive residents were screened to confirm appropriate levels of aggressive behavior. The aggression test was performed in the home cage of the resident by placing an intruder adult OF1 mice in the cage for 3 min. Any resident mouse showing a latency to attack of over 3 min was withdrawn from the experiment.

The social defeat episodes consisted of three phases, each of which began by introducing the "intruder" (the experimental animal) into the home cage of the "resident" (the aggressive opponent) for 10 min. During this initial phase, the intruder was protected from attack, but the wire mesh walls of the cage allowed for social interaction and species-typical threats from the aggressive male resident, thus leading to instigation and provocation. The wire mesh was then removed from the cage to allow physical contact between the two animals for a 5-min period. In the third phase, the wire mesh was put in place again to separate the two animals for another 10 min while allowing social threats by the resident. Intruder mice were exposed to a different aggressor during each episode of social defeat. The criterion used to define an animal as defeated was the adoption of a specific posture signifying defeat, characterized by an upright submissive position, limp forepaws, upwardly angled head, and retracted ears. In order to minimize physical wounding during social defeats, the 5-min direct encounters were interrupted if the intruder displayed a submissive supine posture for more than 8 s or if it was bitten by the aggressor more than 12 times. All agonistic encounters were videotaped to confirm social defeat. The nonISD groups followed the same protocol, but without the presence of a "resident" mouse: the mouse was placed in a new cage enclosed with a wire mesh for 10 min, after which the mesh was removed for 5 min and then returned for the last 10 min of each exploration session.

Conditioned Place Preference (CPP)

The CPP protocol consisted of three phases and took place during the dark cycle following an unbiased procedure in terms of initial spontaneous preference. For place conditioning, we employed sixteen identical Plexiglas boxes with black and white equal sized compartments (30.7 × 31.5 × 34.5 cm) separated by a gray central area (13.8 × 31.5 × 34.5 cm). In brief, during preconditioning (Pre-C), the time spent by the animal in each compartment over a 15-min period was recorded. Mice showing a strong unconditioned aversion (less than 33% of the time spent in both compartments) or preference (more than 67%) for any compartment were excluded from the study.

In the second phase (conditioning), animals underwent two pairings per day. First, they received an injection of

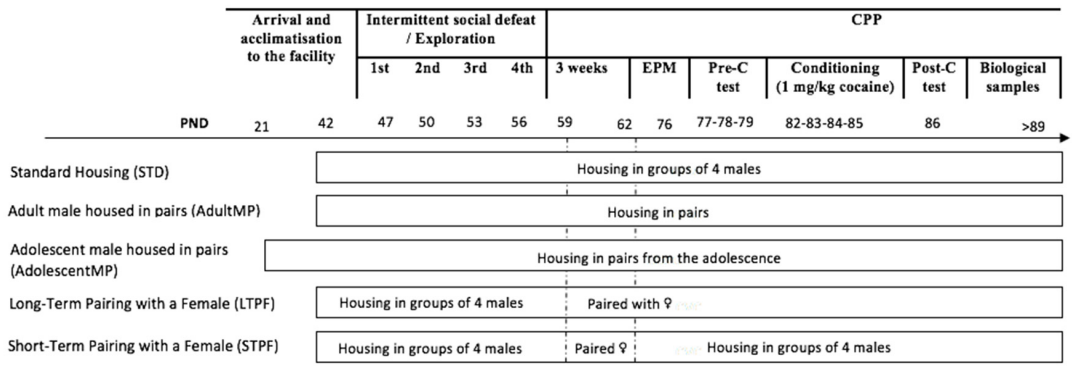


FIGURE 1 | Experimental design. The experimental mice were divided into five different groups according to housing conditions. Animals in the Standard Housing group were housed in groups of four male mice per cage during the whole experiment (STD-nonISD *n* = 12 and STD-ISD *n* = 12). A second group of animals (AdultMP) were housed in pairs upon arrival at the animal facility on PND 42 (AdultMP-nonISD *n* = 12 and AdultMP-ISD *n* = 12). Similarly, a third group of adolescent mice (AdolescentMP) was housed in pairs on their arrival at the laboratory on PND 21 (AdolescentMP-nonISD *n* = 12 and AdolescentMP-ISD *n* = 12). Animals in the Long-Term Pairing with a Female (LTPF) housing condition were initially housed in the same way as those in the STD group, until the end of ISD protocol. Subsequently, 48 h after the last episode of social defeat, they were rehoused in a new cage with a female until the end of the experiments (LTPF-nonISD *n* = 12 and LTPF-ISD *n* = 12). Likewise, animals in the Short-Term Pairing with a Female (STPF) housing condition underwent the same housing procedure as LTPF animals, only that they were housed with the female for 72 h, after which, the experimental animals were returned to the original cage and regrouped as animals in standard housing groups (STPF-nonISD *n* = 8 and STPF-ISD *n* = 12).

physiological saline before being confined to the vehicle-paired compartment for 30 min. After a 4-h interval, they received cocaine immediately before being confined to the drug-paired compartment for 30 min. In the third phase (post-conditioning; Post-C) the conditioned preference was assessed by measuring the time spent by mice in a drug-free state in each compartment during the 15-min observation period. The difference in seconds between the time spent in the drug-paired compartment in the Post-C test and that spent in the Pre-C test is an estimation of the degree of conditioning induced by the drug. If this difference is positive, then the drug is considered to have induced a preference for the drug-paired compartment, whereas the opposite indicates the development of aversion. Additionally, a conditioning score (CS) was calculated for each mouse based on the difference between the time spent in the drug-paired compartment during the Post-C and Pre-C tests. If this difference is positive, then the drug is considered to have induced a preference for the drug-paired compartment, whereas the opposite indicates the induction of an aversion.

Elevated Plus Maze-EPM

The EPM test was carried out essentially following the procedure described by Daza-Losada et al. (2009). The maze consisted of two open arms (30 × 5 × 0.25 cm) and two enclosed arms (30 × 5 × 15 cm), and a central platform (5 × 5 cm) elevated 45 cm above floor level. In order to decrease experimental stress, animals were habituated to the experimental room for 1 h prior to testing. At the beginning of each trial, experimental mice were placed on the central platform so that they were facing an open arm and were allowed to explore for 5 min. The behavior displayed by the mice during the test was recorded by an automated tracking system (EthoVision 3.1, Noldus) that tracks the number of entries and time spent in each section of the maze (open arms, closed arms, central platform). The time and percentage of time spent in the open arms were measured to characterize the anxiolytic effects of the different social housing conditions (Bourin et al., 2007; Blanco-Gandía et al., 2018).

Tissue Sampling

Animals were sacrificed by cervical dislocation and then decapitated to collect blood from the neck in tubes coated with heparin. Blood samples were kept on ice, and plasma was separated from whole blood by centrifugation (5 min, 5,000 G) and transferred to sterile 0.2 ml microcentrifuge tubes. To obtain striatum samples brains were removed immediately after decapitation and dissected following the procedure described by Heffner et al. (1980). Plasma and tissue samples were stored at −80°C until IL-6 and OT determinations.

Determination of Striatal IL-6 and Plasmatic Oxytocin Levels

To determine striatal IL-6 concentration we used a Mouse IL-6 ELISA Kit obtained from Abcam (Ref: Ab100712) following the manufacturer's instructions. Before running the kit, striatum samples were first homogenized and prepared following the procedure described in detail by Ferrer-Pérez et al. (2018a), and protein levels were determined by the Bradford assay from ThermoFisher (Ref: 23227).

For the quantification of plasmatic OT, we used an ELISA kit from Arbor Assays (Ref: K048-H1). Following the recommendation of Leng and Sabatier (2016), we performed an extraction procedure to reduce the non-specific binding of plasmatic proteins in our samples. The extraction procedure was carried out using the extraction solution and the protocol provided by the ELISA kit manufacturer (Arbor Assays). ELISA test results were read using an iMark microplate reader

(Bio-RAD) controlled by Microplate Manager 6.2 software, and the final results were expressed in pg/mg for striatal tissue samples and in pg/ml for plasma.

Statistical Analyses

A preliminary three-way analysis of variance (ANOVA) was carried out with the CPP data of animals under positive social housing condition with two between-subjects variables—Stress, with two levels (ISD and nonISD), and Housing, with four levels (AdultMP, AdolescentMP, LTPF, STPF)—and a within-subjects variable—Days, with two levels (Pre-C and Post-C). The preliminary statistical analysis carried out with the CPP data showed that animals housed in pairs with a female for a short (STPF) or a long term (LTPF) had equivalent results in this test. As a consequence, they were pooled in one single group (pairing with a female, PF) in further analyses. Additionally, the group of adult animals housed in pairs with other males (AdultMP) were removed from further experiment analyses as this intervention showed non-protective effects and both EXP and ISD animals displayed CPP. Outcomes of this group in each test are available as **Supplementary Material** (see **Supplementary Table S1**). Taking these results into account, subsequent ANOVAs included only three intervention groups: standard housed, adolescent male paired, and paired female.

A two-way ANOVA with the aforementioned between-subjects variables (Stress and Housing) was employed to analyze the data of EPM, IL-6, and OT levels. The value of the effect size was evaluated using partial eta-squared. Data are presented as mean ± standard error of the mean (SEM) and a p-value < 0.05 was considered statistically significant. Analyses were performed using SPSS v24. In all cases, *post hoc* comparisons were performed with Bonferroni tests.

RESULTS

Housing Conditions Decrease ISD-Induced Anxiogenic Behavior Evaluated in the EPM

The ANOVA of the EPM data (see **Figure 2**) revealed an effect of the interaction Housing × Stress on the time spent in the open arms ($F_{(2,86)} = 4.454$; $p = 0.014$; effect size 0.094) and on the percentage of open *entries* ($F_{(2,86)} = 4.304$; $p = 0.017$; effect size 0.091). ISD mice housed under the standard condition spent less time and less percentage of time in the open arms than their corresponding non-stress controls (nonISD; $p < 0.01$) and compared to animals housed with a female for long and short terms (PF; $p < 0.001$).

Housing Conditions Modulate the Increase in the Cocaine-Conditioned Reward Induced by ISD Stress

The ANOVA performed for the CPP data (see **Figure 3A**) showed a significant effect of the interaction between the variables Days × Housing × Stress ($F_{(2,85)} = 3.198$; $p = 0.046$; effect size 0.070). As expected, ISD animals housed in the standard condition (STD-ISD) developed CPP, since they spent more time in the drug-paired compartment in the Post-C test than in the Pre-C test ($p < 0.01$). This time was also significantly higher when compared to the time spent in the drug-paired compartment by animals housed with a female for long and short terms (PF, $p < 0.05$).

The ANOVA for the CS (see **Figure 3B**) also revealed an effect of the variable Housing × Stress ($F_{(2,85)} = 3.235$; $p = 0.044$; effect size 0.071). Once again, socially stressed mice under standard condition housing (STD-ISD) had higher CS when compared to non-stressed animals in the same housing conditions (STD-nonISD, $p < 0.05$) and when compared to stressed animals housed with a female for long and short terms (PF, $p < 0.01$).

The Neuroinflammatory Response Induced by Intermittent Social Defeat Stress Is Reduced by Positive Social Housing Conditions

A two-way ANOVA of IL-6 levels in the Striatum (see **Figure 4**) revealed an effect of the variable Housing ($F_{(2,66)} = 4.490$; $p = 0.015$; effect size 0.120). The *post hoc* test revealed that animals in STD housing condition had higher IL-6 levels than animals housed with other males since

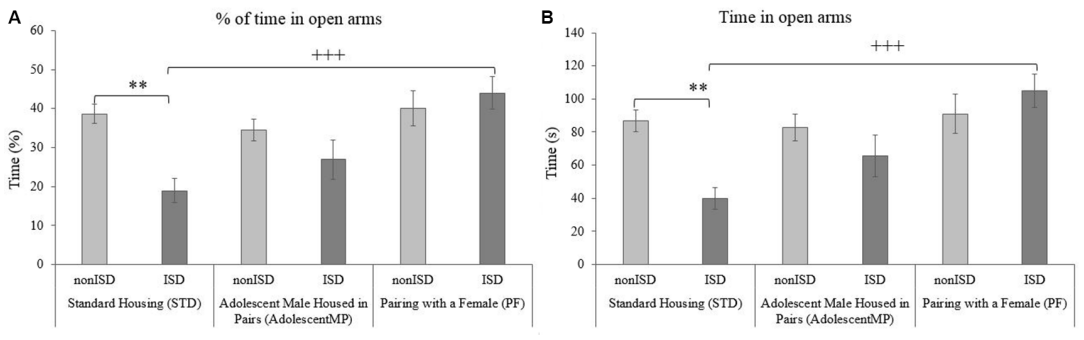


FIGURE 2 | Positive housing conditions decrease ISD-induced anxiogenic behavior evaluated in the elevated plus maze (EPM). **(A)** Percentage of time spent in the open arms of the EPM. **(B)** Time (s) spent in the open arms of the EPM. $^{**}p < 0.01$ significant difference between STD-nonISD vs. STD-ISD. $^{+++}p < 0.001$ significant difference between STD-ISD vs. PF-ISD. Data presented as mean values ± standard error of the mean (SEM).

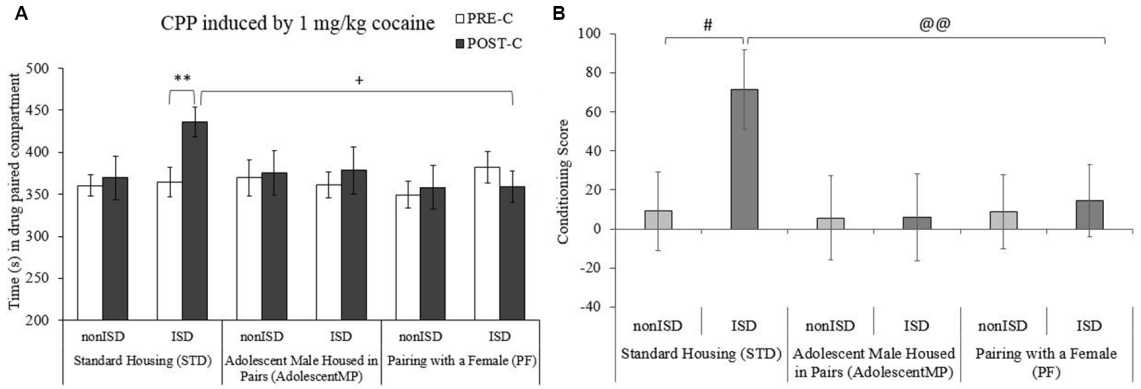


FIGURE 3 | Positive housing conditions decrease the effects of ISD stress on the acquisition of 1 mg/kg cocaine-induced conditioned place preference (CPP). Bars represent the following groups: standard housing (STD-nonISD $n = 12$; STD-ISD $n = 12$); male animals housed in pairs since adolescence (AdolescentMP-nonISD $n = 12$; AdolescentMP-ISD $n = 12$); male animals paired with a female for long or short term (PF-nonISD = 20, PF-ISD = 20). **(A)** The bars represent the time (s) spent in the drug-paired compartment in the PRE-C test (before conditioning sessions; white bars), and in the POST-C test (after conditioning sessions; black bars). Data are presented as mean values ± SEM. Bonferroni's test $^{**}p < 0.01$ significant difference in the time spent in the drug-paired compartment in POST-C vs. PRE-C in STD-ISD animals. $^{+}p < 0.05$ significant differences in the POST-C time between STD-ISD vs. PF-ISD. **(B)** Bars represent the conditioning score (CS), calculated as the time spent in the drug-paired compartment in the Pre-C test minus the time spent there in the Post-C test. $^{\#}p < 0.05$ significant difference between STD-nonISD vs. STD-ISD. $^{@@}p < 0.01$ significant difference between STD-ISD vs. PF-ISD.

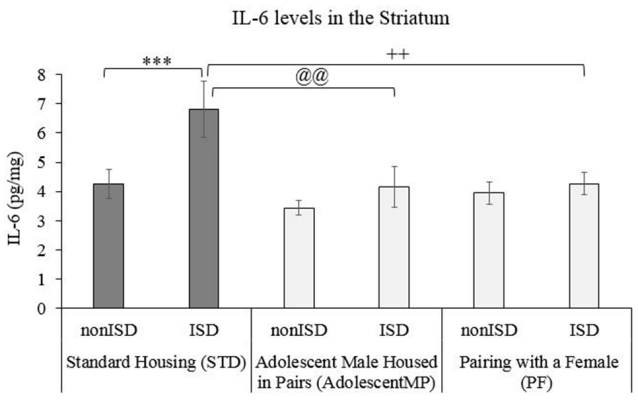


FIGURE 4 | Housing condition modulates the increase in IL-6 levels induced by ISD after CPP. Biological samples were obtained from animals in the following groups: standard housing (STD-nonISD $n = 12$; STD-ISD $n = 12$); Male animals housed in pairs since adolescence (AdolescentMP-nonISD $n = 8$; AdolescentMP-ISD $n = 8$); Male animals paired with a female for long or short term (PF-nonISD = 16, PF-ISD = 16). The bars represent the mean values of IL-6 striatal levels (pg/mg) ± SEM. Bonferroni test $^{***}p < 0.001$ significant difference in IL-6 levels between STD-ISD vs. STD-nonISD. $^{@@}p < 0.01$ significant difference in IL-6 levels between STD-ISD vs. AdolescentMP-ISD. $^{++}p < 0.01$ significant difference in IL-6 levels between STD-ISD vs. PF-ISD.

adolescence (AdolescentMP) or with a female (PF), $p < 0.05$ in both cases.

The ANOVA also revealed an effect of the variable Stress ($F_{(1,66)} = 7.809$; $p = 0.007$; effect size 0.106). ISD animals had higher striatal IL-6 levels when compared to the levels of non-ISD animals ($p < 0.01$).

Finally, the ANOVA also showed an effect of the interaction between Housing × Stress ($F_{(2,66)} = 3.266$; $p = 0.044$; effect size 0.090). Stressed animals under the standard housing condition (STD-ISD) had higher IL-6 striatal levels than non-stressed animals in the same housing condition (STD-nonISD; $p < 0.001$) than defeated animals housed in pairs since adolescence (AdolescentMP-ISD; $p < 0.01$) or those in the PF-IDS group ($p < 0.01$).

Pairing With a Female (PF) Increases Plasmatic OT Levels

A two-way ANOVA of plasmatic OT levels (see **Figure 5**) revealed an effect of the variable Housing ($F_{(2,58)} = 3.154$; $p = 0.05$; effect size 0.098). *Post hoc* test revealed a significant increase of plasmatic OT levels in animals housed with a female for long or short terms (PF) when compared to those housed in the standard condition (STD; $p < 0.05$).

DISCUSSION

The present research highlights how social factors are crucial in defining the individual's response to cocaine. Negative social events, such as agonistic encounters between conspecifics, are powerful stressors capable of altering physiologic and psychological functions. Animals that undergo four sessions of an ISD protocol display long-lasting alterations, including an anxious phenotype, enhanced sensitivity to the rewarding properties of cocaine, and increased pro-inflammatory signaling in the striatum. On the other hand, we have also seen that social enrichment in the form of positive housing conditions has a protective effect by reducing the above-mentioned negative consequences of social stress. Animals housed in positive social conditions—for instance, in pairs with a female or with a familiar male—are buffered against the

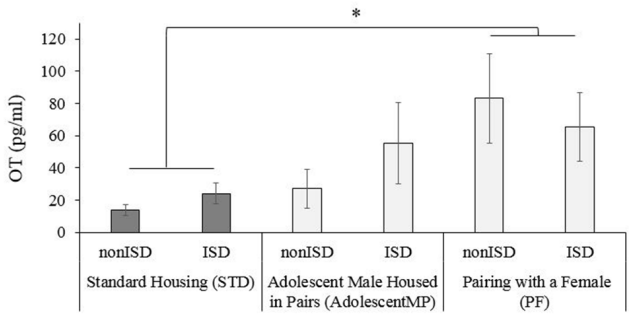


FIGURE 5 | Short and Long-Term Pairing with a Female (PF) increases plasmatic OT levels. The bars represent the plasmatic OT levels of mice in Standard Housing condition (STD-nonISD $n = 8$; STD-ISD $n = 8$); male animals housed in pairs since adolescence (AdolescentMP-nonISD $n = 8$; AdolescentMP-ISD $n = 8$); Male animals paired with a female for long or short term (PF-nonISD = 16, PF-ISD = 16). The bars represent the mean values of concentration (pg/ml) ± SEM. $^*p < 0.05$ significant difference in OT levels compared to Standard Housing (STD) condition.

long-lasting increases in the rewarding properties of cocaine, anxiety-like behavior and the inflammatory response induced by ISD.

It is widely demonstrated that stressful social events have a modulatory effect on the effects of drugs (Gasparotto et al., 2005; Neisewander et al., 2012; Baracz et al., 2018). In our ISD protocol, the experimental mouse was confronted with a territorial (isolated) mouse that threatened and attacked the former, which adopted a defensive/submissive response (Miczek et al., 2008). Our results show that intruder animals experience these interactions as social stressors with a negative valence, and are subject to a series of long-lasting physiological and behavioral consequences that are consistent with previous evidence (Ferrer-Pérez et al., 2018a,b; Montagud-Romero et al., 2018). Socially defeated animals under standard housing condition (STD-ISD) showed increased sensitivity to the conditioned rewarding properties of cocaine, as they developed CPP for a subthreshold dose of cocaine (1 mg/kg), while the same dose was ineffective in animals that were not exposed to the ISD protocol (STD-nonISD). These animals also displayed an anxiety-like behavior phenotype characterized by spending less time in the open arms of the EPM than their non-stressed counterparts.

Rather than owing to a single mechanism, ISD effects are related with multiple and complex changes to peripheral and central systems that are not yet completely understood. Among these alterations, we hypothesize that immune response activation is critical in the appearance of the abovementioned long-lasting stress consequences. The results of the present study confirm this hypothesis by showing that socially defeated animals housed under standard condition (STD-ISD) display higher striatal levels of IL-6 than non-ISD animals. Following the same social defeat protocol, we have previously observed an increase in plasmatic and central levels of the pro-inflammatory cytokine IL-6 that returned to normal 3 weeks after the last defeat and increased again after cocaine-induced CPP (Ferrer-Pérez et al., 2018a). Therefore, we can affirm that intermittent social stress activates an initial immune response that promotes a sensitization of the neuroimmune axis and enhances the potential of cocaine to induce a pro-inflammatory state.

Previous studies indicate that positive social housing conditions are a successful intervention for reducing or preventing the negative consequences of social stress, mostly focus on anxiety behavior (Gasparotto et al., 2005; Nakayasu and Ishii, 2008; Neisewander et al., 2012). Housing with a female—thereby allowing mating behavior—for either long- (LTPF) or short-term (STPF) periods completely counteracted the anxiogenic effects of ISD and blocked cocaine-induced CPP, preventing the sensitization of the reward system by stress. Other researchers have reported that cohabitation with a female has a protective effect against the acquisition and extinction of cocaine CPP (Ribeiro Do Couto et al., 2009) and buffers against the anxiogenic effect of social and physical stress (Gobrogge and Wang, 2015). However, no studies have evaluated this cohabitation after exposure to social stress. We observed that this housing condition also exerted a protective effect against intermittent social stress-induced sensitization of the immune axis, as neuroinflammatory markers were not enhanced after the CPP procedure. We also observed that this housing condition induced a significant increase in plasmatic OT levels, which led us to suspect that this anti-inflammatory effect is mediated by the release of OT during social interaction in the cage. Although it is known that OT can exert an anti-inflammatory effect by decreasing the hypothalamic-adrenal-axis response to stressors (Lee et al., 2009; Karelina et al., 2011; Yuan et al., 2016), in our design, pairing with the female took place after the last defeat. Therefore, another mechanism that may explain the protective effect of this neuropeptide is that OT has the ability to change the focus from drug reward to social reward (McGregor and Bowen, 2012), thus enhancing the ability of a positive social stimulus to compete as an alternative reinforcer. In support of the role of OT in social defeat effects, we have recently reported that an injection of exogenous OT before each defeat episode induced a protective effect by blocking stress-increased anxiety-like behavior and the increased rewarding properties of cocaine in the CPP and the SA while favoring the extinction of drug memory (Ferrer-Pérez et al., 2019).

Free-living male mice prefer to live with females than with other males (Kappel et al., 2017). Group-housed male mice develop a social hierarchy, and under laboratory housing conditions it is common to witness inter-male aggression while dominance is established within the cage (Kappel et al., 2017). Indeed, aggressions can continue even after the establishment of a stable hierarchy, as a consequence of the alteration of territorial scent marking during the cleaning of cages (Poole and Morgan, 1973). Several research works have demonstrated that the status of an animal in the hierarchy of the cage modulates its vulnerability to the negative consequences of social stress. For instance, Yanovich et al. (2018) found that submissive animals are more likely

to display anxiety-like behaviors and enhanced attraction to addictive substances when exposed to stress, while dominant animals are more resilient to the negative consequences of stress. Considering the negative effects of the continuous fight for dominance that characterizes standard housing, we designed a low hierarchic stress housing condition as a buffer against the consequences of social defeat stress. We paired two adult males (AdultMP) with the intention of promoting a more predictable hierarchy and thus reducing the stress derived from fights to establish dominance. Previously, other researchers have reported that the strategy of housing two familiar rats together prevents anxiety-like behavior induced by social stress (Nakayasu and Ishii, 2008). Conversely to previous reports and to our predictions, this pairing of adult mice failed to prevent the negative effect of ISD stress, as the animals in question displayed a similar CPP for a subthreshold dose of cocaine to that registered in defeated animals housed in standard condition (STD-ISD). We should take into consideration that Nakayasu and Ishii (2008) employed a single episode of social defeat, while our protocol consisted of intermittent defeat encounters over several days. It is possible that, given that these housing conditions were established upon arrival of the animals at the laboratory (42 PND), and that social defeat or exploration protocols began immediately after the acclimatization period (on PND 47), animals were experiencing social defeat stress while the cage hierarchy was still being established; in this way, both animals in each pair would have been experiencing the dominance/submission stress that is usually resolved after 21 days (Poole and Morgan, 1973; Rodríguez-Arias et al., 1998). We believe that this initial stress during the early definition of hierarchic positions was less evident in the standard housing condition because of the size of the group (four mice). Not all four animals in standard housing conditions directly experienced the stress of the dichotomy of submissive/dominant roles, as there were animals that occupied an intermediate hierarchic position. To test this hypothesis, we repeated the experiment, but this time established the housing conditions during adolescence, on PND 21 (AdolescentMP), so that social defeat and the exploration protocol would take place after the initial instability of hierarchy establishment. Now, this housing condition became a protective environment, in line with our earlier predictions. The stress-enhanced response to the rewarding properties of cocaine and sensitization to the neuroinflammatory response induced by ISD were both blunted. In this case, the mechanism underlying the protective effect of being housed with a familiar male since adolescence was not directly related to the OT buffering. We hypothesize that the protective effect observed in the AdolescentMP group was the result of a better resolution of the stress response, which limits the negative consequences of social defeat stress that are secondary to maintenance of the cage hierarchy.

The present research highlights how social interactions with conspecifics are powerful mediators of the individual's response to drugs of abuse. All positive social housing conditions analyzed prevented the sensitization of the neuroimmune axis and the pro-inflammatory state induced by ISD. However, we were not able to prove the causal role of OT mediating this anti-inflammatory effect, as OT levels did not predict the variations observed in IL-6 concentration. Therefore, future research will be needed to identify the neurophysiological mechanism that underlies the buffering potential of positive social interactions against long-lasting ISD effects.

ETHICS STATEMENT

The experimental protocol was approved by an Institutional Review Committee for the use of animal subjects (Comité d' Ética d'Experimentació i Benestar Animal, number 2015/VSC/PEA/00168). Procedures involving mice and their care were conducted according to national, regional and local laws and regulations, which are in compliance with the Directive 2010/63/EU. All efforts were made to minimize the animals' suffering and to reduce the number of animals used.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

CM, JM and MR-A designed, funded and administered the study. CM and JM reviewed the manuscript. CF-P, MR and MR-A designed, executed the study, analyzed the data, wrote and reviewed the manuscript.

FUNDING

This work was supported by the Ministerio de Economía, Industria y Competitividad, Gobierno de España (MINECO), Dirección General de Investigación, PSI2014-51847-R and PSI 2017-83023-R; Instituto de Salud Carlos III, Red de Trastornos Adictivos (RTA; RETICS RD16/0017/0007) and Unión Europea, Fondos FEDER "A way to build Europe." CF-P received FPU grant from the Spanish Ministry of Economy, Innovation and Competiveness (14/02279).

ACKNOWLEDGMENTS

We wish to thank Brian Normanly for his English language editing.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2019.00148/full#supplementary-material

REFERENCES

Ajonijebu, D. C., Abboussi, O., Russell, V. A., Mabandla, M. V., and Daniels, W. M. (2017). Epigenetics: a link between addiction and social environment. *Cell. Mol. Life Sci.* 74, 2735–2747. doi: 10.1007/s00018-017-2493-1

Baracz, S. J., Everett, N. A., and Cornish, J. L. (2018). The impact of early life stress on the central oxytocin system and susceptibility for drug addiction: applicability of oxytocin as a pharmacotherapy. *Neurosci. Biobehav. Rev.* doi: 10.1016/j.neubiorev.2018.08.014 [Epub ahead of print].

Beloate, L. N., and Coolen, L. M. (2017). Influences of social reward experience on behavioral responses to drugs of abuse: review of shared and divergent neural plasticity mechanisms for sexual reward and drugs of abuse. *Neurosci. Biobehav. Rev.* 83, 356–372. doi: 10.1016/j.neubiorev.2017.10.024

Björkqvist, K. (2001). Social defeat as a stressor in humans. *Physiol. Behav.* 73, 435–442. doi: 10.1016/s0031-9384(01)00490-5

Blanco-Gandía, M. C., Montagud-Romero, S., Aguilar, M. A., Miñarro, J., and Rodríguez-Arias, M. (2018). Housing conditions modulate the reinforcing properties of cocaine in adolescent mice that binge on fat. *Physiol. Behav.* 183, 18–26. doi: 10.1016/j.physbeh.2017.10.014

Bourin, M., Petit-Demoulière, B., Nic Dhonnchadha, B., and Hascöet, M. (2007). Animal models of anxiety in mice. *Fundam. Clin. Pharmacol.* 21, 567–574. doi: 10.1111/j.1472-8206.2007.00526.x

Carter, C. S. (2003). Developmental consequences of oxytocin. *Physiol. Behav.* 79, 383–397. doi: 10.1016/s0031-9384(03)00151-3

Daza-Losada, M., Rodríguez-Arias, M., Maldonado, C., Aguilar, M. A., Guerri, C., and Miñarro, J. (2009). Acute behavioural and neurotoxic effects of MDMA plus cocaine in adolescent mice. *Neurotoxicol. Teratol.* 31, 49–59. doi: 10.1016/j.ntt.2008.07.005

Duque, A., Vinader-Caerols, C., and Monleón, S. (2017). Indomethacin counteracts the effects of chronic social defeat stress on emotional but not recognition memory in mice. *PLoS One* 12:e0173182. doi: 10.1371/journal.pone.0173182

Ferrer-Pérez, C., Castro-Zavala, A., Luján, M. Á., Filarowska, J., Ballestín, R., Miñarro, J., et al. (2019). Oxytocin prevents the increase of cocaine-related responses produced by social defeat. *Neuropharmacology* 146, 50–64. doi: 10.1016/j.neuropharm.2018.11.011

Ferrer-Pérez, C., Martinez, T. E., Montagud-Romero, S., Ballestín, R., Reguilón, M. D., Miñarro, J., et al. (2018a). Indomethacin blocks the increased conditioned rewarding effects of cocaine induced by repeated social defeat. *PLoS One* 13:e0209291. doi: 10.1371/journal.pone.0209291

Ferrer-Pérez, C., Reguilón, M. D., Manzanedo, C., Aguilar, M. A., Miñarro, J., and Rodríguez-Arias, M. (2018b). Antagonism of corticotropin-releasing factor CRF1 receptors blocks the enhanced response to cocaine after social stress. *Eur. J. Pharmacol.* 823, 87–95. doi: 10.1016/j.ejphar.2018.01.052

Francis, D. D., and Kuhar, M. J. (2008). Frequency of maternal licking and grooming correlates negatively with vulnerability to cocaine and alcohol use in rats. *Pharmacol. Biochem. Behav.* 90, 497–500. doi: 10.1016/j.pbb.2008.04.012

Gasparotto, O. C., Lopes, D. M., and Carobrez, S. G. (2005). Pair housing affects anxiety-like behaviors induced by a social but not by a physiological stressor in male Swiss mice. *Physiol. Behav.* 85, 603–612. doi: 10.1016/j.physbeh.2005.06.014

Gobrogge, K., and Wang, Z. (2015). Neuropeptidergic regulation of pair-bonding and stress buffering: lessons from voles. *Horm. Behav.* 76, 91–105. doi: 10.1016/j.yhbeh.2015.08.010

Grippo, A. J., Pournajafi-Nazarloo, H., Sanzenbacher, L., Trahanas, D. M., McNeal, N., Clarke, D. A., et al. (2012). Peripheral oxytocin administration buffers autonomic but not behavioral responses to environmental stressors in isolated prairie voles. *Stress* 15, 149–161. doi: 10.3109/10253890.2011.605486

Hammels, C., Pishva, E., De Vry, J., van den Hove, D. L., Prickaerts, J., van Winkel, R., et al. (2015). Defeat stress in rodents: from behavior to molecules. *Neurosci. Biobehav. Rev.* 59, 111–140. doi: 10.1016/j.neubiorev.2015.10.006

Heffner, T. G., Hartman, J. A., and Seiden, L. S. (1980). A rapid method for the regional dissection of the rat brain. *Pharmacol. Biochem. Behav.* 13, 453–456. doi: 10.1016/0091-3057(80)90254-3

Heilig, M., Epstein, D. H., Nader, M. A., and Shaham, Y. (2016). Time to connect: bringing social context into addiction neuroscience. *Nat. Rev. Neurosci.* 17, 592–599. doi: 10.1038/nrn.2016.67

Hodes, G. E., Pfau, M. L., Leboeuf, M., Golden, S. A., Christoffel, D. J., Bregman, D., et al. (2014). Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. *Proc. Natl. Acad. Sci. U S A* 111, 16136–16141. doi: 10.1073/pnas.1415191111

Isengulova, A. A., Kalmykova, Z. A., and Miroshnichenko, I. V. (2009). The significance of maternal care for the formation of ethanol preference in rats periodically separated from mothers during the first half of the nest period. *Bull. Exp. Biol. Med.* 147, 390–393. doi: 10.1007/s10517-009-0533-z

Kappel, S., Hawkins, P., and Mendl, M. (2017). To group or not to group? Good practice for housing male laboratory mice. *Animals* 7:88. doi: 10.3390/ani7120088

Karelina, K., Stuller, K. A., Jarrett, B., Zhang, N., Wells, J., Norman, G. J., et al. (2011). Oxytocin mediates social neuroprotection after cerebral ischemia. *Stroke* 42, 3606–3611. doi: 10.1161/STROKEAHA.111.628008

Kessler, R. C., McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., et al. (2010). Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *Br. J. Psychiatry* 197, 378–385. doi: 10.1192/bjp.bp.110.080499

Koob, G. F., and Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology* 35, 217–238. doi: 10.1038/npp.2009.110

Lee, H. J., Macbeth, A. H., Pagani, J. H., and Young, W. S. III. (2009). Oxytocin: the great facilitator of life. *Prog. Neurobiol.* 88, 127–151. doi: 10.1016/j.pneurobio.2009.04.001

Leng, G., and Sabatier, N. (2016). Measuring oxytocin and vasopressin: bioassays, immunoassays and random numbers. *J. Neuroendocrinol.* 28:10. doi: 10.1111/jne.12413

Litt, M. D., Kadden, R. M., Tennen, H., and Kabela-Cormier, E. (2016). Network Support II: randomized controlled trial of network support treatment and cognitive behavioral therapy for alcohol use disorder. *Drug Alcohol Depend.* 165, 203–212. doi: 10.1016/j.drugalcdep.2016.06.010

McGregor, I. S., and Bowen, M. T. (2012). Breaking the loop: oxytocin as a potential treatment for drug addiction. *Horm. Behav.* 61, 331–339. doi: 10.1016/j.yhbeh.2011.12.001

Miczek, K. A., Yap, J. J., and Covington, H. E. III. (2008). Social stress, therapeutics and drug abuse: preclinical models of escalated and depressed intake. *Pharmacol. Ther.* 120, 102–128. doi: 10.1016/j.pharmthera.2008.07.006

Montagud-Romero, S., Blanco-Gandía, M. C., Reguilón, M. D., Ferrer-Pérez, C., Ballestín, R., Miñarro, J., et al. (2018). Social defeat stress: mechanisms underlying the increase in rewarding effects of drugs of abuse. *Eur. J. Neurosci.* 48, 2948–2970. doi: 10.1111/ejn.14127

Montagud-Romero, S., Montesinos, J., Pascual, M., Aguilar, M. A., Roger-Sanchez, C., Guerri, C., et al. (2016). Up-regulation of histone acetylation induced by social defeat mediates the conditioned rewarding effects of cocaine. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 70, 39–48. doi: 10.1016/j.pnpbp.2016.04.016

Nakayasu, T., and Ishii, K. (2008). Effects of pair-housing after social defeat experience on elevated plus-maze behavior in rats. *Behav. Processes* 78, 477–480. doi: 10.1016/j.beproc.2008.02.007

Neisewander, J. L., Peartree, N. A., and Pentkowski, N. S. (2012). Emotional valence and context of social influences on drug abuse-related behavior in animal models of social stress and prosocial interaction. *Psychopharmacology* 224, 33–56. doi: 10.1007/s00213-012-2853-3

Niedhammer, I., David, S., Degioanni, S., Drummond, A., Philip, P., Acquarone, D., et al. (2010). Workplace bullying and psychotropic drug use: the mediating role of physical and mental health status. *Ann. Occup. Hyg.* 55, 152–163. doi: 10.1093/annhyg/meq086

Pfau, M. L., and Russo, S. J. (2016). Neuroinflammation regulates cognitive impairment in socially defeated mice. *Trends Neurosci.* 39, 353–355. doi: 10.1016/j.tins.2016.04.004

Poole, T. B., and Morgan, H. D. R. (1973). Differences in aggressive behaviour between male mice (*Mus musculus L.*) in colonies of different sizes. *Anim. Behav.* 21, 788–795. doi: 10.1016/s0003-3472(73)80105-8

Reguilón, M. D., Montagud-Romero, S., Ferrer-Perez, C., Roger-Sánchez, C., Aguilar, M. A., Miñarro, J., et al. (2017). Dopamine D2 receptors mediate the increase in reinstatement of the conditioned rewarding effects of cocaine induced by acute social defeat. *Eur. J. Pharmacol.* 799, 48–57. doi: 10.1016/j.ejphar.2017.01.039

Ribeiro Do Couto, B., Aguilar, M. A., Lluch, J., Rodríguez-Arias, M., and Miñarro, J. (2009). Social experiences affect reinstatement of cocaine-induced place preference in mice. *Psychopharmacology* 207, 485–498. doi: 10.1007/s00213-009-1678-1

Rodríguez-Arias, M., Miñarro, J., Aguilar, M. A., Pinazo, J., and Simon, V. M. (1998). Effects of risperidone and SCH 23390 on isolation-induced aggression in male mice. *Eur. Neuropsychopharmacol.* 8, 95–103. doi: 10.1016/s0924-977x(97)00051-5

Rodríguez-Arias, M., Montagud-Romero, S., Rubio-Araiz, A., Aguilar, M. A., Martín-García, E., Cabrera, R., et al. (2017). Effects of repeated social defeat on adolescent mice on cocaine-induced CPP and self-administration in adulthood: integrity of the blood-brain barrier. *Addict. Biol.* 22, 129–141. doi: 10.1111/adb.12301

Rodríguez-Ortega, E., and Cubero, I. (2018). Environmental enrichment modulates drug addiction and binge-like consumption of highly rewarding substances: a role for anxiety and compulsivity brain systems? *Front. Behav. Neurosci.* 12:295. doi: 10.3389/fnbeh.2018.00295

Selten, J. P., van der Ven, E., Rutten, B. P., and Cantor-Graae, E. (2013). The social defeat hypothesis of schizophrenia: an update. *Schizophr. Bull.* 39, 1180–1186. doi: 10.1093/schbul/sbt134

Shimamoto, A. (2018). Social defeat stress, sex and addiction-like behaviors. *Int. Rev. Neurobiol.* 140, 271–313. doi: 10.1016/bs.irn.2018.07.009

Stankiewicz, A. M., Goscik, J., Majewska, A., Swiergiel, A. H., and Juszczak, G. R. (2015). The effect of acute and chronic social stress on the hippocampal transcriptome in mice. *PLoS One* 10:e0142195. doi: 10.1371/journal.pone.0142195

Stout, R. L., Kelly, J. F., Magill, M., and Pagano, M. E. (2012). Association between social influences and drinking outcomes across three years. *J. Stud. Alcohol Drugs* 73, 489–497. doi: 10.15288/jsad.2012.73.489

Strickland, J. C., and Smith, M. A. (2014). The effects of social contact on drug use: behavioral mechanisms controlling drug intake. *Exp. Clin. Psychopharmacol.* 22, 23–34. doi: 10.1037/a0034669

Sullivan, T. N., Farrell, A. D., and Kliewer, W. (2006). Peer victimization in early adolescence: association between physical and relational victimization and drug use, aggression and delinquent behaviors among urban middle school students. *Dev. Psychopathol.* 18, 119–137. doi: 10.1017/s0954579406006007X

Thiel, K. J., Pentkowski, N. S., Peartree, N. A., Painter, M. R., and Neisewander, J. L. (2010). Environmental living conditions introduced during forced abstinence alter cocaine-seeking behavior and Fos protein expression. *Neuroscience* 171, 1187–1196. doi: 10.1016/j.neuroscience.2010.10.001

Volkow, N., and Morales, M. (2015). The brain on drugs: from reward to addiction. *Cell* 162, 712–725. doi: 10.1016/j.cell.2015.07.046

Windle, R. J., Shanks, N., Lightman, S. L., and Ingram, C. D. (1997). Central oxytocin administration reduces stress-induced corticosterone release and anxiety behavior in rats. *Endocrinology* 138, 2829–2834. doi: 10.1210/en.138.7.2829

Wohleb, E. S., Hanke, M. L., Corona, A. W., Powell, N. D., La'Tonia, M. S., Bailey, M. T., et al. (2011). β-Adrenergic receptor antagonism prevents anxiety-like behavior and microglial reactivity induced by repeated social defeat. *J. Neurosci.* 31, 6277–6288. doi: 10.1523/JNEUROSCI.0450-11.2011

Wohleb, E. S., Patterson, J. M., Sharma, V., Quan, N., Godbout, J. P., and Sheridan, J. F. (2014). Knockdown of interleukin-1 receptor type-1 on endothelial cells attenuated stress-induced neuroinflammation and prevented anxiety-like behavior. *J. Neurosci.* 34, 2583–2591. doi: 10.1523/JNEUROSCI.3723-13.2014

Wohleb, E. S., Powell, N. D., Godbout, J. P., and Sheridan, J. F. (2013). Stress-induced recruitment of bone marrow-derived monocytes to the brain promotes anxiety-like behavior. *J. Neurosci.* 33, 13820–13833. doi: 10.1523/JNEUROSCI.1671-13.2013

Yanovich, C., Kirby, M. L., Michaelevski, I., Yadid, G., and Pinhasov, A. (2018). Social rank-associated stress vulnerability predisposes individuals to cocaine attraction. *Sci. Rep.* 8:1759. doi: 10.1038/s41598-018-19816-x

Yuan, L., Liu, S., Bai, X., Gao, Y., Liu, G., Wang, X., et al. (2016). Oxytocin inhibits lipopolysaccharide-induced inflammation in microglial cells and attenuates microglial activation in lipopolysaccharide-treated mice. *J. Neuroinflammation* 13:77. doi: 10.1186/s12974-016-0541-7

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 11 July 2019
doi: 10.3389/fnbeh.2019.00149

Dissociable Neural Responses to Monetary and Social Gain and Loss in Women With Major Depressive Disorder

Anjali Sankar[1,2], *Ashley A. Yttredahl*[2,3], *Elizabeth W. Fourcade*[4], *Brian J. Mickey*[5], *Tiffany M. Love*[5], *Scott A. Langenecker*[5] *and David T. Hsu*[2,3,6]*

[1]*Department of Psychiatry, Yale School of Medicine, New Haven, NY, United States,* [2]*Department of Psychiatry and Behavioral Health, Stony Brook University, Stony Brook, NY, United States,* [3]*Department of Psychology, Stony Brook University, Stony Brook, NY, United States,* [4]*Department of Psychiatry, Allegheny Health Network, Pittsburgh, PA, United States,* [5]*Department of Psychiatry, The University of Utah, Salt Lake City, UT, United States,* [6]*Department of Psychiatry, University of Michigan, Ann Arbor, MI, United States*

Neuroimaging studies have revealed aberrant reward and loss processing in patients with major depressive disorder (MDD). While most studies use monetary stimuli to study these processes, it is important to consider social stimuli given that the social environment plays a significant role in the development and maintenance of MDD. In the present study, we examined whether monetary gain/loss and social acceptance/rejection would elicit dissociable salience-related neural responses in women diagnosed with MDD compared to healthy control (HC) women. Twenty women diagnosed with MDD and 20 matched HC women performed the monetary incentive delay task (MID) and the social feedback task (SFT) during functional magnetic resonance imaging (fMRI). This study focused on women since women have a higher rate of MDD, higher frequency of relapse, and are more likely to develop MDD as a consequence of negative interpersonal relationships compared to men. We found that during the MID, HCs but not MDD patients demonstrated strong overlapping activations in the right anterior insula (AI) in response to both monetary gain and loss. During the SFT, MDD patients but not HCs showed overlapping activations in the AI in response to social acceptance and rejection. Our results may suggest a dissociation such that MDD patients show decreased sensitivity to monetary stimuli whether gain or loss, and increased sensitivity to social stimuli whether acceptance or rejection, although this will need to be verified in larger samples with direct comparisons between groups and stimuli. These data demonstrate distinct abnormalities in reward and loss processing that converge within the AI. Our findings also highlight the critical need to assess across both non-social and social domains when examining reward and loss systems in MDD to broaden our understanding of the disorder and identify novel targets for treatment.

Keywords: major depression, women, functional magnetic resonance imaging, social feedback, monetary incentive delay task, reward and loss

OPEN ACCESS

Edited by:
Johanna M. Jarcho,
Temple University, United States

Reviewed by:
Roee Admon,
University of Haifa, Israel
Jillian Lee Wiggins,
University of Michigan, Ann Arbor, United States

***Correspondence:**
David T. Hsu
david.hsu@stonybrookmedicine.edu

Received: *21 February 2019*
Accepted: *20 June 2019*
Published: *11 July 2019*

Citation:
Sankar A, Yttredahl AA, Fourcade EW, Mickey BJ, Love TM, Langenecker SA and Hsu DT (2019) Dissociable Neural Responses to Monetary and Social Gain and Loss in Women With Major Depressive Disorder. Front. Behav. Neurosci. 13:149. doi: 10.3389/fnbeh.2019.00149

INTRODUCTION

Anhedonia, defined as the loss of interest in previously rewarding activities, is a core feature of major depressive disorder (MDD; American Psychiatric Association, 2013), yet it is not effectively managed with first-line antidepressant treatments (Shelton and Tomarken, 2001) and is generally associated with poor treatment outcomes (Spijker et al., 2001). The last decade has seen a preponderance of work on maladaptive neural responses to both reward and loss in MDD. Much of this research has focused on monetary reward and loss (Knutson et al., 2008; Pizzagalli et al., 2009; Smoski et al., 2009; Olino et al., 2011; Chandrasekhar Pammi et al., 2015; Ubl et al., 2015). However, MDD is often caused and maintained by maladaptive responses to *social* reward and loss, defined here as social acceptance and rejection, respectively. Social acceptance includes social support which has been shown to lessen the impact of stressors (Viswesvaran et al., 1999; Kaufman et al., 2004; Zimmer-Gembeck et al., 2007) and mitigates MDD symptoms (George et al., 1989). On the other hand, social rejection—when one is not wanted or liked—includes experiences such as parental rejection, peer victimization, and romantic rejection, all of which are known to precipitate and exacerbate MDD symptoms (Boyce et al., 1992; Rapee, 1997; Joiner and Coyne, 1999; Monroe et al., 1999; Kendler et al., 2003; Slavich et al., 2009; Copeland et al., 2013). Thus, the social environment plays an important role in the development and maintenance of MDD.

In healthy controls (HCs), a recent meta-analysis showed that both monetary and social reward anticipation engaged a common neural circuit encompassing the ventral striatum (nucleus accumbens, NAcc) and anterior insula (AI), along with the ventral tegmental and supplementary motor areas (Gu et al., 2019). The NAcc and the AI have also been shown to be engaged during monetary loss (Dugré et al., 2018; Oldham et al., 2018; Wilson et al., 2018) as well as during social loss (Eisenberger et al., 2003; Gunther Moor et al., 2010). The anterior cingulate cortex (ACC) is also implicated in the processing of monetary and social incentives (Rademacher et al., 2010; Dugré et al., 2018; Wilson et al., 2018), however there is considerable evidence for valence-dependent activations in the ACC with greater sensitivity to losses or reward reduction compared to gains (Bush et al., 2002; Gehring and Willoughby, 2002; Liu et al., 2011). Together, findings from HCs point to a core neural circuitry comprising the ventral striatum, the AI, and potentially the ACC, that is common to monetary and social reward and loss.

Emerging data from MDD studies suggest that abnormal neural responses to reward and loss in MDD depend on the type of stimuli (monetary or social) and particularly the salience associated with them. Studies using monetary incentives have shown reduced neural responsivity in the ventral striatum especially in the NAcc, and in the medial prefrontal cortex to monetary gain and loss in MDD (Steele et al., 2007; Pizzagalli et al., 2009; Stoy et al., 2012; Ubl et al., 2015). On the other hand, positive social feedback in MDD is associated with enhanced neural responsivity in the amygdala (Davey et al., 2011) and social rejection in MDD is associated with enhanced neural responsivity in the NAcc (Silk et al., 2014), AI and the amygdala (Silk et al., 2014; Kumar et al., 2017; Yttredahl et al., 2018). Consistent with the neural responses, behavioral responses also are heightened in response to social acceptance and rejection to MDD (Hsu et al., 2015; Yttredahl et al., 2018), indicating that social feedback may be especially salient in MDD. Thus, it is possible that MDD is characterized by hypo- and hyper-neural and behavioral responsivity to monetary and social stimuli, respectively. However, unlike neuroimaging studies in HCs that compared neural responses to monetary vs. social stimuli in HCs (e.g., Izuma et al., 2008; Rademacher et al., 2010; Lin et al., 2011; Xie et al., 2014), no study has examined if salience-related neural responses are differently represented in MDD based on the type of incentive stimuli.

We focused on the role of the AI and NAcc as *a priori* regions of interest (ROIs) because both are engaged during processing motivationally salient stimuli (Zink et al., 2003; Cooper and Knutson, 2008; Menon and Uddin, 2010), and have shown activations in response to both monetary and social stimuli during both reward and loss in MDD and HC (Elliott et al., 2000; Levita et al., 2009; Rademacher et al., 2010; Liu et al., 2011; Hsu et al., 2013, 2015; Zhang et al., 2013; Floresco, 2015; Achterberg et al., 2016; Dalgleish et al., 2017; Perini et al., 2018). Although the ACC is involved in processing monetary and social incentives (Rademacher et al., 2010; Dugré et al., 2018; Wilson et al., 2018), it appears to be involved mainly in processing monetary or social loss (Bush et al., 2002; Gehring and Willoughby, 2002; Liu et al., 2011; Silk et al., 2014; Yttredahl et al., 2018).

Thus, the goal of the present study was to systematically examine salience-related AI and NAcc activation during monetary and social reward and loss in MDD patients and HCs, in which each participant performed a monetary and social task during the same functional magnetic resonance imaging (fMRI) scan session. For the purpose of this study, the primary analysis for the monetary task focused on a subset of "certain trials" (which cued a guaranteed reward or a loss), as opposed to uncertain trials, as they indicated a known outcome, comparable to the known outcome of receiving acceptance or rejection feedback from the social task used in this study. Although outcomes from uncertain trials also engage the AI and the NAcc, these regions are also seen engaged during certain outcomes. For instance, AI activation was observed during decision making even in the presence of certain outcomes (Feinstein et al., 2006), and the NAcc was shown to be engaged even during certain rewards (Cooper and Knutson, 2008).

We tested MDD women and matched HC women (ages 18–55 years). Compared to men, women have higher rates of MDD, a more chronic course of the disorder (Essau et al., 2010), younger age of onset (Marcus et al., 2005), and more frequent relapse episodes (Oquendo et al., 2013). Furthermore, negative interpersonal relationships have been shown to be more predictive of MDD in women compared to men (Kendler et al., 2005; Kendler and Gardner, 2014). Thus, social stimuli may be more salient in eliciting the neural responses that are critical to understanding the pathophysiology of MDD in women. Since social stimuli are notably salient to MDD patients, we hypothesized heightened activations

during social acceptance and rejection in MDD relative to HCs in these regions. Demonstrating this distinction would be critical in understanding the nature, function, and clinical implications of reward-related abnormalities, ultimately leading to novel treatment strategies in MDD (Stoy et al., 2012; Zhang et al., 2013).

MATERIALS AND METHODS

Participants

Twenty women with MDD (ages 18–55 years; mean age ± standard deviation: 30.00 ± 10.84 years) and 20 HC women (ages 18–53 years; 30.25 ± 10.99 years), matched for age, sexual orientation, ethnicity, and relationship status were recruited from the community through local advertisements. Demographic and clinical characteristics are presented in **Table 1**. MDD patients were assessed for current depressive episode and HCs were screened for current or past history of psychiatric disorders using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 2006). Patient scores ranged from 10 to 21 (mild to moderate; Zimmerman et al., 2013) on the 17-item Hamilton Depression Rating Scale (HAM-D 17; Hamilton, 1960) and had a mean score of 14.88 ± 2.95. All patients had a primary diagnosis of MDD. As expected, most patients (n = 17) reported symptoms of anxiety, however only one met criteria for current comorbid social anxiety disorder (DSM-IV criteria assessed using the MINI). Four MDD patients were taking antidepressants during the course of the study but were on stable doses for at least 4 weeks prior to study recruitment. All other participants were free of psychotropic substances for at least 2 months, regular tobacco use, history of DSM-IV alcohol or drug dependence within the past 5 years, or alcohol or drug abuse in the past 2 years. All protocols were approved by the University of Michigan Medical School Institutional Review Board, and written informed consent was obtained from all participants.

TABLE 1 | Demographics and clinical characteristics.

	MDD Patients	Healthy Controls
Participants	20 women	20 women
Age	30.00 (10.84)	30.25 (10.99)
HAM-D	14.88 (2.95)	NA
Age of MDD onset	18.38 (7.37)	NA
Sexual Orientation (Heterosexual/ Homosexual/Bisexual)	16/0/4	19/1/0
Ethnicity		
Asian	0	2
Caucasian	15	14
Black or African American	4	3
Mixed	1	1
Relationship Status		
Single	11	12
In a relationship	6	5
Married	3	3

Abbreviations: MDD: major depressive disorder; HAM-D: 17-item Hamilton Depression Rating Scale. Mean values and standard deviations in parentheses are presented for Age, HAM-D, and Age of MDD onset. Sexual orientation, ethnicity, and relationship status are presented as the number of participants.

Monetary Incentive Delay Task

We used a version of the Monetary Incentive Delay Task (MID) described in Warthen et al. (2019). Briefly, in this event-related paradigm (**Figure 1A**), participants saw one of five cues (2 s), based on the trial type, followed by a delay phase indicated by a fixation cross (1.3–1.8 s). The delay phase was followed by brief presentation of a solid black triangle (∼250 ms). Participants were instructed to hit the target with a button press as quickly as possible, irrespective of the trial type. We varied the presentation time of the target dynamically based on participant's performance without their knowledge to ensure an average hit rate of about 60%. Following presentation of the brief target, subjects received feedback on whether they won or lost money based on the trial type (randomized 1–1.5 s). The feedback phase was followed by a variable inter-trial interval (ITI) of 2–6 s.

Trial type varied across two dimensions: valence (reward or loss) and certainty (certain or uncertain). Certain and uncertain trials have previously been described as "low-salience" and "high-salience" trials, respectively (Mickey et al., 2016), however, in the present study, we use the terms "certain" and "uncertain" to avoid confusion with discussions of saliency in other contexts in this manuscript. Valence was manipulated by varying the incentive outcome (positive outcomes = reward; and negative outcome = loss). Certainty was manipulated by varying the certainty associated with the outcome. For instance, in uncertain trials, participants were instructed to respond when the target appeared on screen for a chance to win money ($1; reward trials) or to avoid losing money ($1; loss trials). In other words, the outcome was uncertain (Uncertain Wins: UW; Uncertain Losses: UL). In certain trials, participants were instructed to respond to the target but were told that the outcome was certain and that their response did not have an impact on whether they won or lost $1 (Certain Wins: CW; Certain Losses: CL). The neutral trials ($0; Neu) did not have any money at stake, but participants were nevertheless instructed to respond to the target. The five trial types (CW, CL, UW, UL and Neu) were presented 10 times in a pre-defined pseudorandomized order during each run. There was a total of two runs, and a single run consisted of 10 presentations of each trial type (50 presentations in total). Each run lasted approximately 8 min and 30 s plus approximately 30 shim time between runs.

Social Feedback Task

Data collected from our previous study (Yttredahl et al., 2018) using the SFT for fMRI was used in the present study. Several days before the fMRI scan (17.88 ± 9.33 days, range 4–46 days), participants viewed fictitious dating profiles of preferred-sex individuals (potential partners) and were asked to rate these profiles based on how much they liked the potential partner and how much they thought the potential partner would like them back. There was no significant association between the number of days elapsed between profile ratings and behavioral measures collected on the day of the scan (self-esteem, desire to socialize, feeling happy and accepted, and feeling sad and rejected; Pearson's correlation coefficient r's > 0.17, p's > 0.30). In addition, there was no difference in the number of days elapsed

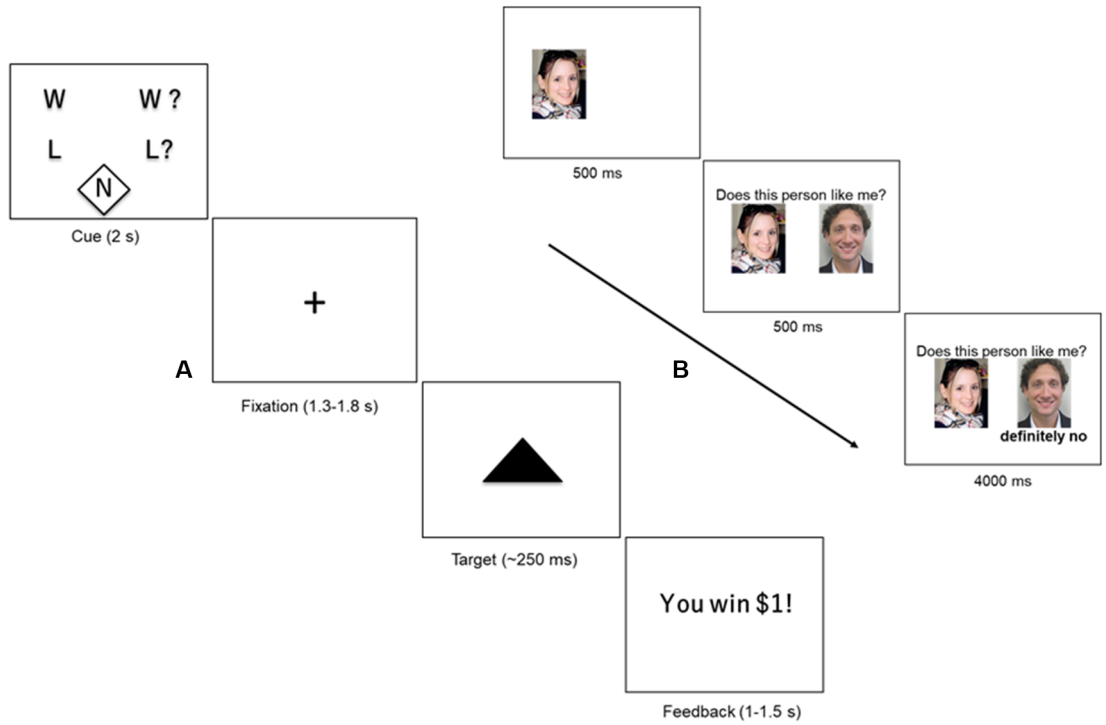


FIGURE 1 | (A) Monetary Incentive Delay Task (MID). Participants were presented with one of five cues (2 s) indicating the type of trial: certain win (W), uncertain win (W?), certain loss (L) uncertain loss (L?), or neutral (N). The cue was followed by a crosshair fixation of variable display period (1.3–1.8 s) followed by a short presentation of a target (~250 ms). Participants were instructed to hit the target using a button-press response box. At the end of the trial, the participant received feedback about the outcome of the trial (1–1.5 s), followed by a variable inter-trial interval (ITI) of 2–6 s. **(B)** Social Feedback Task (SFT). Each trial of the SFT begins with a picture of the subject, displayed for 500 ms, followed by a picture of a highly rated profile (500 ms) along with his/her rating of the subject ("feedback"; 4,000 ms). A rejection trial is presented. Figure adapted from our previous study (Yttredahl et al., 2018).

between ratings and the day of the scan between HCs and MDD (2-tailed t-test, $p > 0.22$).

To enhance the saliency of the feedback, only the highest rated profiles were shown to the participants during the fMRI scan. Participants were reminded at the start of the fMRI scan that they would only see profiles that were highly rated by them. As in our previous studies, the SFT does not involve deception, however, participants were asked to immerse themselves in the experience and respond as if the feedback was real, resulting in significant behavioral and neural responses (Hsu et al., 2013; Yttredahl et al., 2018). Inside the scanner, participants viewed a picture of themselves (500 ms) along with a picture of a highly rated profile (500 ms) followed by one of three types of feedback (4 s): acceptance (Acc), rejection (Rej), and neutral (Neu) in a block design (**Figure 1B**; Yttredahl et al., 2018). Each feedback type was presented in blocks consisting of four trials. fMRI images were collected in four runs, with each run consisting of six pseudorandomized blocks. Each run lasted 3 min and 12 s plus approximately 30 s shim times between runs.

During the screening visit, participants completed questionnaires that measure affect and motivation-related traits. In our previous study (Yttredahl et al., 2018), we found that left and right NAcc mediate trait reward responsiveness and increased ratings of feeling "happy and accepted" following acceptance in HCs, but not in MDD patients.

Emotion Ratings

Changes in emotional states in response to the SFT were measured in a separate testing session outside of the MRI scanner, since performing subjective ratings of emotionally salient stimuli has been shown to attenuate activity in areas such as the AI and amygdala (Taylor et al., 2003). Participants viewed a variant of the SFT whereby they were shown a block of 18 trials of each feedback type and were asked to indicate changes in emotional states following each block (Yttredahl et al., 2018). Responses were recorded on a 5-point Likert-type scale using a button-press response box. Similar to our previous studies (Hsu et al., 2013, 2015), for each participant scores for "sad" and "rejected" were averaged, and "happy" and "accepted" were averaged. These averaged scores were correlated with neural activations in the NAcc and AI during social acceptance and social rejection.

fMRI Acquisition

Functional image volumes (BOLD signal) were obtained using a T2*-weighted pulse sequence on a 3.0 Tesla GE Sigma 9.0 scanner (Milwaukee, WI, USA) with a standard radiofrequency coil at

the University of Michigan, Ann Arbor, MI, USA. Images were acquired using a single-shot combined spiral in/out sequence to reduce signal dropout in subcortical areas and around sinus regions. For each volume, 29 slices were acquired using the following parameters: repetition time, TR: 2,000 ms; echo time, TE: 30 ms; flip angle: 90°; field of view, FoV: 20 cm × 20 cm, 64 × 64 matrix; in-plane resolution: 3.13 × 3.13 mm; slice thickness: 4 mm.

A high-resolution T1-weighted pulse sequence provided anatomical localization (3D spoiled gradient recalled echo; TR, 12 ms; TE, 5 ms; TI, 500 ms; flip angle, 15°; FoV, 26 cm × 26 cm, 256 × 256 matrix; in-plane resolution, 1.02 × 1.02 mm; slice thickness, 1.2 mm).

fMRI Image Analysis

Functional images were preprocessed using a standard pipeline in FMRIB Software Library (FSL). Images were slice-time corrected and realigned to correct for motion artefacts. Images were reviewed for head movement >3 mm translation or 3° rotation. All 40 participants were included in the analysis of the MID (i.e., 20 MDD and 20 HCs). SFT data from one MDD patient was excluded from further analyses due to broad signal dropout in the striatum across all runs of the SFT (Yttredahl et al., 2018). SFT data from one HC were excluded due to excessive movement beyond our specified threshold of movement ≥3 mm maximum displacement (x, y or z direction) or ≥3 degrees of angular motion. Thus, the final sample for the SFT consisted of 19 MDD patients and 19 HCs. The six motion parameters were added as nuisance regressors to our fMRI model.

Using FSL, high-resolution T1 images were co-registered to the participants' functional images, segmented into tissue probability maps, and normalized to Standard Montreal Neurological Institute (MNI) space. The functional images were normalized using FSL and smoothed (5 mm full-width at half maximum) using a Gaussian Kernel.

First-level analysis was performed in Statistical Parametric Mapping v.8 (SPM8; Wellcome Institute of Cognitive Neurology, London, UK) using the General Linear Model (GLM), and maps were created for the primary contrasts of interest. The primary contrasts of interest were CW-Neu and CL-Neu, however, an exploratory analysis examined the neural response to the cue phase for "uncertain" wins and losses (i.e., UW-Neu and UL-Neu; **Supplementary Tables S2, S3**). For the SFT task, the primary contrasts of interest were Acc-Neu and Rej-Neu. Based on our hypothesis, we examined activations in the NAcc and AI during responses to both positive and negative monetary and social incentive stimuli. ROIs were anatomically defined using the Harvard Brain Atlas probability masks, thresholded at 0.25 confidence, and binarized (Yttredahl et al., 2018). The AI masks were bounded posteriorly at $y = 8$, based on a previous study that investigated neural responses to social exclusion (Way et al., 2009). A single mask comprising bilateral AI and bilateral NAcc was used for analysis in SPM8. All ROI analyses reported herein used an initial height threshold of $p_{\text{uncorrected}} < 0.001$ ($k > 10$), and subsequent small volume correction in *a priori* ROIs [SVC using family wise-error correction (FWE)] at $p_{\text{FWE-SVC}} < 0.05$).

Conjunction Analysis

To test our hypothesis that AI and NAcc were associated with salience of the stimuli regardless of valence, we performed a logical "AND" conjunction analysis (Subramaniam et al., 2015, 2016) to determine if there were voxels within the individual ROIs that were common to both certain wins and certain losses, as well as social acceptance and rejection. ROIs were chosen for conjunction only if both contrasts within the same task (i.e., CW-Neu and CL-Neu or Acc-Neu and Rej-Neu) showed activations either during within-group or between-group analyses.

Using Imcalc in SPM8, SVC thresholded maps ($p_{\text{FWE-SVC}} < 0.05$) were binarized for each condition. The binarized images were used to produce conjunction maps using the equation: i1 + (2 ∗ i2) (Subramaniam et al., 2015).

RESULTS

Behavior

MID Task

A repeated measures ANOVA showed a significant main effect of task condition on hit rate ($F_{(3.52,\ 133.91)} = 10.04$, $p < 0.001$) as well as reaction time ($F_{(4,152)} = 15.79$, $p < 0.001$) across all participants.

We did not find a significant group × condition interaction either for hit rate ($F_{(3.52,133.91)} = 0.31$, $p = 0.85$) or for reaction time ($F_{(4,152)} = 0.28$, $p = 0.89$) suggesting that the MDD group did not differ from the HCs in their performance on the MID. Additional analyses of behavioral data for the MID are reported in **Supplementary Table S1**.

SFT

MDD patients showed enhanced behavioral responses to social acceptance as well as social rejection compared to HCs, as shown by significantly greater increases in feeling "happy and accepted" during social acceptance ($t_{(36)} = 2.03$, $p = 0.05$), as well as a trend for greater decreases in feeling "happy and accepted" during social rejection ($t_{(30)} = 1.65$, $p = 0.11$). In addition, MDD patients also exhibited significantly increased desire to socialize ($t_{(27.16)} = 3.06$, $p = 0.005$), and decreased "sad and rejected" ($t_{(27.15)} = 2.64$, $p = 0.01$), as well as a trend for significant increases in self-esteem ($t_{(21.37)} = 1.81$, $p = 0.09$) during social acceptance compared with HCs.

Functional MRI

MID Task

HCs showed significant right AI activations during monetary wins ($x, y, z = 40, 20, -6$, $t = 4.92$, $k = 74$, $p_{\text{FWE-SVC}} = 0.027$) as well as losses ($x, y, z = 30, 12, -8$, $t = 8.29$, $k = 144$, $p_{\text{FWE-SVC}} < 0.001$; **Figure 2**). In MDD patients, significant activations were not found within the *a priori* regions AI or NAcc for certain wins or certain losses (both $p_{\text{FWE-SVC}} > 0.05$). Between-group analyses did not reveal significant differences between MDD patients and HCs during anticipation of either wins (CW-Neu) or losses (CL-Neu).

Conjunction analysis of monetary gain (CW-NT) and monetary loss (CL-NT; individual SVC thresholded maps) in

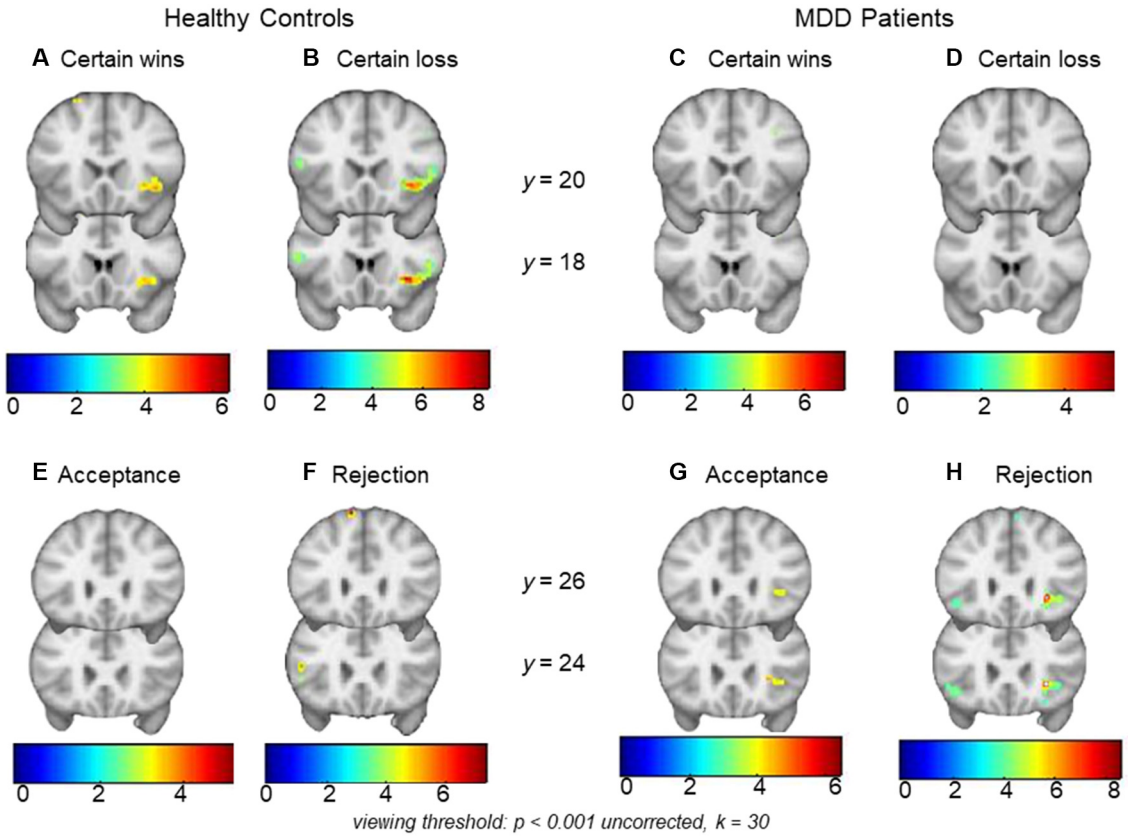


FIGURE 2 | Top row: panels **(A)** and **(B)** show right anterior insula (AI) activations during monetary certain wins and losses (minus neutral) respectively in healthy controls (HCs). Within-group analysis showed significant activations during monetary wins and loss in the right AI. Within-group analysis in major depressive disorder (MDD) did not show significant right AI activations either during **(C)** monetary wins or during **(D)** monetary loss (minus neutral). Bottom row: panels **(E)** and **(F)** show an absence of activation in HCs during social acceptance and rejection (minus neutral), whereas **(G)** and **(H)** show right AI activations during social acceptance and social rejection (minus neutral) in MDD patients. Within-group analysis showed significant activations during social rejection and a trend for significant activations during acceptance in the right AI. Viewing threshold: $p < 0.001$ (uncorrected), $k = 30$. Color bars represent range of t-values. Coronal sections of the brain are presented with the montreal neurological institute (MNI) y coordinates.

HCs revealed overlapping voxels in the right AI (center of mass: $x, y, z = 36.6, 21.5, -3.8$; $k = 126$; **Figure 3A**).

SFT

MDD patients showed significant activations in the right AI during social rejection ($x, y, z = 28, 24, -4$, $t = 8.57$, $k = 26$, $p_{\text{FWE-SVC}} < 0.001$), and a trend for significance in the same region during social acceptance ($x, y, z = 28, 24, 2$, $t = 4.66$, $k = 16$, $p_{\text{FWE-SVC}} = 0.051$; **Figure 2**). In HCs, significant activations were not found within the *a priori* regions AI or NAcc during acceptance or rejection trials (both $p_{\text{FWE-SVC}} > 0.05$). Between-group analyses did not reveal significant differences between MDD patients and HCs either during social acceptance (Acc-Neu) or during social rejection (Rej-Neu; both $p_{\text{FWE-SVC}} > 0.05$). Parameter estimates for the right AI during social acceptance and rejection were extracted in MDD patients. We did not find significant associations between neural activations and emotional rating scores (p's > 0.05).

Conjunction analysis of acceptance (Acc-Neu) and rejection (Rej-Neu; individual SVC thresholded maps) in MDD patients revealed overlapping voxels in the right AI (center of mass: $x, y, z = 35.6, 24.4, -2.0$; $k = 5$; **Figure 3B**).

DISCUSSION

The aim of the present study was to examine salience-related neural representation of monetary and social reward and loss in women with a diagnosis of MDD compared to HC women. Several studies have compared responses to monetary vs. social stimuli in HCs (Izuma et al., 2008; Rademacher et al., 2010; Lin et al., 2011; Xie et al., 2014), however, no study to our knowledge has examined these responses in MDD patients. Investigating how salience-related neural responses are differently represented in MDD based on the type of the incentive stimuli is important for improving our understanding of the nature, function, and clinical implications of reward-related abnormalities in MDD.

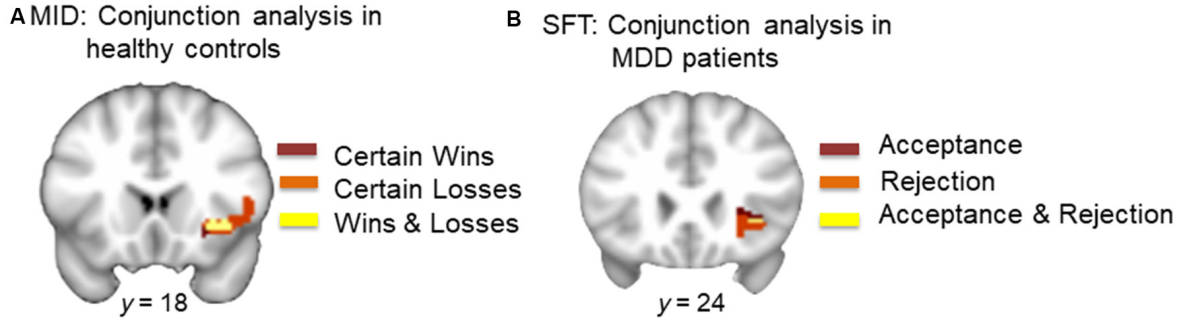


FIGURE 3 | (A) Conjunction analysis of monetary wins and losses in HCs. Dark red represents voxels in the right AI during certain wins (minus neutral). Orange represents voxels in the right AI during certain loss (minus neutral). Yellow represents overlapping voxels in the AI during both win and loss (center of mass: $x = 36.6$, $y = 21.5$, $z = -3.8$, $k = 126$). **(B)** Conjunction analysis of acceptance and rejection in MDD patients. Dark red represents voxels in the right AI during acceptance (minus neutral). Orange represents voxels in the right AI during rejection (minus neutral). Yellow represents overlapping voxels in the AI during both social acceptance and social rejection (center of mass: $x = 35.6$, $y = 24.4$, $z = -2.0$, $k = 5$).

Our results highlight two important findings. First, the within-group analysis showed that in response to monetary stimuli, HCs but not MDD patients showed significant activations in the right AI during both monetary gain and monetary loss. Conjunction analysis further showed that monetary gain and loss activated overlapping voxels within the right AI (**Figure 3A**). Second, patients with MDD, but not HCs showed a trend for significant activations in the right AI during social acceptance as well as strong activations in the same region during social rejection, in the within-group analysis. Conjunction analysis showed overlapping voxels within the right AI that responded to both acceptance and rejection (**Figure 3B**). Although direct comparisons between HCs and MDD patients in response to the MID or SFT were not significant, the within-group and conjunction analyses suggest a dissociable processing of reward and loss in MDD vs. HCs. This highlights the critical need to assess neural responses to both positive and negative stimuli, especially in the social domain in MDD. This differential response is particularly notable given that participants were informed that monetary incentives were real (i.e., participants were paid for money won during the MID), whereas the social feedback was only simulated (i.e., no deception was involved), suggesting that MDD patients experienced real monetary incentives as less salient than simulated social feedback.

The AI plays a key role in diverse functions and behaviors such as interoception, attention, and saliency, *via* projections to the NAcc and reciprocal connections with limbic and reward-related brain regions such as the amygdala, anterior and middle cingulate and the orbitofrontal cortex (Allen et al., 1991; Flynn, 1999; Rolls, 2016). In the social context, the AI is activated to understand the feelings of others (Lamm and Singer, 2010), and in response to both social inclusion and exclusion (Dalgleish et al., 2017). In patients with MDD relative to HCs, greater activations in the AI were found in response to both positive and control feedback conditions (Davey et al., 2011) as well as social exclusion (Kumar et al., 2017). In accordance with these studies, we found heightened AI activations in response to both social acceptance and rejection in MDD, which was not found in HCs. Overall, our results are supported by studies suggesting a more general role for the AI in salience processing during social feedback (Dalgleish et al., 2017) especially feedback directed at the self vs. others (Perini et al., 2018), rather than the valence of feedback.

A role for the AI in salience processing is not restricted to social stimuli. A number of neuroimaging studies have demonstrated a role for the AI during anticipation of aversive imagery, anticipation and experience of painful stimuli, and the encoding of monetary loss (Ploghaus et al., 1999; O'Doherty J. et al., 2003; Simmons et al., 2004; Koyama et al., 2005). However, the AI also responds to rewarding stimuli (Jessup and O'Doherty, 2014) suggesting that the salience of the outcome, and not only the valence drives activation in this region. As a key node of the salience network, AI initiates signals to engage higher order brain regions important for attentional processing and cognitive control (Menon and Uddin, 2010). In addition to assigning significance to the external stimuli, the AI is important for perception of internal bodily states (Craig, 2002, 2009; Critchley et al., 2004) and activations are found to correlate with participants' subjective emotional experiences (Zaki et al., 2012), suggesting an association between AI activations, subjective states, and experience of emotions (Critchley et al., 2004). In the present study, AI activations in MDD patients likely reflect the detection of salient social information, rather than interoception-related activations, since AI activations and subjective emotional experiences to feedback were not significantly correlated in this study.

Our results indicate that social feedback is a salient event that elicits a greater response in MDD patients. In HCs, AI activations in response to monetary stimuli are consistent with its role in the anticipation of a salient outcome and might suggest increased sensitivity to monetary cues, a finding absent in MDD patients. The increased AI activation in HCs in the present study in response monetary reward and loss cues is consistent with previous meta-analyses in HCs showing increased engagement

in the AI during both reward and loss anticipation (Oldham et al., 2018). Whether these dissociable responses to social and monetary incentive stimuli are also found in men will need to be ascertained in future studies.

Optimal activity in the AI is crucial to initiate appropriate responses to salient events (Uddin and Menon, 2009). Negative emotional stimuli (Hamilton et al., 2012) and to some extent positive and neutral stimuli (Davey et al., 2011) are shown to elicit greater AI activations in MDD patients vs. HCs, suggesting an over-reactive salience detection system. Not surprisingly, enhanced baseline activation in the AI in MDD is also predictive of poor response to any subsequent treatment (Fu et al., 2013). Whether AI in our MDD patients represent a pathological response to social feedback and the mechanisms by which this response contributes to dysfunctional reward and loss processing need to be ascertained in future studies.

We did not find significant differences in NAcc activations between MDD patients and HCs in either the MID or SFT. The NAcc has been shown to be more strongly recruited during the anticipation of rewards (Knutson et al., 2001; Ernst et al., 2004; Carter et al., 2009) and losses (Carter et al., 2009) compared to reinforcing outcomes (Knutson et al., 2001; Ernst et al., 2004), indicating that activity in this region may be more strongly activated by uncertain or unpredictable events. In support, several studies showed the association between NAcc and prediction error (Pagnoni et al., 2002; O'Doherty J. P. et al., 2003; Rodriguez et al., 2006), and that uncertainty of both wins, as well as losses, engaged the NAcc (Cooper and Knutson, 2008). The lack of significant activations in the NAcc may reflect limited uncertainty in the MID and SFT, since we modeled expected wins and losses in the MID, and the SFT only models expected outcome of acceptance or rejection feedback. Exploratory analyses showed that both uncertain wins, as well as uncertain losses, activated NAcc in both HCs and MDD patients (**Supplementary Material, Results**), confirming that uncertainty of monetary wins and losses more strongly activate the NAcc.

The majority of MDD patients (n = 17) in our sample exhibited sub-threshold symptoms of anxiety, and one met DSM-IV criteria for social anxiety disorder, raising the possibility that anxiety may have contributed to our findings. Previous studies have shown heightened striatal activation in response to unexpected positive feedback in socially anxious adolescents (Jarcho et al., 2015), or striatal hypersensitivity to increasing magnitudes of monetary gains or losses in adolescents with social phobia (Guyer et al., 2012). However, it is unclear how these findings relate to the present study, given our focus on adults with a primary diagnosis of MDD, and our findings in the AI but not the striatum. Nevertheless, future studies will need to examine differential responses to monetary and social incentives in MDD with and without comorbid social phobia.

Several limitations should be noted. First, the MID is designed as an event-related fMRI task that examines neural activation during *anticipation* of expected reward or loss, whereas the SFT is a blocked design that examined neural activation during the *consummatory* experience of social acceptance or rejection. Thus, it is possible that while MDD patients showed deficits in the anticipation of reward or loss, this may also occur in a task examining the *anticipation* of acceptance and rejection. A previous study showed that the anticipation of monetary and social rewards activated similar brain regions whereas the consumption of monetary and social rewards activated different areas (Rademacher et al., 2010), however, another study found that the consumption of monetary and social rewards activated similar areas (Wake and Izuma, 2017). Together these studies provide partial support that anticipation and consumption of monetary rewards activate similar areas. More fine-grained studies will need to examine both the anticipatory and consummatory phases of monetary vs. social reward in identical tasks, in both MDD patients and HCs. Second, our modest sample sizes may have led to insufficient power to detect significant between-group effects. Future studies will need to examine sex differences in AI activation during acceptance and rejection in MDD patients vs. HCs. Third, emotion ratings in response to the SFT were assessed after the scan, which may not be the most accurate representation of emotional responses during the scan. Fourth, connectivity analyses may have provided additional information on regional networks that may be altered across social and non-social contexts in MDD

In conclusion, we present preliminary evidence for dissociable neural responses to monetary and social stimuli in HC and MDD women. In response to the MID, HCs but not patients with MDD showed AI activations during both monetary reward and loss. In response to the SFT, MDD patients but not HCs showed AI activations during both social acceptance and rejection. The common neural responses in the AI across both positive and negative stimuli may indicate activations associated with the detection of salient information regardless of valence. Importantly, these findings highlight differential neural representations of salience to monetary and social domains as a function of MDD diagnosis in women, suggesting that future investigations of reward and loss systems in MDD need to consider both domains.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the University of Michigan Medical School Institutional Review Board, with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by University of Michigan Medical School Institutional Review Board.

AUTHOR CONTRIBUTIONS

AS analyzed the data, interpreted results, and wrote the manuscript. AY and EF assisted with data analyses

and interpretation. BM, TL, and SL assisted with research design, data analyses and interpretation, and manuscript edits. DH designed and conducted the study, and assisted with data analysis, interpretation, and manuscript edits.

FUNDING

This work was supported by the National Institutes of Mental Health grants K01 MH085035 (DH) and R01 MH102264 (DH).

ACKNOWLEDGMENTS

We thank the subjects for participation in the study. We also thank Mr. Ben Sanford for assisting with participant recruitment, MRI scanning and data processing.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2019.00149/full#supplementary-material

REFERENCES

Achterberg, M., van Duijvenvoorde, A. C. K., Bakermans-Kranenburg, M. J., and Crone, E. A. (2016). Control your anger! The neural basis of aggression regulation in response to negative social feedback. *Soc. Cogn. Affect. Neurosci.* 11, 712–720. doi: 10.1093/scan/nsv154

Allen, G. V., Saper, C. B., Hurley, K. M., and Cechetto, D. F. (1991). Organization of visceral and limbic connections in the insular cortex of the rat. *J. Comp. Neurol.* 311, 1–16. doi: 10.1002/cne.903110102

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®).* 5th Edn. Arlington, VA: American Psychiatric Association.

Boyce, P., Hickie, I., Parker, G., Mitchell, P., Wilhelm, K., and Brodaty, H. (1992). Interpersonal sensitivity and the one-year outcome of a depressive episode. *Aust. N. Z. J. Psychiatry* 26, 156–161. doi: 10.3109/00048679209072022

Bush, G., Vogt, B. A., Holmes, J., Dale, A. M., Greve, D., Jenike, M. A., et al. (2002). Dorsal anterior cingulate cortex: a role in reward-based decision making. *Proc. Natl. Acad. Sci. U S A* 99, 523–528. doi: 10.1073/pnas.012470999

Carter, R. M., Macinnes, J. J., Huettel, S. A., and Adcock, R. A. (2009). Activation in the VTA and nucleus accumbens increases in anticipation of both gains and losses. *Front. Behav. Neurosci.* 3:21. doi: 10.3389/neuro.08.021.2009

Chandrasekhar Pammi, V. S., Pillai Geethabhavan Rajesh, P., Kesavadas, C., Rappai Mary, P., Seema, S., Radhakrishnan, A., et al. (2015). Neural loss aversion differences between depression patients and healthy individuals: a functional MRI investigation. *Neuroradiol. J.* 28, 97–105. doi: 10.1177/1971400915576670

Cooper, J. C., and Knutson, B. (2008). Valence and salience contribute to nucleus accumbens activation. *Neuroimage* 39, 538–547. doi: 10.1016/j.neuroimage.2007.08.009

Copeland, W. E., Wolke, D., Angold, A., and Costello, E. J. (2013). Adult psychiatric outcomes of bullying and being bullied by peers in childhood and adolescence. *JAMA Psychiatry* 70, 419–426. doi: 10.1001/jamapsychiatry.2013.504

Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nat. Rev. Neurosci.* 3, 655–666. doi: 10.1038/nrn894

Craig, A. D. (2009). How do you feel—now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* 10, 59–70. doi: 10.1038/nrn2555

Critchley, H. D., Wiens, S., Rotshtein, P., Öhman, A., and Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nat. Neurosci.* 7, 189–195. doi: 10.1038/nn1176

Dalgleish, T., Walsh, N. D., Mobbs, D., Schweizer, S., van Harmelen, A.-L., Dunn, B., et al. (2017). Social pain and social gain in the adolescent brain: a common neural circuitry underlying both positive and negative social evaluation. *Sci. Rep.* 7:42010. doi: 10.1038/srep42010

Davey, C. G., Allen, N. B., Harrison, B. J., and Yücel, M. (2011). Increased amygdala response to positive social feedback in young people with major depressive disorder. *Biol. Psychiatry* 69, 734–741. doi: 10.1016/j.biopsych.2010.12.004

Dugré, J. R., Dumais, A., Bitar, N., and Potvin, S. (2018). Loss anticipation and outcome during the *Monetary Incentive Delay Task*: a neuroimaging systematic review and meta-analysis. *PeerJ* 6:e4749. doi: 10.7717/peerj.4749

Eisenberger, N. I., Lieberman, M. D., and Williams, K. D. (2003). Does rejection hurt? An fMRI study of social exclusion. *Science* 302, 290–292. doi: 10.1126/science.1089134

Elliott, R., Friston, K. J., and Dolan, R. J. (2000). Dissociable neural responses in human reward systems. *J. Neurosci.* 20, 6159–6165. doi: 10.1523/JNEUROSCI.20-16-06159.2000

Ernst, M., Nelson, E. E., McClure, E. B., Monk, C. S., Munson, S., Eshel, N., et al. (2004). Choice selection and reward anticipation: an fMRI study. *Neuropsychologia* 42, 1585–1597. doi: 10.1016/j.neuropsychologia.2004.05.011

Essau, C. A., Lewinsohn, P. M., Seeley, J. R., and Sasagawa, S. (2010). Gender differences in the developmental course of depression. *J. Affect. Disord.* 127, 185–190. doi: 10.1016/j.jad.2010.05.016

Feinstein, J. S., Stein, M. B., and Paulus, M. P. (2006). Anterior insula reactivity during certain decisions is associated with neuroticism. *Soc. Cogn. Affect. Neurosci.* 1, 136–136. doi: 10.1093/scan/nsl016

Floresco, S. B. (2015). The nucleus accumbens: an interface between cognition, emotion, and action. *Annu. Rev. Psychol.* 66, 25–52. doi: 10.1146/annurev-psych-010213-115159

Flynn, F. G. (1999). Anatomy of the insula functional and clinical correlates. *Aphasiology* 13, 55–78. doi: 10.1080/026870399402325

Fu, C. H., Steiner, H., and Costafreda, S. G. (2013). Predictive neural biomarkers of clinical response in depression: a meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies. *Neurobiol. Dis.* 52, 75–83. doi: 10.1016/j.nbd.2012.05.008

Gehring, W. J., and Willoughby, A. R. (2002). The medial frontal cortex and the rapid processing of monetary gains and losses. *Science* 295, 2279–2282. doi: 10.1126/science.1066893

George, L. K., Blazer, D. G., Hughes, D. C., and Fowler, N. (1989). Social support and the outcome of major depression. *Br. J. Psychiatry* 154, 478–485. doi: 10.1192/bjp.154.4.478

Gu, R., Huang, W., Camilleri, J., Xu, P., Wei, P., Eickhoff, S. B., et al. (2019). Love is analogous to money in human brain: coordinate-based and functional connectivity meta-analyses of social and monetary reward anticipation. *Neurosci. Biobehav. Rev.* 100, 108–128. doi: 10.1016/j.neubiorev.2019.02.017

Gunther Moor, B., van Leijenhorst, L., Rombouts, S. A., Crone, E. A., and Van der Molen, M. W. (2010). Do you like me? Neural correlates of social evaluation and developmental trajectories. *Soc. Neurosci.* 5, 461–482. doi: 10.1080/17470910903526155

Guyer, A. E., Choate, V. R., Detloff, A., Benson, B., Nelson, E. E., Perez-Edgar, K., et al. (2012). Striatal functional alteration during incentive anticipation in pediatric anxiety disorders. *Am. J. Psychiatry* 169, 205–212. doi: 10.1176/appi.ajp.2011.11010006

Hamilton, M. (1960). A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 23, 56–62. doi: 10.1136/jnnp.23.1.56

Hamilton, J. P., Etkin, A., Furman, D. J., Lemus, M. G., Johnson, R. F., and Gotlib, I. H. (2012). Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of baseline activation and neural response data. *Am. J. Psychiatry* 169, 693–703. doi: 10.1176/appi.ajp.2012.11071105

Hsu, D. T., Sanford, B. J., Meyers, K. K., Love, T. M., Hazlett, K. E., Walker, S. J., et al. (2015). It still hurts: altered endogenous opioid activity in the brain during social rejection and acceptance in major depressive disorder. *Mol. Psychiatry* 20, 193–200. doi: 10.1038/mp.2014.185

Hsu, D. T., Sanford, B. J., Meyers, K. K., Love, T. M., Hazlett, K. E., Wang, H., et al. (2013). Response of the μ-opioid system to social rejection and acceptance. *Mol. Psychiatry* 18, 1211–1217. doi: 10.1038/mp.2013.96

Izuma, K., Saito, D. N., and Sadato, N. (2008). Processing of social and monetary rewards in the human striatum. *Neuron* 58, 284–294. doi: 10.1016/j.neuron.2008.03.020

Jarcho, J. M., Romer, A. L., Shechner, T., Galvan, A., Guyer, A. E., Leibenluft, E., et al. (2015). Forgetting the best when predicting the worst: preliminary observations on neural circuit function in adolescent social anxiety. *Dev. Cogn. Neurosci.* 21–31. doi: 10.1016/j.dcn.2015.03.002

Jessup, R. K., and O'Doherty, J. P. (2014). Distinguishing informational from value-related encoding of rewarding and punishing outcomes in the human brain. *Eur. J. Neurosci.* 39, 2014–2026. doi: 10.1111/ejn.12625

Joiner, T. E., and Coyne, J. C. (1999). *The Interactional Nature of Depression: Advances in Interpersonal Approaches.* Washington, DC: American Psychological Association (APA).

Kaufman, J., Yang, B.-Z., Douglas-Palumberi, H., Houshyar, S., Lipschitz, D., Krystal, J. H., et al. (2004). Social supports and serotonin transporter gene moderate depression in maltreated children. *Proc. Natl. Acad. Sci. U S A* 101, 17316–17321. doi: 10.1073/pnas.0404376101

Kendler, K. S., and Gardner, C. O. (2014). Sex differences in the pathways to major depression: a study of opposite-sex twin pairs. *Am. J. Psychiatry* 171, 426–435. doi: 10.1176/appi.ajp.2013.13101375

Kendler, K. S., Hettema, J. M., Butera, F., Gardner, C. O., and Prescott, C. A. (2003). Life event dimensions of loss, humiliation, entrapment and danger in the prediction of onsets of major depression and generalized anxiety. *Arch. Gen. Psychiatry* 60, 789–796. doi: 10.1001/archpsyc.60.8.789

Kendler, K. S., Myers, J., and Prescott, C. A. (2005). Sex differences in the relationship between social support and risk for major depression: a longitudinal study of opposite-sex twin pairs. *Am. J. Psychiatry* 162, 250–256. doi: 10.1176/appi.ajp.162.2.250

Knutson, B., Bhanji, J. P., Cooney, R. E., Atlas, L. Y., and Gotlib, I. H. (2008). Neural responses to monetary incentives in major depression. *Biol. Psychiatry* 63, 686–692. doi: 10.1016/j.biopsych.2007.07.023

Knutson, B., Fong, G. W., Adams, C. M., Varner, J. L., and Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport* 12, 3683–3687. doi: 10.1097/00001756-200112040-00016

Koyama, T., McHaffie, J. G., Laurienti, P. J., and Coghill, R. C. (2005). The subjective experience of pain: where expectations become reality. *Proc. Natl. Acad. Sci. U S A* 102, 12950–12955. doi: 10.1073/pnas.0408576102

Kumar, P., Waiter, G. D., Dubois, M., Milders, M., Reid, I., and Steele, J. D. (2017). Increased neural response to social rejection in major depression. *Depress. Anxiety* 34, 1049–1056. doi: 10.1002/da.22665

Lamm, C., and Singer, T. (2010). The role of anterior insular cortex in social emotions. *Brain Struct. Funct.* 214, 579–591. doi: 10.1007/s00429-010-0251-3

Levita, L., Hare, T. A., Voss, H. U., Glover, G., Ballon, D. J., and Casey, B. (2009). The bivalent side of the nucleus accumbens. *Neuroimage* 44, 1178–1187. doi: 10.1016/j.neuroimage.2008.09.039

Lin, A., Adolphs, R., and Rangel, A. (2011). Social and monetary reward learning engage overlapping neural substrates. *Soc. Cogn. Affect. Neurosci.* 7, 274–281. doi: 10.1093/scan/nsr006

Liu, X., Hairston, J., Schrier, M., and Fan, J. (2011). Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. *Neurosci. Biobehav. Rev.* 35, 1219–1236. doi: 10.1016/j.neubiorev.2010.12.012

Marcus, S. M., Young, E. A., Kerber, K. B., Kornstein, S., Farabaugh, A. H., Mitchell, J., et al. (2005). Gender differences in depression: findings from the STAR* D study. *J. Affect. Disord.* 87, 141–150. doi: 10.1016/j.jad.2004.09.008

Menon, V., and Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Struct. Funct.* 214, 655–667. doi: 10.1007/s00429-010-0262-0

Mickey, B. J., Heffernan, J., Heisel, C., Peciña, M., Hsu, D. T., Zubieta, J.-K., et al. (2016). Oxytocin modulates hemodynamic responses to monetary incentives in humans. *Psychopharmacology* 233, 3905–3919. doi: 10.1007/s00213-016-4423-6

Monroe, S. M., Rohde, P., Seeley, J. R., and Lewinsohn, P. M. (1999). Life events and depression in adolescence: relationship loss as a prospective risk factor for first onset of major depressive disorder. *J. Abnorm. Psychol.* 108, 606–614. doi: 10.1037/0021-843x.108.4.606

O'Doherty, J., Critchley, H., Deichmann, R., and Dolan, R. J. (2003). Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. *J. Neurosci.* 23, 7931–7939. doi: 10.1523/JNEUROSCI.23-21-07931.2003

O'Doherty, J. P., Dayan, P., Friston, K., Critchley, H., and Dolan, R. J. (2003). Temporal difference models and reward-related learning in the human brain. *Neuron* 38, 329–337. doi: 10.1016/s0896-6273(03)00169-7

Oldham, S., Murawski, C., Fornito, A., Youssef, G., Yücel, M., and Lorenzetti, V. (2018). The anticipation and outcome phases of reward and loss processing: a neuroimaging meta-analysis of the monetary incentive delay task. *Hum. Brain Mapp.* 39, 3398–3418. doi: 10.1002/hbm.24184

Olino, T. M., McMakin, D. L., Dahl, R. E., Ryan, N. D., Silk, J. S., Birmaher, B., et al. (2011). "I won, but I'm not getting my hopes up": depression moderates the relationship of outcomes and reward anticipation. *Psychiatry Res.* 194, 393–395. doi: 10.1016/j.pscychresns.2011.04.009

Oquendo, M. A., Turret, J., Grunebaum, M. F., Burke, A. K., Poh, E., Stevenson, E., et al. (2013). Sex differences in clinical predictors of depression: a prospective study. *J. Affect. Disord.* 150, 1179–1183. doi: 10.1016/j.jad.2013.05.010

Pagnoni, G., Zink, C. F., Montague, P. R., and Berns, G. S. (2002). Activity in human ventral striatum locked to errors of reward prediction. *Nat. Neurosci.* 5, 97–98. doi: 10.1038/nn802

Perini, I., Gustafsson, P. A., Hamilton, J. P., Kämpe, R., Zetterqvist, M., and Heilig, M. (2018). The salience of self, not social pain, is encoded by dorsal anterior cingulate and insula. *Sci. Rep.* 8:6165. doi: 10.1038/s41598-018-24658-8

Pizzagalli, D. A., Holmes, A. J., Dillon, D. G., Goetz, E. L., Birk, J. L., Bogdan, R., et al. (2009). Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am. J. Psychiatry* 166, 702–710. doi: 10.1176/appi.ajp.2008.08081201

Ploghaus, A., Tracey, I., Gati, J. S., Clare, S., Menon, R. S., Matthews, P. M., et al. (1999). Dissociating pain from its anticipation in the human brain. *Science* 284, 1979–1981. doi: 10.1126/science.284.5422.1979

Rademacher, L., Krach, S., Kohls, G., Irmak, A., Gründer, G., and Spreckelmeyer, K. N. (2010). Dissociation of neural networks for anticipation and consumption of monetary and social rewards. *Neuroimage* 49, 3276–3285. doi: 10.1016/j.neuroimage.2009.10.089

Rapee, R. M. (1997). Potential role of childrearing practices in the development of anxiety and depression. *Clin. Psychol. Rev.* 17, 47–67. doi: 10.1016/s0272-7358(96)00040-2

Rodriguez, P. F., Aron, A. R., and Poldrack, R. A. (2006). Ventral-striatal/nucleus-accumbens sensitivity to prediction errors during classification learning. *Hum. Brain Mapp.* 27, 306–313. doi: 10.1002/hbm.20186

Rolls, E. T. (2016). Functions of the anterior insula in taste, autonomic, and related functions. *Brain Cogn.* 110, 4–19. doi: 10.1016/j.bandc.2015.07.002

Sheehan, D. V., Janavs, J., Baker, R., Sheehan, K. H., Knapp, E., and Sheehan, M. (2006). *The Mini-International Neuropsychiatric Interview (MINI) English Version 5.0. 0. 0-DSM-IV*. Tampa, FL: University of South Florida.

Shelton, R. C., and Tomarken, A. J. (2001). Can recovery from depression be achieved? *Psychiatr. Serv.* 52, 1469–1478. doi: 10.1176/appi.ps.52.11.1469

Silk, J. S., Siegle, G. J., Lee, K. H., Nelson, E. E., Stroud, L. R., and Dahl, R. E. (2014). Increased neural response to peer rejection associated with adolescent depression and pubertal development. *Soc. Cogn. Affect. Neurosci.* 9, 1798–1807. doi: 10.1093/scan/nst175

Simmons, A., Matthews, S. C., Stein, M. B., and Paulus, M. P. (2004). Anticipation of emotionally aversive visual stimuli activates right insula. *Neuroreport* 15, 2261–2265. doi: 10.1097/00001756-200410050-00024

Slavich, G. M., Thornton, T., Torres, L. D., Monroe, S. M., and Gotlib, I. H. (2009). Targeted rejection predicts hastened onset of major depression. *J. Soc. Clin. Psychol.* 28, 223–243. doi: 10.1521/jscp.2009.28.2.223

Smoski, M. J., Felder, J., Bizzell, J., Green, S. R., Ernst, M., Lynch, T. R., et al. (2009). fMRI of alterations in reward selection, anticipation, and feedback in major depressive disorder. *J. Affect. Disord.* 118, 69–78. doi: 10.1016/j.jad.2009.01.034

Spijker, J., Bijl, R. V., De Graaf, R., and Nolen, W. A. (2001). Determinants of poor 1-year outcome of DSM-III-R major depression in the general population: results of the Netherlands Mental Health Survey and Incidence

Study (NEMESIS). *Acta Psychiatr. Scand.* 103, 122–130. doi: 10.1034/j.1600-0447.2001.103002122.x

Steele, J., Kumar, P., and Ebmeier, K. P. (2007). Blunted response to feedback information in depressive illness. *Brain* 130, 2367–2374. doi: 10.1093/brain/awm150

Stoy, M., Schlagenhauf, F., Sterzer, P., Bermpohl, F., Hägele, C., Suchotzki, K., et al. (2012). Hyporeactivity of ventral striatum towards incentive stimuli in unmedicated depressed patients normalizes after treatment with escitalopram. *J. Psychopharmacol.* 26, 677–688. doi: 10.1177/0269881111416686

Subramaniam, K., Gill, J., Slattery, P., Shastri, A., Mathalon, D. H., Nagarajan, S., et al. (2016). Neural mechanisms of positive mood induced modulation of reality monitoring. *Front. Hum. Neurosci.* 10:581. doi: 10.3389/fnhum.2016.00581

Subramaniam, K., Hooker, C. I., Biagianti, B., Fisher, M., Nagarajan, S., and Vinogradov, S. (2015). Neural signal during immediate reward anticipation in schizophrenia: Relationship to real-world motivation and function. *Neuroimage Clin.* 9, 153–163. doi: 10.1016/j.nicl.2015.08.001

Taylor, S. F., Phan, K. L., Decker, L. R., and Liberzon, I. (2003). Subjective rating of emotionally salient stimuli modulates neural activity. *Neuroimage* 18, 650–659. doi: 10.1016/s1053-8119(02)00051-4

Ubl, B., Kuehner, C., Kirsch, P., Ruttorf, M., Diener, C., and Flor, H. (2015). Altered neural reward and loss processing and prediction error signalling in depression. *Soc. Cogn. Affect. Neurosci.* 10, 1102–1112. doi: 10.1093/scan/nsu158

Uddin, L. Q., and Menon, V. (2009). The anterior insula in autism: under-connected and under-examined. *Neurosci. Biobehav. Rev.* 33, 1198–1203. doi: 10.1016/j.neubiorev.2009.06.002

Viswesvaran, C., Sanchez, J. I., and Fisher, J. (1999). The role of social support in the process of work stress: a meta-analysis. *J. Vocat. Behav.* 54, 314–334. doi: 10.1006/jvbe.1998.1661

Wake, S. J., and Izuma, K. (2017). A common neural code for social and monetary rewards in the human striatum. *Soc. Cogn. Affect. Neurosci.* 12, 1558–1564. doi: 10.1093/scan/nsx092

Warthen, K. G., Sanford, B., Walker, K., Jones, K. G., Angstadt, M., Sripada, C., et al. (2019). Neuropeptide Y and representation of salience in human nucleus accumbens. *Neuropsychopharmacology* 44, 495–502. doi: 10.1038/s41386-018-0230-6

Way, B. M., Taylor, S. E., and Eisenberger, N. I. (2009). Variation in the μ-opioid receptor gene (OPRM1) is associated with dispositional and neural sensitivity to social rejection. *Proc. Natl. Acad. Sci. U S A* 106, 15079–15084. doi: 10.1073/pnas.0812612106

Wilson, R. P., Colizzi, M., Bossong, M. G., Allen, P., Kempton, M., and Bhattacharyya, S. (2018). Correction to: the neural substrate of reward anticipation in health: a meta-analysis of fMRI findings in the monetary incentive delay task. *Neuropsychol. Rev.* 28, 507–508. doi: 10.1007/s11065-018-9390-8

Xie, W., Yan, C., Ying, X., Zhu, S., Shi, H., Wang, Y., et al. (2014). Domain-specific hedonic deficits towards social affective but not monetary incentives in social anhedonia. *Sci. Rep.* 4:4056. doi: 10.1038/srep04056

Yttredahl, A. A., McRobert, E., Sheler, B., Mickey, B. J., Love, T. M., Langenecker, S. A., et al. (2018). Abnormal emotional and neural responses to romantic rejection and acceptance in depressed women. *J. Affect. Disord.* 234, 231–238. doi: 10.1016/j.jad.2018.02.083

Zaki, J., Davis, J. I., and Ochsner, K. N. (2012). Overlapping activity in anterior insula during interoception and emotional experience. *Neuroimage* 62, 493–499. doi: 10.1016/j.neuroimage.2012.05.012

Zhang, W.-N., Chang, S.-H., Guo, L.-Y., Zhang, K.-L., and Wang, J. (2013). The neural correlates of reward-related processing in major depressive disorder: a meta-analysis of functional magnetic resonance imaging studies. *J. Affect. Disord.* 151, 531–539. doi: 10.1016/j.jad.2013.06.039

Zimmer-Gembeck, M. J., Hunter, T. A., and Pronk, R. (2007). A model of behaviors, peer relations and depression: perceived social acceptance as a mediator and the divergence of perceptions. *J. Soc. Clin. Psychol.* 26, 273–302. doi: 10.1521/jscp.2007.26.3.273

Zimmerman, M., Martinez, J. H., Young, D., Chelminski, I., and Dalrymple, K. (2013). Severity classification on the Hamilton depression rating scale. *J. Affect. Disord.* 150, 384–388. doi: 10.1016/j.jad.2013.04.028

Zink, C. F., Pagnoni, G., Martin, M. E., Dhamala, M., and Berns, G. S. (2003). Human striatal response to salient nonrewarding stimuli. *J. Neurosci.* 23, 8092–8097. doi: 10.1523/JNEUROSCI.23-22-08092.2003

Conflict of Interest Statement: BM has acted as a consultant to Alkermes and has received research funds from Novartis for work unrelated to this manuscript.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer JLW declared a shared affiliation, with no collaboration, with one of the authors, DH, to the handling editor at time of review.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 16 July 2019
doi: 10.3389/fnbeh.2019.00160

Neural Mechanisms Involved in Social Conformity and Psychopathic Traits: Prediction Errors, Reward Processing and Saliency

Sandy Overgaauw[1,2]*, *Myrthe Jansen*[1,2], *Naomi J. Korbee*[1,2] and *Ellen R. A. de Bruijn*[1,2]

[1]*Department of Clinical Psychology, Institute of Psychology, Leiden University, Leiden, Netherlands,* [2]*Leiden Institute for Brain and Cognition (LIBC), Leiden University, Leiden, Netherlands*

Aligning behavior in favor of group norms, i.e., social conformity, can help to successfully adapt to uncertain environments and may result in social approval. This may lead to enhanced feelings of belongingness and is found to be associated with reward-related activations in the brain. Individuals high on psychopathic traits violate group norms regularly. Yet, it is unclear how psychopathic traits are related to neural mechanisms involved in social conformity. This functional magnetic resonance imaging (fMRI) study includes 42 healthy females scoring low or high on the Psychopathic Personality Inventory questionnaire (PPI). Participants were asked to rate the trustworthiness of 120 faces while lying in the scanner. After rating each face, participants were presented with the group rating of European students. In an unanticipated second part participants rated all faces again, allowing us to focus on two main contrasts: (1) "Social conflict": group opinion in conflict with the participant's rating vs. group opinion aligned with participant rating; and (2) "Conformity": conflict trials followed by conformity vs. conflict trials followed by non-conformity. Behaviorally, the two groups showed similar conformity behavior. fMRI results showed that both groups activated the nucleus accumbens (NAc) following alignment, suggesting the central role of prediction errors and reward. The data also showed a significant interaction between group and conformity in the amygdala. Following conflicts, females scoring low on psychopathic traits showed a trend in enhanced amygdala activation for conformity relative to non-conformity. Additionally, results showed a trend significant group effect for non-conformity. Females scoring high on psychopathic traits showed more activation for non-conformity compared to females scoring low on psychopathic traits, suggesting altered emotional salience of experiencing conflict depending on psychopathic traits. Taken together, these results support the importance of investigating the role of relevant traits in adaptive behavior when facing uncertain social situations and the neural mechanisms involved in this process.

Keywords: social conformity, social reward, psychopathic traits, amygdala, fMRI

OPEN ACCESS

Edited by:
Jason M. Chein,
Temple University, United States

Reviewed by:
Johanna M. Jarcho,
Temple University, United States
Edgardo O. Alvarez,
Laboratorio de Neuropsicofarmacología Experimental-CONICET Mendoza, Argentina
Esther Kristina Diekhof,
Universität Hamburg, Germany

***Correspondence:**
Sandy Overgaauw
s.overgaauw@fsw.leidenuniv.nl

Received: *21 November 2018*
Accepted: *01 July 2019*
Published: *16 July 2019*

Citation:
Overgaauw S, Jansen M, Korbee NJ and de Bruijn ERA (2019) Neural Mechanisms Involved in Social Conformity and Psychopathic Traits: Prediction Errors, Reward Processing and Saliency. Front. Behav. Neurosci. 13:160. doi: 10.3389/fnbeh.2019.00160

INTRODUCTION

People regularly change their opinion and behavior in order to align with group norms. For example, when you stop talking to your friend because the people around you fall silent complying with 2 min of silence on the Dutch day of remembrance. Acquiring knowledge by observing how other people behave or how they make decisions can help in making adequate adjustments to specific circumstances (Van de Waal et al., 2013), but it also helps in gaining social approval of others (Bond and Smith, 1996). This phenomenon of aligning behavior in favor of group norms is called social conformity (for a review, see Cialdini and Goldstein, 2004).

Adopting the opinion or behavior of a group can facilitate successful adaptation to uncertain social environments and may result in social approval leading to greater feelings of belongingness (Cialdini and Goldstein, 2004). Previous studies already showed that aligning with group norms can result in the involvement of the nucleus accumbens (NAc), demonstrating that adapting your behavior adequately and according to the social norms is associated with feelings of (social) reward (Campbell-Meiklejohn et al., 2010; Nook and Zaki, 2015). However, not everyone seems to care as much about adhering to social norms. Previous studies focusing on incarcerated individuals scoring high on psychopathic traits demonstrated that these individuals show a persistent violation of social norms and expectations (Hare et al., 1991; Lilienfeld and Andrews, 1996). They also suffer from affective and interpersonal deficits such as a lack of empathy, guilt and remorse, shallow emotions, and manipulative behavior (Hare et al., 1991; Lilienfeld and Andrews, 1996). However, prior studies did find that psychopaths experience social approval as rewarding. Nonetheless, their motivation seems to be different, as they might see social approval as a conformation that they successfully manipulated others and that they can use others for personal gain (Foulkes et al., 2014a). Yet, it is unclear how individual differences in psychopathic traits within a non-clinical sample are related to the neural mechanisms involved in social conformity. Therefore, the current study will investigate the neural mechanisms involved in conflicting feedback situations in which an individual opinion deviates from that of a group. Additionally, this study aims to unravel the neural mechanisms involved in aligning with group norms—i.e., social conformity—in subjects scoring low or high on psychopathic traits in order to test for group differences.

Social conformity was first demonstrated experimentally by Asch (1951) and has become a well-established and well-studied phenomenon over the years (for a review, see Stallen and Sanfey, 2015). Yet, only more recently neuroimaging studies have started to investigate the neural mechanisms of social conformity (for a review, see Schnuerch and Gibbons, 2014). Klucharev et al. (2009) designed a social conformity paradigm, in which participants were asked to rate the attractiveness of female faces, and subsequently were presented with a group norm (the average rating of European students), which could be either in conflict or in alignment with their own initial opinion. In order to detect whether participants would conform to the (simulated) attractiveness norm of European students, participants were asked to rate the same faces again (behaviorally) after they finished the functional magnetic resonance imaging (fMRI) session. Using this conformity paradigm, conflict with group opinion has been found to elicit prediction error signals in the rostral cingulate zone (RCZ) and the NAc. Additionally, Klucharev et al. (2009) showed that the neural signals in RCZ (activation) and NAc (deactivation) predicted participant's subsequent decision to conform to the group.

Evidence thus suggests that conformity is based on neural reinforcement-learning mechanisms, meaning that conforming behavior is reinforced by neural signals evoked by the conflict and alignment of own opinion with group norms (Schnuerch and Gibbons, 2015). These strong mechanisms are crucial for our motivation to be compliant with social norms and are essential for our survival (Cialdini and Goldstein, 2004). Posterior medial frontal cortex (including RCZ) and NAc play an important role in reinforcement learning (Holroyd and Coles, 2002; O'Doherty et al., 2004; Ridderinkhof et al., 2004; Klucharev et al., 2011), but also in the detection of errors and conflict, as well as in monitoring unfavorable outcomes (Ridderinkhof et al., 2004; de Bruijn et al., 2009; Radke et al., 2011). The NAc is also thought to play a central role in signaling errors in reward prediction (O'Doherty et al., 2004), and is implicated in the anticipation (Harsay et al., 2011) and experience of reward (O'Doherty et al., 2004).

When being part of a group, the implicit social rule to comply with the opinion of the majority is very common. Interestingly, when experiencing a conflict with a group norm, several processes could play a role: (1) detection of conflict; (2) reinforcement-learning; (3) monitoring of negative outcomes; but also (4) emotions elicited in response to a conflict. For example, in the study by Berns et al. (2005), participants performed a mental rotation task, either together with a group of peers or with a computer. Group and computer responses were manipulated so that the incorrect answer was given in one-third of the trials to induce conformity behavior. The authors demonstrated that when participants were in conflict with the group vs. the computer, amygdala activation was found. This brain area is involved in emotional learning, most notably in aversive learning (Berns et al., 2005; Belova et al., 2008; Roesch et al., 2010; Li et al., 2011; Klavir et al., 2013). As this activation was unique for situations in which participants were interacting with humans, Berns et al. (2005) suggested that this activation likely reflected the aversiveness and emotional salience of experiencing a social conflict. This outcome may, therefore, reflect an emotional route towards conformity, as amygdala activation during conflict with the group could signal the presence of an aversive event that one wants to avoid in the future.

How psychopathic traits are associated with neural mechanisms involved in social (non)conformity is yet unclear. We know from literature examining psychopaths in the criminal justice system that their failure to conform to social norms is often one of the reasons leading to their incarceration (Hare and Neumann, 2009). However, there are to our knowledge no

studies that investigated the relationship between psychopathy or psychopathic traits and brain activation when experiencing a social conflict. There is, nonetheless, some indirect evidence linking psychopathic traits to disturbed prediction error signaling in the brain. The prediction error signal in the RCZ is thought to be reflected by an event-related component called the feedback-related negativity (FRN; Ridderinkhof et al., 2004). The FRN has been found to predict behavioral adjustments, including adjustments in conformity paradigms involving, for example, line- and facial judgment tasks (Chen et al., 2012; Schnuerch and Gibbons, 2015). Prior electrophysiological studies have linked psychopathy-related constructs to decreased amplitudes of the FRN (Schulreich et al., 2013; Leno et al., 2016; Schulreich, 2016). Other studies, however, failed to find an association between the FRN and psychopathic traits (von Borries et al., 2010; Varlamov et al., 2011; Salim et al., 2015). Although findings are mixed, there is evidence for aberrant prediction error signaling.

Apart from EEG studies showing indirect evidence for the link between psychopathic traits and aberrant prediction error signaling on a neural level, there are also some fMRI studies supporting this. A fMRI study performed by White et al. (2013) suggested that psychopathic traits might be related to impaired prediction error signaling in the NAc. Their results showed that youth with conduct and oppositional defiant disorder showed reduced responsiveness to positive prediction errors (unexpected reward) and increased responsiveness to negative prediction errors (unexpected omission of reward) within the NAc while receiving feedback in a passive avoidance task. Moreover, Geurts et al. (2016) studied the neural mechanisms underlying reward expectations in psychopathic criminals and showed enhanced reward-related connectivity between the striatum (part of the NAc) and the dorsomedial prefrontal cortex—a region involved in cognitive control—during reward vs. no reward expectancy compared to healthy controls. Taken together, these studies additionally suggest that psychopathic traits could be related to disturbed prediction error signaling and reward expectancy in the RCZ and the NAc during social conflict in a social conformity task.

Another region involved in social conformity, which has repeatedly been found to show altered activations in individuals scoring high on psychopathic traits, is the amygdala. Several fMRI studies investigating social functioning in incarcerated psychopaths showed decreased amygdala and rostral anterior cingulate cortex (rACC) activation when facing immoral situations (Glenn et al., 2009; Harenski et al., 2010, 2014; Carré et al., 2013). The study by Carré et al. (2013) focused on psychopathic traits in community samples and how these traits related to brain activation following social cues. Evidence has been found for distinct neural activity while observing angry faces. Exclusively in females, Carré et al. (2013) found a positive association between ventral striatum (part of NAc) activity and coldheartedness, whereas exclusively in males they found a positive association between amygdala and impulsivity. Overall, these findings indicate that psychopathy might be associated with disturbances in neural areas thought to be involved in social conformity (i.e., RCZ, NAc, and amygdala). However, it remains unclear how psychopathic traits relate to neural activity while showing (non)conformity behavior following a social conflict. In order to test this, we used the social conformity paradigm designed by Klucharev et al. (2009), while focusing on the trustworthiness of female faces in line with Campbell-Meiklejohn et al. (2010).

The trustworthiness of someone's face is important for deciding whether to approach or to avoid this person, especially without additional contextual information (for example when only seeing a picture of a neutral face; Todorov, 2008). Relying on the group norm about whether or not to trust a person could help in preventing threatening situations. Previous studies including male violent offenders have demonstrated a lack of threat-avoiding abilities when facing social threat (Louise von Borries et al., 2012; Vieira et al., 2014), which has been found to be related to amygdala dysfunction (Kennedy et al., 2009). This distorted ability in approach/avoidance tendency could influence the extent to which individuals scoring high on psychopathic traits will conform to the group norm regarding the trustworthiness of faces, based on their altered perception. Additionally, a prior study found that females high on psychopathy reported lower levels of trust in response to a cooperative situation (Rilling et al., 2007), which could again influence their social conformity behavior.

In the current study, we hypothesized that females scoring high on psychopathic traits would show reduced conformity to a normative group opinion compared to females scoring low on these traits. Studying females in the context of conformity behavior is relevant as several prior studies have shown that females tend to conform more than males (Cooper, 1979; Eagly and Carli, 1981; Bond and Smith, 1996). In addition, our decision to only include women was also based on the findings of several prior studies that demonstrated significant higher psychopathic trait scores in males compared to females in community samples (Cale and Lilienfeld, 2002; Hemphälä and Tengström, 2010; Berkout et al., 2011). The present study addresses gaps in current knowledge on psychopathic traits by focusing on performance monitoring in a social context and by comparing the top 25% and bottom 25% of self-reported psychopathic traits (in line with Shao and Lee, 2017) in healthy female volunteers.

Although we know from previous studies that psychopathy is associated with norm-violating behavior and reduced empathic concern, which could lead to less conformity behavior (Kiehl and Hoffman, 2011; Seara-Cardoso et al., 2012; Foulkes et al., 2014b), we also take into account the possibility that females scoring high on psychopathic traits show no difference in conformity behavior. Perhaps they also experience social approval as rewarding, although with a different motivation (Foulkes et al., 2014a). On a neural level, we hypothesized, based on the findings by Klucharev et al. (2009), Campbell-Meiklejohn et al. (2010) and Berns et al. (2005), that overall conflict with group opinion would result in activation in the RCZ, amygdala, and deactivation in the NAc. Moreover, if activity in these regions predicts a participant's subsequent decision to conform to group opinion following a conflicting situation, then activation should be stronger in those trials where conflict with the group led to conformity than in trials where social conflict did not result

in conformity (Klucharev et al., 2009). Furthermore, based on the evidence summarized above suggesting impaired prediction error signaling in the RCZ and NAc in individuals scoring high on psychopathic traits in several reinforcement learning and error monitoring paradigms (Pfabigan et al., 2011; Schulreich et al., 2013; White et al., 2013; Leno et al., 2016), and based on the abundance of studies showing an association between psychopathy and amygdala dysfunction (Blair, 2008, 2013), we hypothesized that activity in the RCZ, NAc and amygdala would be modulated by individual differences in psychopathic traits in a social conformity task. In order to test this, we focused on two contrasts: (1) the "Social conflict" contrast: group opinion in conflict with participant rating vs. group opinion aligned with participant rating; and (2) the "Conformity" contrast: conflict trials followed by conformity vs. conflict trials followed by no conformity.

MATERIALS AND METHODS

Participants

The 42 participants that were included in this study (M = 19.85 years, SD = 1.34) were all female, right-handed, fluent in Dutch, and without neurological or psychiatric disorders; see **Table 1** for an overview of the group characteristics. To recruit females scoring low or high on psychopathic traits, we created a large pool of potential participants through advertisements on social media and the Leiden University Research Participation System called SONA. Participants completed a battery of questionnaires including the validated Dutch translation of the short-form of the Psychopathic Personality Inventory (PPI-SF: Tonnaer et al., 2013; see "Measures" section). We selected females scoring low (25th percentile) or high (75th percentile) on the PPI-SF from a total of 1,057 female adults. Participants completed the experiment for course credits or monetary compensation and provided written informed consent. The study was approved by the Institutional Review Board of the University Medical Center and conducted in accordance with the Declaration of Helsinki.

Measures

To assess psychopathic traits, participants completed the PPI-SF (Tonnaer et al., 2013). The 100-item PPI-SF is answered on a 4-point Likert scale (1-*false* and 4-*true*) and contains eight subscales: (1) machiavellian egocentricity (ruthlessness and narcissism in interpersonal functioning); (2) social potency (perceived ability to influence and manipulate others); (3) coldheartedness (callousness, guiltlessness, and unsentimentality); (4) carefree nonplanfulness (attitude of indifference in planning one's actions); (5) fearlessness (absence of anticipatory anxiety concerning harm and risk-taking behavior); (6) blame externalization (externalizing and rationalizing misbehavior); (7) impulsive nonconformity (reckless lack of concern regarding social mores); and (8) stress immunity (absence of emotional reactions to anxiety-provoking events).

TABLE 1 | Group characteristics of females scoring low and high on psychopathic traits (means and SDs).

	Low PPI (N = 22)	High PPI (N = 20)	p-value
Age	19.97 (1.48)	19.71 (1.20)	0.536
PPI-SF			
Total	162.86 (12.76)	229.25 (10.22)	<0.001
Machievellian egocentricity	25.68 (4.47)	39.50 (5.91)	<0.001
Social potency	31.59 (6.88)	47.05 (7.05)	<0.001
Fearlessness	19.09 (5.02)	29.35 (4.97)	<0.001
Coldheartedness	18.77 (4.48)	25.55 (10.35)	0.012
Impulsive non-conformity	19.00 (2.89)	26.30 (4.58)	<0.001
Externalization of guilt	15.36 (3.31)	21.85 (5.25)	<0.001
Carefree non-planfulness	19.36 (5.23)	23.40 (7.65)	0.051
Stress immunity	14.00 (4.26)	16.25 (4.55)	0.106

PPI-SF, Psychopathic Personality Inventory Short-Form.

Stimuli

We used a validated set of 120 digital photos of European females previously employed by Klucharev et al. (2009) and in accordance to Campbell-Meiklejohn et al. (2010). In our study, we focused on trustworthiness ratings in contrast to the attractiveness ratings used by Klucharev et al. (2009), but in line with Campbell-Meiklejohn et al. (2010). Trustworthiness judgments are positively correlated with judgments of attractiveness (Todorov et al., 2008), which means that, similar to attractiveness judgments, cross-gender ratings of trustworthiness might be associated with mate selection. By using only female faces and female participants, this gender bias was avoided.

Experimental Paradigm

Participants were told that they were taking part in a large scale European study called EuroTrust that aims to investigate how students at European universities perceive human trustworthiness. The logos of the "participating" European universities were included at the bottom of the instruction screen. During the fMRI session, participants rated the trustworthiness of 120 female faces on a scale from 1 (untrustworthy) to 8 (trustworthy; see **Figure 1**). Participants were able to answer as soon as the face was presented, but only after 2 s the participant's rating was visualized on the screen. The participant's decision was indicated by a green vertical rectangle frame (jittered between 1,500 and 2,750 ms). Then, during a 2 s period, the participant was presented with the group rating of the "average European student" of the same face indicated by a blue horizontal rectangle frame. The difference between the participant's rating and the "average European student" group rating was also presented above the scale and could be: −3, −2, 0, +2, or +3 points. The inter-trial interval was jittered between 2 and 4 s. Participants were informed that the "average European student" group ratings that matched their own rating within a 1 point range were perceived as no difference (i.e., 0 points). The task was programmed so that the "average European student" group rating agreed with the participant's rating in 33 percent of the trials (= 40 trials), whereas in 67 percent of the trials the "average European student" group ratings were either above or below participant's rating by 2 or 3 points (each 20 trials).

In an unanticipated second part, about 20 min after the fMRI session, participants rated all 120 faces again (in a newly

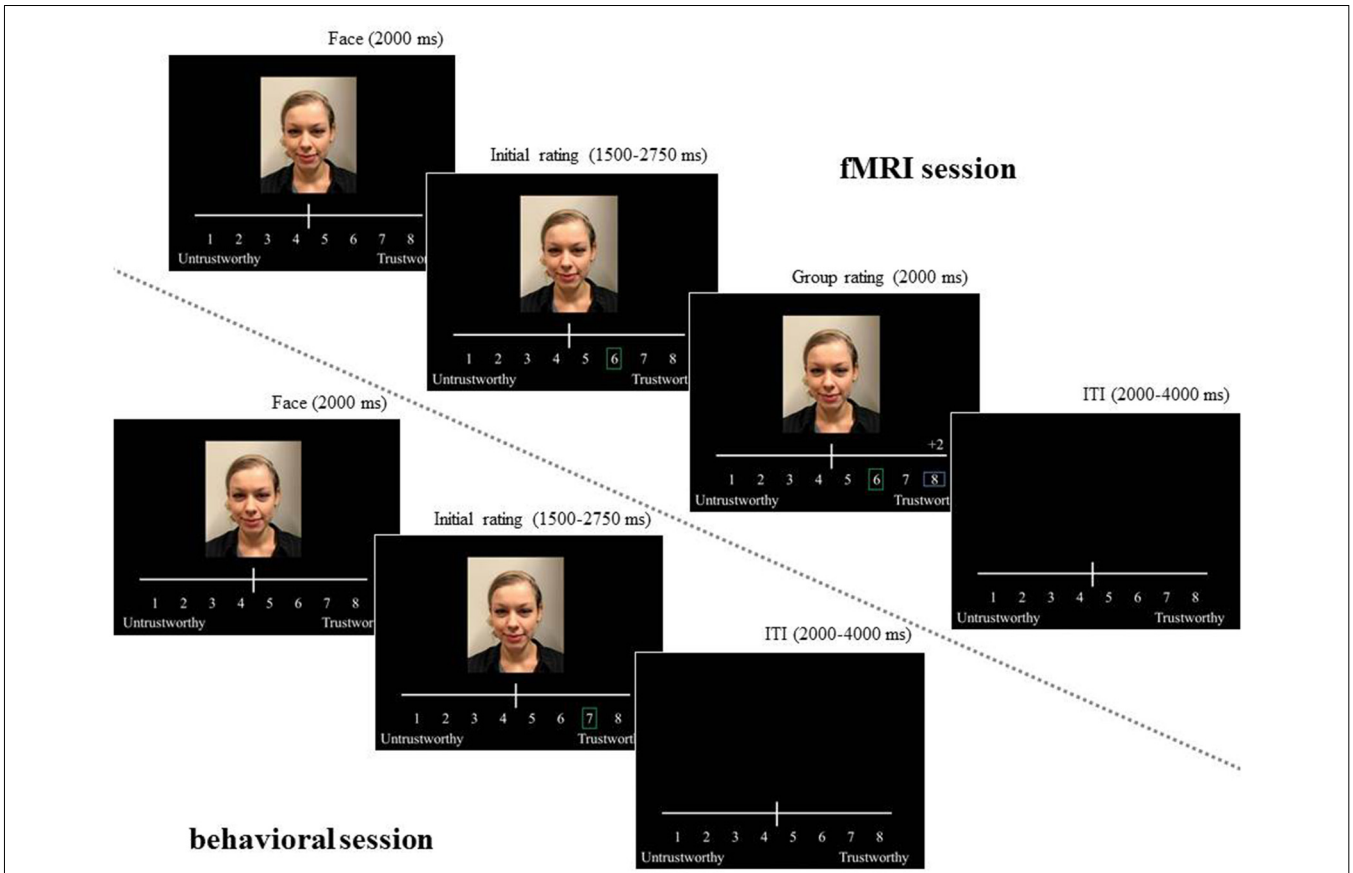


FIGURE 1 | Example of trial during functional magnetic resonance imaging (fMRI) and behavioral session of the Social Conformity Task. During the fMRI session, participants were asked to rate the trustworthiness of female faces on a scale from 1 (untrustworthy) to 8 (trustworthy). The participant's rating was visualized by a green rectangle frame that was followed by a presentation of the group rating of European students (blue horizontal rectangle frame). The difference in rating was presented above the "average European student" group rating (−3, −2, 0, +2, or +3). During the behavioral session (±20 min after fMRI session), participants were asked to rate the same faces again. This time, participants did not see the opinion of the European students. The subject in the figure gave permission to use her image by providing written informed consent.

randomized order), but this time without presentation of group feedback and outside of the scanner (see **Figure 1**). At the end of the experiment, participants received both oral and written questions about their responses on the task to check whether the manipulation worked as intended.

Alongside this study, we performed a behavioral control study. Participants in the control study (N = 32) also performed the task twice. However, in their version of the task, participants were simply instructed to rate the faces without group opinion being mentioned or presented. This was done in order to control for the effect of regression to the mean (RTM; Schnuerch et al., 2015); see behavioral data analyses for a complete description.

Behavioral Data Analyses

Prior to the analyses, we mean-centered all ratings by subtracting the mean of all trustworthiness ratings from each separate rating. Subsequently, we subtracted the first session trustworthiness ratings from the second session ratings to obtain a rating change score for each item. We followed the approach by Schnuerch et al. (2015) of adding a control group in order to assess and rule out the effect of RTM. RTM is the phenomenon that extreme values at first measurement tend to approach the mean on subsequent measurement (Barnett et al., 2005). By using a control group, which merely rated all images twice without being presented with group opinion (i.e., the social-influence manipulation), we could assess the isolated effect of initial ratings on subsequent rating changes. From the control group, a hierarchical linear model was derived that allowed to predict rating changes on the basis of initial ratings. In line with Schnuerch et al. (2015), a random-coefficient model was fitted using R packages lme4 (Bates et al., 2015) and lmerTest (Kuznetsova et al., 2017), which uses Satterthwaite's degrees of freedom method. Subsequently, this model was applied to the experimental group in order to estimate the expected rating change caused by the level of the initial rating (i.e., RTM). This RTM estimate was then used to obtain a corrected rating-change estimate per item for the experimental group that captured only the influence of group deviation. A 3-level factor "social influence" was created, consisting of group

lower (group deviation −2 and −3), group equal (deviation −1, 0 and +1), and group higher (+2 and +3). Then, a repeated measures ANOVA was performed, with the corrected trustworthiness rating change scores as dependent variable, the "average European student" group deviation as within-subjects factor and PPI-group (low vs. high) as between-subjects factor. We also calculated the proportion of conformity (the percentage of trials in which group conflict was followed by conformity) using the corrected rating change estimates and performed a repeated measures ANOVA with proportion conformity as dependent variable, the "average European student" group rating (lower vs. higher) as within-subjects factor and PPI-group as between-subjects factor.

Data Acquisition

Participants were scanned using a 3.0-Tesla Philips Achieva-scanner at the Leiden University Medical Center. Head motion was restricted using foam inserts surrounding the head. fMRI was performed using T2*-weighted Echo-Planar Images (EPI; TR: 2.2 s, TE: 30 ms, slicematrix 80 × 80, slice thickness: 2.75, FOV: 220 × 220 × 115 mm, slice gap 0.28 mm) in a functional run of 153 volumes. After the functioning scanning, a high resolution T1 structural scan was also acquired (TR: 9.76 ms, TE: 4.59 ms, 140 slices, voxel size: 0.875 mm, FOV: 224 × 177 × 168 mm).

Image analysis was carried out with SPM8 (Welcome Department of Cognitive Neurology, London, UK). The first two volumes of the run were discarded to allow for equilibration of T1 saturation effects and remaining images were realigned to the first volume. For each participant, the images were corrected for differences in slice acquisition time and spatially normalized using the default parameters. The images were corrected for motion, co-registered with the T1 anatomical image and spatially normalized to a T1 template based on the MNI305 stereotaxic space (Cocosco et al., 1997). The normalization algorithm used a 12-parameter affine transformation together with a non-linear transformation involving cosine basic functions and resampled the volumes to 3 mm cubic voxels. Images were spatially smoothed with a Gaussian kernel of 6 mm full-width at half-maximum. Translational movement parameters never exceeded one voxel (<3 mm) in any direction for any subject or scan. The participants who participated had a mean and maximum head movement of 0.08 and 2.52 mm. None of the participants had to be excluded due to excessive head movement.

fMRI Data Analysis

Statistical analyses were performed on individual participant's data using the general linear model in SPM8. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function (HRF). "Social conflict" was modeled as a separate event and was labeled as: Conflict > NoConflict, NoConflict > Conflict; i.e., trials in which individual judgment was in conflict with group opinion vs. trials in which individual judgment was in alignment with the group and reversed. Subsequently, we compared conflict trials followed by conformity vs. conflict trials not followed by conformity and reversed (based on the behavioral results): Conformity > Non-Conformity, and Non-Conformity > Conformity. The duration of the separate events was time-locked with a zero duration. The modeled events based on performed trials were used as covariates of interest in a general linear model along with a basic set of cosine functions that high-pass filtered the data and a covariate for run effects. The least-squares parameter estimates of height of the best-fitting canonical HRF for each condition were used in pairwise contrasts.

Anatomical region of interest (ROI) analyses were performed using a MarsBar toolbox in SPM8 (Brett et al., 2002) to further investigate brain activation for the "Social conflict" and "Conformity" contrasts. We selected anatomical regions based on previous studies (Berns et al., 2005; Klucharev et al., 2009) of the NAc and the amygdala derived from the MarsBaR anatomical toolbox. Additionally, since there is no anatomical RCZ available in the MarsBaR anatomical toolbox, we performed ROI analyses on a 10 mm radius sphere of the RCZ centered on −3, 14, 48 (Klucharev et al., 2009). Beta values reflecting activity were averaged across all voxels in the cluster, resulting in a mean value per ROI for each condition for each participant.

RESULTS

Behavioral Results

Total PPI scores ranged between 140 and 181 in the bottom quartile (N = 22; M = 162.86, SD = 12.76) and from 213–250 for females in the top quartile (N = 20; M = 229.25, SD = 10.22). An independent-samples t-test showed no significant differences in initial trustworthiness ratings between females scoring low (M = 4.85, SE = 0.12) or high (M = 4.69, SE = 0.12) on psychopathic traits as measured by the PPI, $t_{(40)}$ = 0.93, p = 0.359 nor between the experimental (N = 42, M = 4.77, SE = 0.08) and control group (N = 32, M = 5.07, SE = 0.15), $t_{(51.072)} = -1.771$, $p = 0.083$.

In line with Schnuerch et al. (2015), a random-coefficients model was fitted to the control group, which revealed that the fixed effect of initial rating was a significant predictor of subsequent rating change (γ_{10} = −0533, SE = 0.031, $t_{(32.96)} = -16.99$, $p < 0.001$. The random effect analyses showed that the slopes of initial rating showed little differences between participants (σ_δ^2 = 0.025) The fixed effect coefficient (γ_{10}) was then used to calculate rating changes scores adjusted for RTM in the experimental group following the formula described by Schnuerch et al. (2015). A repeated measures ANOVA revealed a significant main effect of group deviation on RTM-corrected rating change scores in the experimental group, $F_{(2,80)}$ = 8.19, p = 0.001, η_p^2 = 0.17, ε = 0.95. Pairwise comparisons showed that rating changes were significantly higher when the group had higher trustworthiness ratings (Δ = 0.13, SE = 0.04) compared to when the group rating was lower (Δ = −0.09, SE = 0.04, $p < 0.001$) and compared to trials where the group did not conflict with individual ratings (Δ = −0.05, SE = 0.03, $p < 0.001$). The difference in rating changes between trials with lower group ratings and trials where group ratings were equal to individual ratings did, however, not reach significance (p = 0.422). The effect of deviation was not modulated by PPI group, as the interaction of group

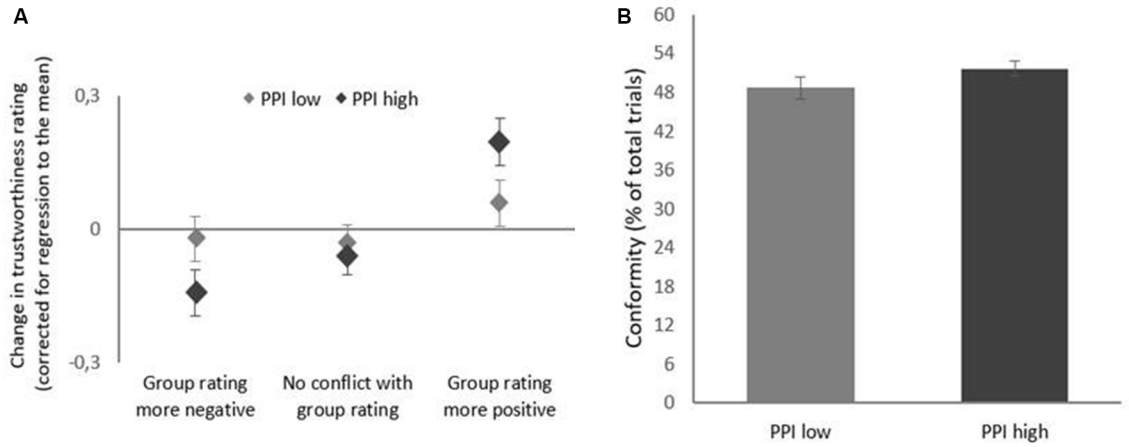


FIGURE 2 | (A) Mean behavioral conformity effect for each Psychopathic Personality Inventory (PPI) group, after correction for regression to the mean (RTM). The graph displays the change in trustworthiness ratings following: (1) a more negative (lower trustworthiness) "average European student" group rating compared to individual rating; (2) following no conflict with (same trustworthiness) "average European student" group rating; and (3) following a more positive (higher trustworthiness) "average European student" group rating. Bars indicate standard errors of the mean. **(B)** Mean percentage of conformity for both PPI groups, after correction for RTM.

deviation and PPI score did not reach significance (p = 0.084; see **Figure 2A**).

The rating change scores in the ANOVA used above not only incorporated the occurrence of behavioral conformal adjustments, but also the magnitude of these adjustments. For example, if the trustworthiness of a face is rated with a 3, and the group rated the trustworthiness with a 6, participants can conform to the group by choosing a 4 in the second session, but also by a 5 or 6. When opting for a 5 or 6, rating change score will be larger than when choosing a 4. Thus, the extent to which one adjusts their rating, influences the mean rating change scores. Therefore, we were also interested to see whether the mere occurrence of conformity would differ between PPI groups, regardless of how extreme this conformity-related adjustment was. To this end, we tested whether the total proportion of conformity differed between these groups while taking into account the direction of the group deviation. A repeated measures ANOVA revealed no significant main effect of group deviation (p = 0.889) nor any significant interaction effects of group deviation*PPI group (p = 0.171). The between-subjects effects was also not significant (p = 0.259; see **Figure 2B**).

fMRI Results

Anatomical ROIs and Sphere

First, we performed a 2 × 2 Mixed ANOVA with Conflict/NoConflict as within-subjects variable, and with Group (Low and High) as between-subjects variable separately for the RCZ, and for the NAc. The results for the RCZ demonstrated no significant main or interaction effects (all p's > 0.12). The results for the left NAc showed no significant main or interaction effects (all p's > 0.13). For the right NAc we did find a significant main effect ($F_{(1,40)}$ = 6.50, p = 0.015; η^2 = 0.14), demonstrating less deactivation for NoConflict (M = −0.24, SD = 0.14) vs. Conflict (M = −0.48, SD = 0.14). Yet, neither a main effect for group nor an interaction effect for Conflict/NoConflict*Group was found (p's > 0.41).

For the amygdala, a 2 × 2 Mixed ANOVA with Conformity/Non-Conformity as within-subjects variable, and Group (Low and High) as between-subjects variable showed an interaction effect for Conformity/Non-Conformity*Group ($F_{(1,40)}$ = 5.98, p = 0.019; η^2 = 0.13; see **Figure 3**). We performed pairwise comparisons to test for within and between group differences. The results showed a trend significant within-group-effect for the low scoring group (p = 0.081), with higher activation for Conformity (M = 0.49, SD = 0.15) vs. Non-Conformity (M = 0.17, SD = 0.15). Next, we tested for between group differences, showing a trend significant between-group-effect for Non-Conformity (p = 0.078). Females scoring high on psychopathic traits showed more activation for Non-Conformity (M = 0.49, SD = 0.15) compared to the females scoring low on psychopathic traits (M = 0.25, SD = 0.16).

DISCUSSION

The current study was the first to investigate how individual differences in psychopathic traits in females are associated with the neural mechanisms involved in social (non)conformity. We used an established social conformity paradigm to detect conformity to group opinion and to investigate associated neural processing of group opinion (Berns et al., 2005; Klucharev et al., 2009; Campbell-Meiklejohn et al., 2010, 2012; Nook and Zaki, 2015). First, our behavioral results show that conformity behavior does not differ between females scoring low and high on psychopathic traits. Second, neuroimaging results showed that social conflict did not activate the RCZ in either

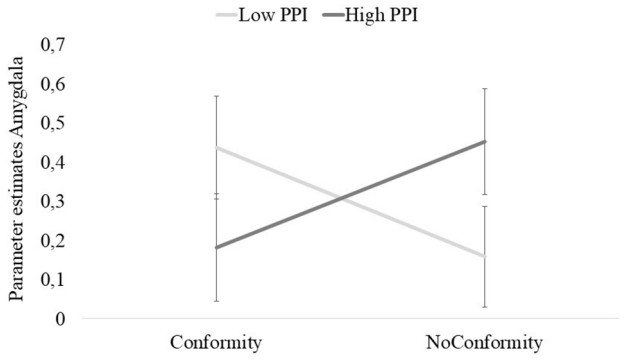


FIGURE 3 | Parameter estimates of the anatomical region of interest (ROI) of the amygdala. The results showed a significant interaction-effect for Conformity*Group (PPI low: females scoring low on psychopathic traits, *N* = 22; PPI high: females scoring high on psychopathic traits, *N* = 20). Females scoring low on psychopathic traits showed a trend in enhanced amygdala activation for conformity relative to non-conformity following conflicts. Additionally, results showed a trend significant between-group-effect for Non-Conformity. Females scoring high on psychopathic traits showed more activation for Non-Conformity compared to the females scoring low on psychopathic traits.

group, whereas alignment activated the NAc similarly in both groups. Third, we found that the amygdala was differently involved for conflict trials that were followed by conformity or non-conformity depending on the group: females scoring low on psychopathic traits tended to show higher amygdala activation for conformity relative to non-conformity following conflicts, whereas females scoring high on psychopathic traits showed higher activation than the low scoring group when conflicting feedback resulted in not conforming. Overall, this study partly replicates previous findings of Klucharev et al. (2009) and Berns et al. (2005) but also extends these outcomes by showing activation patterns that seem to be dependent on the level of psychopathic traits.

Our behavioral results showed that the groups showed no differences in conformity behavior. Numerically, females scoring high on psychopathic traits even seemed to conform to a greater extent compared to the females scoring low. These results contradict our initial hypothesis. Based on evidence for norm-violating behavior in psychopaths and reduced concern for others in individuals scoring high on psychopathic traits, we expected that conformity to a normative group opinion would be decreased in females with high levels of self-reported psychopathic traits (Kiehl and Hoffman, 2011; Seara-Cardoso et al., 2012; Foulkes et al., 2014b). However, our results suggest that these females show typical conformity behavior. In interpreting this finding, it is important to note that our participants were high-functioning university students. These students are considered "successful" within society, which could be explained by intact or even enhanced neurobiological and cognitive functioning. This allows them to achieve goals using more covert and nonviolent methods (Gao and Raine, 2010). In line with this, several experimental studies indicate that individuals in the general population do not possess the same behavioral deficits that characterize the clinical population in a range of social and emotional tasks (Gordon et al., 2004; Glenn et al., 2009; Marsh et al., 2011; Vieira et al., 2014). Yet, some experimental studies in the general population do indicate alterations in social behavior in relation to psychopathic traits (Rilling et al., 2007; Curry et al., 2011). For example, Rilling et al. (2007) reported that healthy participants with high levels of psychopathic traits defected more often and were less likely to continue cooperating after establishing mutual cooperation with a partner in a prisoner's dilemma game, but this effect was significant only in male participants. In favor of this notion, it has been argued that gender and societal factors may affect the expression of psychopathic traits (Forouzan and Cooke, 2005; Kreis and Cooke, 2011). For example, females are generally more fearful and risk-averse, and have better social skills. In contrast, males are usually more assertive and fearless compared to females (Kreis and Cooke, 2011). This suggests that typical traits associated with psychopathy such as reduced interpersonal concern might be less prominent in females. Moreover, gender roles and societal expectations might also shape differences in behavior. For example, whereas the masculine gender roles endorse being independent, dominant and assertive, the feminine gender roles promote passivity, compliance and conformity, as well as the expression of empathy (Block, 1983; Blashill, 2011). Females might benefit more from subtle techniques to attain their goals, and therefore can be expected to show enhanced submissive and adaptive behavior including conformity. It has also been suggested that psychopathic females use these stereotypical female traits as a manipulative facade to exploit others using more subtle interpersonal strategies (Kreis and Cooke, 2011). Another explanation for the lacking difference in behavior could be related to the different underlying motivations in females scoring low vs. females scoring high on psychopathic traits. Females scoring low on psychopathic traits could be motivated by a desire for social approval leading to feelings of belongingness, whereas females scoring high on psychopathic traits could be motivated by a desire for manipulation or by doing what's right in order to prevent to be conspicuous (Cialdini and Goldstein, 2004; Foulkes et al., 2014a). An alternative explanation, apart from gender, could be that some inventories might be more sensitive for psychopathy than others, which could explain differential findings between males and females. Taken together, female psychopathic traits seem to be less apparent on the behavioral level, which may be due to gender, societal factors, psychopathy inventories, and different underlying motivations. Future research on psychopathic traits and social conformity should, therefore, focus on direct comparisons between the female and male population using the same psychopathy inventories, and on inward beliefs.

Imaging findings of the social conflict contrast showed that for both groups, conflict with group opinion did not activate the RCZ differently compared to no conflict, whereas no conflict or alignment with the group activated the NAc. These results are therefore only partly comparable with the results of Klucharev et al. (2009). In contrast with their study, conflict with group

opinion did not activate the RCZ. Additionally, in contrast with Klucharev et al. (2009), we observed NAc activation during social alignment (no conflict) rather than NAc deactivation during social conflict. In agreement with our findings, other studies on social conformity have also found activation of the NAc during social alignment with group opinion rather than deactivation during social conflict (Campbell-Meiklejohn et al., 2010; Nook and Zaki, 2015). NAc activation during social alignment is thought to reflect the rewarding value of being in alignment with the opinion of others, and as such, could reflect a positive (social) prediction error (Campbell-Meiklejohn et al., 2010). Prior studies investigating social prediction errors also found an important role for the NAc. For example the study by Jones et al. (2011), reporting that the striatum plays an important role in positive social prediction errors by updating social expectations in order to adapt to changing environments. An important role for the NAc in social learning through prediction errors has also been shown in the study by Jarcho et al. (2015), who investigated social prediction errors in socially anxious vs. non-socially anxious adolescents and adults while receiving positive or negative feedback from peers they were not interested to chat with (low-value peers) and peers they were interested to chat with (high-value peers). The results showed that specifically in socially anxious adolescents, unexpected positive feedback from high-valued peers corresponded to heightened striatal activity and a failure to recall the positive feedback. Although we did not investigate social anxiety in our sample, the study by Jarcho et al. (2015) shows that how we value the other party can influence the saliency of our neural network. Therefore, it would be interesting to include this factor in future studies investigating psychopathic traits in order to disentangle the complex (neural) social learning mechanisms.

The fact that we did not find group differences regarding the social conflict contrast suggests that females high on psychopathic traits might not be characterized by the neural impairments in prediction error signaling that have previously been observed in the mainly (clinical) male population. This appears consistent with the behavioral results that showed intact conformity behavior in females high in psychopathic traits. According to the reinforcement learning account of social conformity (e.g., Klucharev et al., 2009), the prediction-error related signals in the RCZ and Nac indicate the need for behavioral adjustment, and as such, should serve to reinforce conformity behavior. If activity in these areas indeed predicts subsequent conformity, then activity should be stronger for trials in which social conflict was followed by conformity. However, when comparing conflict trials followed by conformity vs. no conformity, we did not find enhanced RCZ and Nac (de)activation in conformity trials. Therefore, the data do not seem to support the notion that larger RCZ and NAc responses may lead to more conformity. Notably, several other studies did not find the expected correlations between the behavioral and neural effects in the social conformity paradigm either (Kim et al., 2012; Shestakova et al., 2013; Huang et al., 2014). Using facial judgment tasks similar to the task we employed, these EEG studies showed that the conflict with group opinion triggered prediction error-signals (FRN), yet no relation between these components and conformity behavior was obtained. Therefore, we need more research in order to get a better understanding of other factors involved in the detection of social conflict and the subsequent behavioral change.

Next, our results showed that conflicts followed by (non)conformity were associated with amygdala activation. The follow-up analyses revealed trend-significant effects, suggesting that conflicts followed by conformity showed similar amygdala activation in both groups, whereas conflicts followed by non-conformity was associated with higher amygdala activation in the high scoring females. Although we are cautious in interpreting this outcome, it is remarkably in line with repeatedly demonstrated distorted amygdala activation in individuals scoring high on psychopathic traits when studying non-social aversive learning, suggesting altered emotional salience of experiencing a social conflict (e.g., Birbaumer et al., 2005; Schultz et al., 2016). A possible explanation for this could be that females with high levels of psychopathic traits attribute higher salience (as indicated by enhanced amygdala activation) to those conflicts that were followed by non-conformity compared to conflicts followed by conformity. As the amygdala is thought to play an important role in stimulus-reinforcement learning, and particularly aversive learning (Blair, 2007), this activity pattern seems counterintuitive. From an aversive learning perspective, enhanced salience or aversiveness of conflicts as indicated by increased amygdala activation should serve to adapt behavior as to avoid these conflicts in the future, and thus stimulate conformity rather than non-conformity. As such, the higher amygdala activation observed in high scoring females might be dysfunctional, as increased activity in this area seems to interfere with making the most adaptive choice, namely conformity. Additionally, it should be noted that when contrasting conformity vs. non-conformity, the low scoring group showed a tendency for higher amygdala activation. The higher amygdala activation observed in the low scoring females fits with prior studies including healthy individuals, as higher activity in this region is indicative for conformity behavior (Berns et al., 2005).

We speculate that the between-group pattern of amygdala activation might be explained by the concept of "memory conformity," which has been explained as a change of memory by social influence. According to the social psychology literature, conformity can be separated into two forms: (1) private conformity: conforming to a group norm, leading to (long-term) altered persistent memory errors; and (2) public conformity: conforming to a group norm, while inwardly remaining convinced of own memories and beliefs (Wright et al., 2009). Edelson et al. (2011) investigated the role of the amygdala in "memory conformity" in a social context, using a protocol in order to test for the persistence of memory errors following social manipulation. First, participants performed a memory test individually from which the correct trials were selected in order to use them in the second social manipulation test. Before performing the second test themselves, they observed four co-participants performing the task in which the co-participants, unknown to the

participant, structurally gave false answers. Finally, conformity behavior was tested by measuring persistent memory errors while participants performed the same memory test later in time, without the social manipulation. Results of the study of Edelson et al. (2011) showed enhanced amygdala activation when participants showed persistent memory errors, specifically after the social manipulation. Overall, these results indicate that the memory of participants was altered by social influence (i.e., private conformity). This finding is in line with the outcomes of our study as females scoring low on psychopathic traits demonstrated a tendency for heightened amygdala activity when conforming to the group following a conflict. Since the amygdala plays an important role in persistent memory errors following social manipulation, this specific outcome in the low scoring group suggests similar private conformity behavior compared to the findings of Edelson et al. (2011). Additionally, our results showed a trend significant group effect for non-conformity, with females scoring high on psychopathic traits showing more activation for non-conformity compared to females scoring low on psychopathic traits. The enhanced amygdala activity in the high scoring females, when not conforming to the group norm, might suggest that they only publicy conformed to the group norm, an interpretation that is obviously in need of future investigation. Therefore, we again would like to emphasize that we are cautious in interpreting these results, as the follow-up analyses of the significant interaction only revealed trend-significant effects.

The current study also holds some limitations. First, although we included enough participants to compare groups on a neural level, on a behavioral level the groups are rather small to make a sufficient comparison. Future studies should further investigate whether higher levels of psychopathic traits are of influence regarding conformity behavior while taking into account the possibility that individuals scoring high on psychopathic traits might over-conform as was suggested by the trend significant effect in the current study. Second, we created groups based on the total scores on the PPI-SF (Tonnaer et al., 2013), which limits the opportunity to test for sub-dimensions. We know from previous studies that psychopathy is a multidimensional construct (Lilienfeld, 2018), which also shows different profiles for males and females (Cale and Lilienfeld, 2002). As such, it might be worthwhile for future studies to include larger samples and to investigate the neural correlates of these distinct psychopathic subtypes in females using a dimensional approach. Moreover, participants experienced a social conflict in 67% of trials, which could have led to conflict habituation resulting in the absent RCZ main effect for conflict vs. no conflict. This is also in line with prior studies (e.g., Braver et al., 2001) who found that conflict-related brain responses are particularly enhanced if the conflict occurs infrequently (e.g., in 20% of the trials). Therefore, future studies might benefit from using a lower conflict frequency combined with more trials in order to create extra power to analyze conflict level and valence. Lastly, we did not account for female hormonal status as a possible confounding factor. Since we included an all-female sample, and prior studies have found oral contraceptives to influence amygdala and salience resting-state network (Petersen and Cahill, 2015; Engman et al., 2018), future studies should take this into account.

In summary, our results showed no behavioral differences in conformity to a normative group opinion in a sample of high-functioning females scoring low or high on psychopathic traits. Additionally, fMRI results showed no RCZ activity in both groups in case their opinion was conflicting with the opinion of the group, contrary to the findings of Klucharev et al. (2009). In case of no conflict, both groups showed reward-related activity in the NAc suggesting the involvement of (social) reward processes or social prediction errors when being in alignment with the group. Finally, we observed differential brain patterns for both groups in the amygdala during social conflict with group opinion, specifically related to (non)conformity behavior. We speculate that this might suggest that dependent on the level of psychopathic traits people used distinct neural mechanisms in order to achieve similar behavioral outcomes, possibly reflecting altered emotional salience of experiencing social conflict. Our findings emphasize the need to further explore the role of individual differences in social conformity, especially since the effects are rather small and only tested in relatively small groups. However, our sample was unique in its focus on psychopathic traits in an all-female sample. Gaining more insights into psychopathic traits in females is important, as it might have implications for the diagnosis and treatment of psychopathic traits in women (Wynn et al., 2012). Future studies should further investigate alterations in the neural mechanisms of social conformity, not only in females, but also in the male and clinical population. Additionally, future studies should collect data on how conformity is experienced. Perhaps individuals with high levels of psychopathic traits do not experience non-conformity as a social aversive learning signal. In that case, conforming to group norms might only be a strategy to successfully adapt to uncertain circumstances for the females scoring high on psychopathic traits, whereas the low scoring females might be predominantly motivated by a desire for social approval. Moreover, it would also be interesting to focus on whether individuals scoring high on psychopathic traits publically conform to group norms in order to be able to successfully adapt to uncertain circumstances or out of a desire for social approval, possibly reflecting a discrepancy between conformity behavior and inward beliefs. Such investigations could provide us with broader insights into the behavioral and neural anomalies associated with psychopathic traits, as well as potential gender differences. To conclude, the current study takes a first step in investigating individual differences in adaptive behavior when facing uncertain social situations and the neural mechanisms involved in this process.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Institutional Review Board of the Leiden University Medical Center with written

informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of the Leiden University Medical Center.

AUTHOR CONTRIBUTIONS

SO, MJ, and NK collected the data. SO, MJ, NK, and EB analyzed the data. SO, MJ, and EB wrote the manuscript, provided feedback, and revised the manuscript. All authors approved the final version.

FUNDING

This work was supported by a personal grant from Netherlands Organization for Scientific Research (Nederlandse Organisatie voor Wetenschappelijk Onderzoek) to EB (NWO; VIDI Grant No. 452-12-005).

ACKNOWLEDGMENTS

We are grateful to Merel de Bie, Nadine Jansen, Kelly Knoors, Sandor de Munck, and Margit Ruissen for assistance in recruiting participants and for assistance in scanning.

REFERENCES

Asch, S. E. (1951). "Effects of group pressure upon the modification and distortion of judgments," in *Groups, Leadership and Men Research in Human Relations*, ed. H. S. Guetzkow (Pittsburgh, PA: Carnegie Press), 177–190

Barnett, A. G., van der Pols, J. C., and Dobson, A. J. (2005). Regression to the mean: what it is and how to deal with it. *Int. J. Epidemiol.* 34, 215–220. doi: 10.1093/ije/dyh299

Bates, D., Mächler, M., Bolker, B., and Walker, S. (2015). Fitting linear mixed-effects models using lme4. *J. Stat. Softw.* 67:2015. Available online at: http://CRAN.R-project.org/package=lme4. Accessed March 05, 2019.

Belova, M. A., Paton, J. J., and Salzman, C. D. (2008). Moment-to-moment tracking of state value in the amygdala. *J. Neurosci.* 28, 10023–10030. doi: 10.1523/jneurosci.1400-08.2008

Berkout, O. V., Young, J. N., and Gross, A. M. (2011). Mean girls and bad boys: recent research on gender differences in conduct disorder. *Aggress. Violent Behav.* 16, 503–511. doi: 10.1016/j.avb.2011.06.001

Berns, G. S., Chappelow, J., Zink, C. F., Pagnoni, G., Martin-Skurski, M. E., and Richards, J. (2005). Neurobiological correlates of social conformity and independence during mental rotation. *Biol. Psychiatry* 58, 245–253. doi: 10.1016/j.biopsych.2005.04.012

Birbaumer, N., Veit, R., Lotze, M., Erb, M., Hermann, C., Grodd, W., et al. (2005). Deficient fear conditioning in psychopathy a functional magnetic resonance imaging study. *Arch. Gen. Psychiatry* 62, 799–805. doi: 10.1001/archpsyc.62.7.799

Blair, R. J. (2007). The amygdala and ventromedial prefrontal cortex in morality and psychopathy. *Trends Cogn. Sci.* 11, 387–392. doi: 10.1016/j.tics.2007.07.003

Blair, R. J. R. (2008). The amygdala and ventromedial prefrontal cortex: functional contributions and dysfunction in psychopathy. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 363, 2557–2565. doi: 10.1098/rstb.2008.0027

Blair, R. J. R. (2013). Psychopathy: cognitive and neural dysfunction. *Dialogues Clin. Neurosci.* 15, 181–190.

Blashill, A. J. (2011). Gender roles, eating pathology, and body dissatisfaction in men: a meta- analysis. *Body Image* 8, 1–11. doi: 10.1016/j.bodyim.2010.09.002

Block, J. H. (1983). Differential premises arising from differential socialization for the sexes: some conjectures. *Child Dev.* 54, 1335–1354. doi: 10.2307/1129799

Bond, R., and Smith, P. B. (1996). Culture and conformity: a meta-analysis of studies using Asch's (1952, 1956) line judgment task. *Psychol. Bull.* 119, 111–137. doi: 10.1037/0033-2909.119.1.111

Braver, T., Barch, D. M., Gray, J. R., Molfese, D. L., and Snyder, A. (2001). Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. *Cereb. Cortex* 11, 825–836. doi: 10.1093/cercor/11.9.825

Brett, M., Anton, J. L., Valabregue, R., and Poline, J. B. (2002). "Region of interest analysis using an SPM toolbox," in *Paper Presented at 8th International Conference on Functional Mapping of the Human Brain*, Sendai.

Cale, E. M., and Lilienfeld, S. O. (2002). Sex differences in psychopathy and antisocial personality disorder: a review and integration. *Clin. Psychol. Rev.* 22, 1179–1207. doi: 10.1016/s0272-7358(01)00125-8

Campbell-Meiklejohn, K., Bach, D. R., Roepstorff, A., Dolan, R. J., and Frith, C. D. (2010). How the opinion of others affects our valuation of objects. *Curr. Biol.* 20, 1165–1170. doi: 10.1016/j.cub.2010.04.055

Campbell-Meiklejohn, D. K., Simonsen, A., Jensen, M., Wohlert, V., Gjerloff, T., Scheel- Kruger, J., et al. (2012). Modulation of social influence by methylphenidate. *Neuropsychopharmacology* 37, 1517–1525. doi: 10.1038/npp.2011.337

Carré, J. M., Hyde, L. W., Neumann, C. S., Viding, E., and Hariri, A. R. (2013). The neural signatures of distinct psychopathic traits. *Soc. Neurosci.* 8, 122–135. doi: 10.1080/17470919.2012.703623

Chen, J., Wu, Y., Tong, G., Guan, X., and Zhhou, X. (2012). ERP correlates of social conformity in a line judgment task. *BMC Neurosci.* 13:43. doi: 10.1186/1471-2202-13-43

Cialdini, R. B., and Goldstein, N. J. (2004). Social influence: compliance and conformity. *Ann. Rev. Psychol.* 55, 591–621. doi: 10.1146/annurev.psych.55.090902.142015

Cocosco, C. A., Kollokian, V., Kwam, R. K. S., and Evans, A. C. (1997). Brain web: online interface to a 3D MRI simulated brain database. *Neuroimage* 5:452.

Cooper, H. M. (1979). Statistically combining independent studies: a meta-analysis of sex differences in conformity research. *J. Pers. Soc. Psychol.* 37, 131–146. doi: 10.1037/0022-3514.37.1.131

Curry, O., Chesters, M. J., and Viding, E. (2011). The psychopath's dilemma: the effects of psychopathic personality traits in one-shot games. *Pers. Individ. Diff.* 50, 804–809. doi: 10.1016/j.paid.2010.12.036

de Bruijn, E. R. A., de Lange, F. P., von Cramon, D. Y., and Ullsperger, M. (2009). When errors are rewarding. *J. Neurosci.* 29, 12183–12186. doi: 10.1523/JNEUROSCI.1751-09.2009

Eagly, A. H., and Carli, L. L. (1981). Sex of researchers and sex-typed communications as determinants of sex differences in influenceability: a meta-analysis of social influence studies. *Psychol. Bull.* 90, 1–20. doi: 10.1037/0033-2909.90.1.1

Edelson, M., Sharot, T., Dolan, R. J., and Dudai, Y. (2011). Following the crowd: brain substrates of long-term memory conformity. *Science* 333, 108–111. doi: 10.1126/science.1203557

Engman, J., Sundström Poromaa, I., Moby, L., Wikström, J., Fredrikson, M., and Gingnell, M. (2018). Hormonal cycle and contraceptive effects on amygdala and salience resting-state networks in women with previous affective side effects on the pill. *Neuropsychopharmacology* 43, 555–563. doi: 10.1038/npp.2017.157

Forouzan, E., and Cooke, D. J. (2005). Figuring out la femme fatale: conceptual and assessment issues concerning psychopathy in females. *Behav. Sci. Law* 23, 765–778. doi: 10.1002/bsl.669

Foulkes, L., McCrory, E. J., Neumann, C. S., and Viding, E. (2014a). Inverted social reward: associations between psychopathic traits and self-report and experimental measures of social reward. *PLoS One* 9:e106000. doi: 10.1371/journal.pone.0106000

Foulkes, L., Seara-Cardoso, A., Neumann, C. S., Rogers, J. S. C., and Viding, E. (2014b). Looking after number one: associations between psychopathic traits and measures of social motivation and functioning in a community sample of males. *J. Psychopathol. Behav. Assess.* 36, 22–29. doi: 10.1007/s10862-013-9381-2

Gao, Y., and Raine, A. (2010). Successful and unsuccessful psychopaths: a neurobiological model. *Behav. Sci. Law* 28, 194–210. doi: 10.1002/bsl.924

Geurts, D. E. M., von Borries, K., Volman, I., Bulten, B. H., Cools, R., and Verkes, R.-J. (2016). Neural connectivity during reward expectation dissociates psychopathic criminals from non-criminal individuals with high impulsive/antisocial psychopathic traits. *Soc. Cogn. Affect. Neurosci.* 11, 1326–1334. doi: 10.1093/scan/nsw040

Glenn, A. L., Raine, A., and Schug, R. A. (2009). The neural correlates of moral decision- making in psychopathy. *Mol. Psychiatry* 14, 5–6. doi: 10.1038/mp.2008.104

Gordon, H. L., Baird, A. A., and End, A. (2004). Functional differences among those high and low on a trait measure of psychopathy. *Biol. Psychiatry* 56, 516–521. doi: 10.1016/j.biopsych.2004.06.030

Hare, R. D., Hart, S. D., and Harpur, T. J. (1991). Psychopathy and the DSM-IV criteria for antisocial personality disorder. *J. Abnorm. Psychol.* 100, 391–398. doi: 10.1037/0021-843x.100.3.391

Hare, R. D., and Neumann, C. S. (2009). Psychopathy: assessment and forensic implications. *Can. J. Psychiatry* 54, 791–802. doi: 10.1177/070674370905401202

Harenski, C. L., Edwards, B. G., Harenski, K. A., and Kiehl, K. A. (2014). Neural correlates of moral and non-moral emotion in female psychopathy. *Front. Hum. Neurosci.* 8:741. doi: 10.3389/fnhum.2014.00741

Harenski, C. L., Harenski, K. A., Shane, M. S., and Kiehl, K. A. (2010). Aberrant neural processing of moral violations in criminal psychopaths. *J. Abnorm. Psychol.* 119, 863–874. doi: 10.1037/a0020979

Harsay, H. A., Cohen, M. X., Oosterhof, N. N., Forstmann, B. U., Mars, R. B., and Ridderinkhof, K. R. (2011). Functional connectivity of the striatum links motivation to action control in humans. *J. Neurosci.* 31, 10701–10711. doi: 10.1523/jneurosci.5415-10.2011

Hemphälä, M., and Tengström, A. (2010). Associations between psychopathic traits and mental disorders among adolescents with substance use problems. *Br. J. Clin. Psychol.* 49, 109–122. doi: 10.1348/014466509x439216

Holroyd, C. B., and Coles, M. G. (2002). The neural basis of human error processing: reinforcement learning, dopamine and the error-related negativity. *Psychol. Rev.* 109, 679–709. doi: 10.1037/0033-295x.109.4.679

Huang, Y., Kendrick, K. M., and Yu, R. (2014). Social conflicts elicit an N400-like component. *Neuropsychologia* 65, 211–220. doi: 10.1016/j.neuropsychologia.2014.10.032

Jarcho, J. M., Romer, A. L., Shechner, T., Galvan, A., Guyer, A. E., Leibenluft, E., et al. (2015). Forgetting the best when predicting the worst: preliminary observations on neural circuit function in adolescent social anxiety. *Dev. Cogn. Neurosci.* 13, 21–31. doi: 10.1016/j.dcn.2015.03.002

Jones, R. M., Somerville, L. H., Li, J., Ruberry, E. J., Libby, V., Glover, G., et al. (2011). Behavioral and neural properties of social reinforcement learning. *J. Neurosci.* 31, 13039–13045. doi: 10.1523/JNEUROSCI.2972-11.2011

Kennedy, D. P., Glascher, J., Tyszka, J. M., and Adolphs, R. (2009). Personal space regulation by the human amygdala. *Nat. Neurosci.* 12, 1226–1227. doi: 10.1038/nn.2381

Kiehl, K. A., and Hoffman, M. B. (2011). The criminal psychopath: history, neuroscience, treatment, and economics. *Jurimetrics* 51, 355–397.

Kim, B., M Liss, A., Rao, M., Singer, Z., and Compton, R. J. (2012). Social deviance activates the brain's error-monitoring system. *Cogn. Affect. Behav. Neurosci.* 12, 65–73. doi: 10.3758/s13415-011-0067-5

Klavir, O., Genud-Gabai, R., and Paz, R. (2013). Functional connectivity between amygdala and cingulate cortex for adaptive aversive learning. *Neuron* 80, 1290–1300. doi: 10.1016/j.neuron.2013.09.035

Klucharev, V., Hytönen, K., Rijpkema, M., Smidts, A., and Fernández, G. (2009). Reinforcement signal predicts social conformity. *Neuron* 61, 140–151. doi: 10.1016/j.neuron.2008.11.027

Klucharev, V., Munneke, M. A. M., Smidts, A., and Fernández, G. (2011). Downregulation of the posterior medial frontal cortex prevents social conformity. *J. Neurosci.* 31, 11934–11940. doi: 10.1523/jneurosci.1869-11.2011

Kreis, M. K., and Cooke, D. J. (2011). Capturing the psychopathic female: a prototypicality analysis of the comprehensive assessment of psychopathic personality (CAPP) across gender. *Behav. Sci. Law* 29, 634–648. doi: 10.1002/bsl.1003

Kuznetsova, A., Brockhoff, P. B., and Christensen, R. H. B. (2017). lmerTest package: tests in linear mixed effects models. Journal of statistical software. 82. Available online at: http://CRAN.R-project.org/package=lmerTest. Accessed February 11, 2019.

Leno, V. C., Naples, A., Cox, A., Rutherford, H., and McPartland, J. C. (2016). Common and distinct modulation of electrophysiological indices of feedback processing by autistic and psychopathic traits. *Soc. Neurosci.* 11, 455–466. doi: 10.1080/17470919.2015.1108223

Li, J., Schiller, D., Schoenbaum, G., Phelps, E. A., and Daw, N. D. (2011). Differential roles of human striatum and amygdala in associative learning. *Nat. Neurosci.* 14, 1250–1252. doi: 10.1038/nn.2904

Lilienfeld, S. O. (2018). The multidimensional nature of psychopathy: five recommendations for research. *J. Psychopathol. Behav. Assess.* 40, 79–85. doi: 10.1007/s10862-018-9657-7

Lilienfeld, S. O., and Andrews, B. P. (1996). Development and preliminary validation of self- report measure of psychopathic personality traits in noncriminal populations. *J. Pers. Assess.* 66, 488–524. doi: 10.1207/s15327752jpa6603_3

Louise von Borries, A. K., Volman, I., de Bruijn, E. R. A., Bulten, B. H., Verkes, R.-J., and Roelofs, K. (2012). Psychopaths lack the automatic avoidance of social threat: relation to instrumental aggression. *Psychiatry Res.* 200, 761–766. doi: 10.1016/j.psychres.2012.06.026

Marsh, A. A., Finger, E. C., Fowler, K. A., Jurkowitz, I. T. N., Schechter, J. C., Yu, H. H., et al. (2011). Reduced amygdala-orbitofrontal connectivity during moral judgments in youths with disruptive behavior disorders and psychopathic traits. *Psychiatry Res.* 194, 279–286. doi: 10.1016/j.pscychresns.2011.07.008

Nook, E. C., and Zaki, J. (2015). Social norms shift behavioral and neural responses to foods. *J. Cogn. Neurosci.* 27, 1412–1426. doi: 10.1162/jocn_a_00795

O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., and Dolan, R. J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science* 304, 452–454. doi: 10.1126/science.1094285

Petersen, N., and Cahill, L. (2015). Amygdala reactivity to negative stimuli is influenced by oral contraceptive use. *Soc. Cogn. Affect. Neurosci.* 10, 1266–1272. doi: 10.1093/scan/nsv010

Pfabigan, D. M., Alexopoulos, J., Bauer, H., Lamm, C., and Sailer, U. (2011). All about the money - external performance monitoring is affected by monetary, but not by socially conveyed feedback cues in more antisocial individuals. *Front. Hum. Neurosci.* 5:100. doi: 10.3389/fnhum.2011.00100

Radke, S., de Lange, F. P., Ullsperger, M., and de Bruijn, E. R. A. (2011). Mistakes that affects others: an fMRI study on processing of own errors in a social context. *Exp. Brain Res.* 211, 405–413. doi: 10.1007/s00221-011-2677-0

Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., and Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. *Science* 306, 443–447. doi: 10.1126/science.1100301

Rilling, J. K., Glenn, A. L., Jairam, M. R., Pagnoni, G., Goldsmith, D. R., Elfenbein, H. A., et al. (2007). Neural correlates of social cooperation and non-cooperation as a function of psychopathy. *Biol. Psychiatry* 61, 1260–1271. doi: 10.1016/j.biopsych.2006.07.021

Roesch, M. R., Calu, D. J., Esber, G. R., and Schoenbaum, G. (2010). Neural correlates of variations in event processing during learning in basolateral amygdala. *J. Neurosci.* 30, 2464–2471. doi: 10.1523/jneurosci.5781-09.2010

Salim, M. A., van der Veen, F. M., van Dongen, J. D. M., and Franken, I. H. A. (2015). Brain activity elicited by reward and reward omission in individuals with psychopathic traits: an ERP study. *Biol. Psychol.* 110, 50–58. doi: 10.1016/j.biopsycho.2015.07.001

Schnuerch, R., and Gibbons, H. (2014). A review of neurocognitive mechanisms of social conformity. *Soc. Psychol.* 45, 466–478. doi: 10.1027/1864-9335/a000213

Schnuerch, R., and Gibbons, H. (2015). Social proof in the human brain: electrophysiological signatures of agreement and disagreement with the majority. *Psychophysiology* 52, 1328–1342. doi: 10.1111/psyp.12461

Schnuerch, R., Schnuerch, M., and Gibbons, H. (2015). Assessing and correcting for regression toward the mean in deviance-induced social conformity. *Front. Psychol.* 6:669. doi: 10.3389/fpsyg.2015.00669

Schulreich, S. (2016). Altered performance monitoring in psychopathy: a review of studies on action selection, error and feedback processing. *Curr. Behav. Neurosci. Rep.* 3, 19–27. doi: 10.1007/s40473-016-0061-x

Schulreich, S., Pfabigan, D. M., Dertnl, B., and Sailer, U. (2013). Fearless dominance and reduced feedback-related negativity amplitudes in a time-estimation task—Further neuroscientific evidence for dual-process models of psychopathy. *Biol. Psychol.* 93, 352–363. doi: 10.1016/j.biopsycho.2013.04.004

Schultz, D. H., Balderston, N. L., Baskin-Sommers, A. R., Larson, C. L., and Helmstetter, F. J. (2016). Psychopaths show enhanced amygdala activation during fear conditioning. *Front. Psychol.* 7:348. doi: 10.3389/fpsyg.2016.00348

Seara-Cardoso, A., Neumann, C., Roiser, J., McCrory, E., and Viding, E. (2012). Investigating associations between empathy, morality and psychopathic personality traits in the general population. *Pers. Individ. Diff.* 52, 67–71. doi: 10.1016/j.paid.2011.08.029

Shao, R., and Lee, T. M. C. (2017). Are individuals with higher psychopathic traits better learners at lying? Behavioural and neural evidence. *Transl. Psychiatry* 7:e1175. doi: 10.1038/tp.2017.147

Shestakova, A., Rieskamp, J., Tugin, S., Ossadtchi, A., Krutitskaya, J., and Klucharev, V. (2013). Electrophysiological precursors of social conformity. *Soc. Cogn. Affect. Neurosci.* 8, 756–763. doi: 10.1093/scan/nss064

Stallen, M., and Sanfey, A. G. (2015). The neuroscience of social conformity: implications for fundamental and applied research. *Front. Neurosci.* 9:337. doi: 10.3389/fnins.2015.00337

Todorov, A. (2008). Evaluating faces on trustworthiness: an extension of systems for recognition of emotions signaling approach/avoidance behaviors. *Ann. N Y Acad. Sci.* 1124, 208–224. doi: 10.1196/annals.1440.012

Todorov, A., Said, C. P., Engell, A. D., and Oosterhof, N. N. (2008). Understanding evaluation of faces on social dimensions. *Trends Cogn. Sci.* 12, 455–460. doi: 10.1016/j.tics.2008.10.001

Tonnaer, F., Cima, M., Sijtsma, K., Uzieblo, K., and Lilienfeld, S. O. (2013). Screening for psychopathy: validation of the psychopathic personality inventory-short form with reference scores. *J. Psychopathol. Behav. Assess.* 35, 153–161. doi: 10.1007/s10862-012-9333-2

Van de Waal, E., Borgeaud, C., and Whiten, A. (2013). Potent social learning and conformity shape a wild primate's foraging decisions. *Science* 340, 483–485. doi: 10.1126/science.1232769

Varlamov, A., Khalifa, N., Liddle, P. F., Duggan, C., and Howard, R. (2011). Cortical correlates of impaired self-regulation in personality disordered patients with traits of psychopathy. *J. Pers. Disord.* 25, 75–88. doi: 10.1521/pedi.2011.25.1.75

Vieira, J. B., Almeida, P. R., Ferreira-Santos, F., Barbosa, F., Marques-Teixeira, J., and Marsh, A. A. (2014). Distinct neural activation patterns underlie economic decisions in high and low psychopathy scorers. *Soc. Cogn. Affect. Neurosci.* 9, 1099–1107. doi: 10.1093/scan/nst093

von Borries, A. K. L., Brazil, I. A., Bulten, B. H., Buitelaar, J. K., Verkes, R. J., and de Bruijn, E. R. A. (2010). Neural correlates of error-related learning deficits in individuals with psychopathy. *Psychol. Med.* 40, 1559–1568. doi: 10.1017/s0033291709992017

White, S. F., Pope, K., Sinclair, S., Fowler, K. A., Brislin, S. J., Williams, W. C., et al. (2013). Disrupted expected value and prediction error signaling in youths with disruptive behavior disorders during a passive avoidance task. *Am. J. Psychiatry* 170, 315–323. doi: 10.1176/appi.ajp.2012.12060840

Wright, D. B., Memon, A., Skagerberg, E. M., and Gabbert, F. (2009). When eyewitnesses talk. *Curr. Dir. Psychol. Sci.* 18, 174–178. doi: 10.1111/j.1467-8721.2009.01631.x

Wynn, R., Høiseth, M., and Pettersen, G. (2012). Psychopathy in women: theoretical and clinical perspectives. *Int. J. Womens Health* 4, 257–263. doi: 10.2147/ijwh.s25518

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 23 July 2019
doi: 10.3389/fnbeh.2019.00158

Behavioral and Neural Dysregulation to Social Rewards and Links to Internalizing Symptoms in Adolescents

*Seh-Joo Kwon[1], Susannah L. Ivory[2], Ethan M. McCormick[1] and Eva H. Telzer[1]**

[1] Department of Psychology and Neuroscience, The University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [2] Department of Psychology, Pennsylvania State University, State College, PA, United States

Adolescence is a time of unique sensitivity to socially salient stimuli such as social rewards. This period overlaps with the onset of psychopathology such as internalizing and externalizing symptoms. In the current studies, we examined behavioral and neural patterns of dysregulation to social rewards and threats, and links to internalizing and externalizing symptoms in youths. In study 1, we used a social Go/NoGo cognitive control task using peer faces to test for age-related behavioral differences in inhibitory failures in adolescents (N = 53, M_{age} = 13.37 years), and adults (N = 51, M_{age} = 43.71 years). In study 2, an independent adolescent sample (N = 51, M_{age} = 13.98 years) completed a similar social Go/NoGo cognitive control task during fMRI. Results show that adolescents had greater inhibitory failures – as measured by false alarm rate – to both social reward and threat cues than adults, and more so to social reward than threat cues. Greater inhibitory failures to social reward than threat cues were associated with greater internalizing symptoms, but were not significantly related to externalizing symptoms. At the neural level, greater inhibitory failures to social reward than threat cues as well as greater internalizing symptoms were both associated with heightened amygdala-ventral striatum connectivity. Our findings indicate that subcortico-subcortical connectivity, which is deemed to occur chronologically earlier and thus necessary for subcortico-cortical circuits, may serve as an early biomarker for emotion dysregulation and a risk factor for internalizing symptoms.

Keywords: adolescence, social reward, inhibitory failures, cognitive control, internalizing symptoms, connectivity, fMRI

OPEN ACCESS

Edited by:
Johanna M. Jarcho, Temple University, United States

Reviewed by:
Justin Daniel Caouette, Oregon Health & Science University, United States
Johnna Swartz, University of California, Davis, United States

***Correspondence:**
Eva H. Telzer
ehtelzer@unc.edu

Received: *18 March 2019*
Accepted: *28 June 2019*
Published: *23 July 2019*

Citation:
Kwon S-J, Ivory SL, McCormick EM and Telzer EH (2019) Behavioral and Neural Dysregulation to Social Rewards and Links to Internalizing Symptoms in Adolescents. Front. Behav. Neurosci. 13:158. doi: 10.3389/fnbeh.2019.00158

INTRODUCTION

Adolescence is a period of unique development characterized by a social reorientation in the brain (Nelson et al., 2005). That is, the adolescent brain undergoes neural plasticity and growth during the onset of puberty such that it becomes more sensitive to socially salient stimuli in the environment (Blakemore, 2008; Crone and Dahl, 2012; Pfeifer et al., 2013). During this neurobiological transformation, the adolescent brain shows greater sensitivity to social rewards as evidenced by heightened recruitment of limbic regions (e.g., amygdala, ventral striatum) in response to socially affective cues (Crone and Dahl, 2012; Galván, 2013). This social reorientation

explains, in part, why peers become an increasingly powerful influence in adolescents' lives, and why adolescents become more driven by socially appetitive cues such as social rewards (Galván, 2013; Smith et al., 2015; Foulkes and Blakemore, 2016). This bias toward social rewards may facilitate adolescents' desire to seek and value peer acceptance and group membership more so than children and adults (Brown et al., 1986; McElhaney et al., 2008), guiding adolescents to adjust their motivations to match their social context, and needs (Crone and Dahl, 2012). While developmentally normative (e.g., Perino et al., 2016), this heightened orientation to peer acceptance and social rewards may lead to emotion dysregulation (Masten et al., 2009; Breiner et al., 2018), and place adolescents at risk for psychopathology (Nelson et al., 2005).

During the adolescent years, a social reorientation toward peers and gaining social acceptance coincides with a heightened risk for psychopathology including internalizing (e.g., depression and anxiety) and externalizing (e.g., impulsivity, aggression, and conduct problems) symptoms (e.g., Achenbach, 1966; Costello et al., 2011). Internalizing and externalizing symptoms involve affective dysregulation and compromised executive functioning (Kerestes et al., 2014; Mullin et al., 2018) such as poorer cognitive control (Snyder and Hankin, 2016), as measured by lower inhibitory control (Schulz et al., 2004; Vuontela et al., 2013), and altered reaction times during inhibitory failures (Albrecht et al., 2005; Ladouceur et al., 2006). This ultimately has lasting implications on adolescents' lives (e.g., Fergusson and Woodward, 2002; Bongers et al., 2008). For instance, youths with internalizing and externalizing symptoms are more susceptible to experience internalizing disorders and substance use, respectively, in the future (e.g., Pine et al., 1998; Fergusson and Woodward, 2002; King et al., 2004). Youths with internalizing symptoms also experience social dysfunction such that those who perceive low acceptance tend to be more depressed (Zimmer–Gembeck et al., 2007) while those with externalizing symptoms have atypical socially rewarding experiences (Foulkes et al., 2014). Given the prevalence and enduring impact of internalizing and externalizing symptoms, it is therefore necessary to better understand neurodevelopmental risk factors in youths.

Emotional dys(regulation) is thought to underlie both internalizing and externalizing symptoms in adolescence and arises due to neural changes in the developing brain (e.g., Casey et al., 2019). While many neurodevelopmental models have been proposed to explain adolescents' enhanced orientation toward social rewards and their subsequent inabilities to engage in effective regulation [e.g., dual systems model (Steinberg, 2010); imbalance model (Casey et al., 2008)], these models and much of the empirical work focuses on cortico-subcortical (e.g., prefrontal cortex-ventral striatum) connectivity. However, prior to the development of down-regulation via the prefrontal cortex, emotional development is marked by a hierarchical cascade of changes in functional connectivity patterns, whereby development of subcortico-subcortical connectivity (e.g., amygdala-ventral striatum connectivity) occurs before that of cortico-subcortical connectivity, and serves as a necessary precursor to more complex neural interactions (Casey et al., 2019).

To date, there has been a wealth of research on amygdala and ventral striatum activation in tandem, however, only a few have probed connectivity between the two subcortical regions in humans. Amygdala-VS connectivity plays a vital role in relevance detection (Ousdal et al., 2012), affective valuation (Everitt and Robbins, 1992), and incentive-based learning (Fareri et al., 2015), which may promote downstream motivated cognition, and behavior (Ousdal et al., 2012; Fareri et al., 2015). Longitudinal (Pfeifer et al., 2011) and cross-sectional (Heller et al., 2016) studies highlight developmental decreases in amygdala-VS connectivity from childhood to adulthood, suggesting that strengthened connectivity between these regions is a developmentally immature neural phenotype and may underlie difficulties in emotion regulation in adolescence. Indeed, greater amygdala-VS connectivity is associated with behavioral disinhibition to emotional cues (Heller et al., 2016), which may place youth at risk for psychopathology. While there indeed is a large body of literature on the links between alternations in amygdala and ventral striatum activation and internalizing and externalizing symptoms in adolescents, especially in a socially rewarding context (e.g., Scheres et al., 2007; Guyer et al., 2008; Monk et al., 2008; Davey et al., 2011; Telzer et al., 2014; Olino et al., 2015; Fareri and Tottenham, 2016), little to no research has probed how alterations in amygdala-VS connectivity relate to internalizing and externalizing symptoms (but see Roy et al., 2013). This calls for further investigation into how maladaptive processing of social rewards relate to subcortico-subcortical connectivity and internalizing and externalizing symptoms.

In the current studies, we sought to investigate the behavioral and neural correlates of disinhibition to socially affective cues (social rewards and social threats) and links to internalizing and externalizing symptoms in adolescents. In the current study, participants completed a social Go/NoGo task where "go" and "no-go" cues were superimposed onto social reward (e.g., happy peer face), social threat (e.g., angry peer face), or neutral (i.e., neutral peer face) images. Past studies have utilized similar Go/NoGo tasks to assess inhibitory failures operationalized by false alarm rates (i.e., pressing a button on no-go trials; e.g., Somerville et al., 2011; Perino et al., 2016). Positive (e.g., happy) and negative (e.g., angry) facial expressions serve as social reinforcers that induce approach/reward and avoidance/threat responses, which can alter the probability of enacting executive functions such as response latencies (e.g., Hare et al., 2005; Kohls et al., 2009). Thus, happy and angry faces are frequently used in fMRI research to elicit social reward and social threat processing, respectively (e.g., Gorno-Tempini et al., 2001; Hare et al., 2008; Somerville et al., 2011; Cremers et al., 2015). Moreover, social reward (happy faces) and social threat (angry faces) cues recruit amygdala-striatal circuitry (Pfeifer et al., 2011; Heller et al., 2016).

In study 1, adolescent and adult participants completed the social Go/NoGo task behaviorally to test for developmental differences. The task was developmentally congruent, such

that adolescents viewed adolescent faces and adults viewed adult faces. The goal of study 1 was to ensure ecological validity of the task that utilizes peer faces by replicating prior behavioral findings that have shown that adolescents relative to children and adults make more false alarms in the presence of social reward cues (Somerville et al., 2011; Perino et al., 2016). Thus, we hypothesized that adolescents relative to adults would show greater behavioral disinhibition to social reward cues relative to social threat and neutral cues (Somerville et al., 2011; Perino et al., 2016).

In study 2, an independent sample of adolescents completed the social Go/NoGo task during an fMRI session. Prior developmental neuroimaging work has shown that adolescents show greater amygdala-VS connectivity relative to adults, and heightened connectivity is associated with greater behavioral disinhibition to emotional cues on a social Go/NoGo task (Heller et al., 2016). Thus, we hypothesized that greater disinhibition to social reward cues would be associated with greater amygdala-VS connectivity since heightened subcortical coupling is seen as developmentally immature (Casey et al., 2019).

Finally, we examined behavioral and neural links with internalizing and externalizing symptoms. At the behavioral level, we hypothesized that greater disinhibition to social reward cues relative to social threat cues would be associated with higher internalizing and externalizing symptoms. At the neural level, we hypothesized that stronger amygdala-VS connectivity to social rewards would be associated with greater internalizing and externalizing symptoms.

MATERIALS AND METHODS

Participants

Participants consisted of a community sample recruited via flyers, listservs, and outreach at local events. We obtained informed consent/assent from all participants. The University's Institutional Review Board approved all procedures and materials.

Study 1 (Behavioral)

Participants included 51 adults (M_{age} = 43.71 years, *SD* = 6.76 years, range = 27.49–55.91 years; 41 female; 31 White, 13 African American/Black, 2 Asian/Pacific Islander, 2 Latino/Hispanic, and 3 multiethnic) and 55 adolescents. Two adolescent participants were excluded from study 1 due to an inability to follow the task instructions, leaving a total of 53 adolescent participants (M_{age} = 13.37 years, *SD* = 0.61 years, range = 12.18–14.82 years; 27 female; 25 White, 14 African American/Black, 4 Asian/Pacific Islander, 2 Latino/Hispanic, and 8 multiethnic; Maternal education: 1 some high school, 3 high school degree, 12 some college, 21 college degree, 1 some medical, law, or graduate school, 14 medical, law, or graduate school degree, 1 missing).

Study 2 (fMRI)

Participants included an independent sample of 59 adolescents. 7 participants were excluded from analyses because they could not complete the task properly (e.g., technical problems, misunderstanding of task) and 1 participant was excluded because of excessive motion during the scan. In total, 51 participants were included in the present analyses (M_{age} = 13.98 years, *SD* = 1.24 years, range = 12.03–15.94 years; 25 female; 32 White, 9 African American/Black, 1 Asian/Pacific Islander, 1 Latino/Hispanic, and 8 multiethnic; Maternal education: 4 some high school, 4 high school degree, 2 trade or vocational schools, 8 some college, 19 college degree, 3 some medical, law, or graduate school, 11 medical, law, or graduate school degree).

Social Go-Nogo Task

Study 1 (Behavioral)

Participants completed a behavioral inhibition task, during which they were instructed to inhibit a motor response in the presence

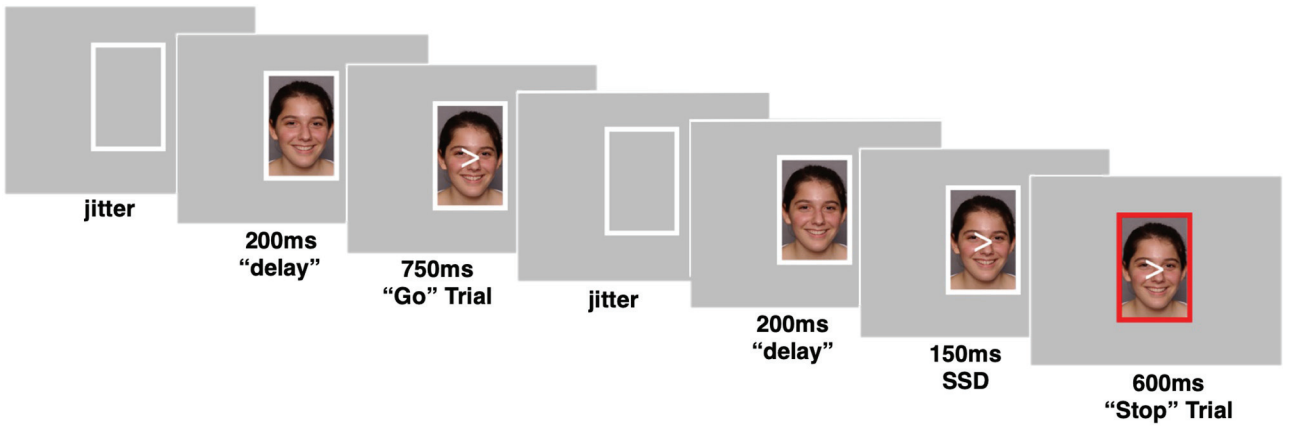


FIGURE 1 | Example trials of the social stop signal task. Go trials when frame enclosing peer's photo remains white and No-go trials when frame enclosing peer's photo turns red. Pictures were taken from a publicly available dataset (Egger et al., 2011). Parent permission and actor assent were obtained by a contractual arrangement so that pictures are publicly available for researchers and can be reproduced in scientific dissemination.

of happy, angry, and neutral faces (**Figure 1**). Participants viewed a sequence of arrows ("<" or ">") superimposed on top of pictures of faces enclosed within a white rectangular frame. Participants were instructed to press a button with their right or left pointer finger depending on the direction of the arrow. No instructions were given regarding the faces (e.g., participants were not told to attend to the faces in any way). In some trials, the white frame would turn red and participants were instructed to withhold their response if the frame turned red. The faces in the photos were age-matched such that the adolescents viewed photos of adolescents [drawn from the NIMH Child Emotional Faces Picture Set (NIMH-ChEFS); Egger et al., 2011] and adult participants viewed adult faces (drawn from the NimStim; Tottenham et al., 2009). Faces were of diverse races and ethnicities. Each photo displayed one of three emotional facial expressions: happy, angry, or neutral. The same faces (with different facial expressions) were displayed in all 3 conditions.

The task consisted of 207 trials in total, which were divided by emotional facial expression into 3 blocks of 69 trials each. Within each block, two thirds of the trials (46) were "go" trials, where the correct response was to press a button. One third of the trials (23) were "no-go" trials, where the correct response was to withhold a button press. The direction of the arrow ("<" or ">") was assigned randomly to each trial. During a go trial, the photo was first presented for 200 ms within the white frame, then an arrow appeared superimposed on top of the photo for 750 ms. Next, the photo and arrow disappeared, leaving only the white frame for a jittered intertrial period. During a no-go trial, the photo was presented for 200 ms within the white frame, then the arrow appeared superimposed on top of the photo for 150 ms, while still enclosed within the white frame. Next, the frame surrounding the photo and arrow turned red for 600 ms. Then the photo and arrow disappeared, and the frame returned to its original white color for the jittered intertrial period.

Study 2 (fMRI)

The task used in study 2 was extremely similar to that described above for study 1 with minor updates to optimize the task for fMRI use. The number of trials was increased to a total of 333 trials with 111 trials per emotion block. The ratio of go to no-go trials was kept at two thirds go (74) trials and one third no-go (37) trials within each block. Additionally, the task was updated so that the task difficulty would adapt to the individual's performance, ensuring the task is similarly, difficult across participants. Specifically, the amount of time before the frame turned red (referred to here as the "Stop Signal Duration" or SSD) on no-go trials adapted to the participants' performance. The SSD was variable and was determined by the participant's performance on the task. If a participant successfully withheld a button press on a no-go trial, then the SSD for the next no-go trial would increase by 50 ms, making the task more difficult. Conversely, if a participant failed to withhold their button press on a no-go trial, the SSD for their next no-go trial would decrease by 50 ms. The initial SSD was set to 150 ms, and bounded at 50 ms (minimum) and 350 ms (maximum). A go trial in the task followed the same pattern and timing as described in study 1. A no-go trial in study 2 followed this sequence: the photo was presented within the white frame for 200 ms. The arrow then appeared superimposed on the top of the photo for a variable SSD, after which the frame turned red. The frame remained red for the period of time necessary for the total amount of time the arrow was displayed to equal 750 ms. For example, if the SSD was 250 ms, the red frame was displayed for 500 ms. Finally, the arrow and photo disappeared for a jittered intertrial period.

Self-Report Measures

To measure internalizing and externalizing symptoms, adolescents in study 2 completed the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). Internalizing symptoms were measured using the Emotional and Peer Problems subscales and externalizing symptoms were measured using the Behavioral and Hyperactivity subscales. For each measure, the combination of the two subscales created a second-order factor that measures broad internalizing or externalizing symptoms, especially for low-risk, non-clinical youth samples (Goodman et al., 2010). Adolescents reported the extent to which the 10 items of internalizing symptoms (e.g., "I am often unhappy, down-hearted or tearful") and 10 items of externalizing symptoms (e.g., "I am often restless, overactive, cannot stay still for long") were true of them. Participants use a 3-point Likert scale (0 = *Not True* to 2 = *Certainly True*). Scores were calculated as the sum of the 10 items for each measure ($\alpha = 0.64$ for internalizing, $\alpha = 0.75$ for externalizing). Mean scores in the current sample were 5.86 (SE = 0.47; median = 5; range = 1–14) for internalizing symptoms and 6.04 (SE = 0.54; median = 6; range = 0–14) for externalizing symptoms.

fMRI Data Acquisition

Imaging data were collected using a 3 Tesla Siemens Magnetom Trio MRI scanner. The task consisted of T2*-weighted echoplanar images (EPI; 300 volumes; slice thickness = 3 mm; 38 slices; TR = 2 s; TE = 25 ms; matrix = 92 × 92; FOV = 230 mm; voxel size = 2.5 mm^3 × 2.5 mm^3 × 3 mm^3). Structural scans, including a T1* magnetization-prepared rapid-acquisition gradient echo (MPRAGE; 192 slices; TR = 1.9 s; TE = 2.32 ms; FOV = 230 mm; matrix = 256 × 256; sagittal acquisition plane; slice thickness = 0.9 mm) and a T2*-weighted, matched-bandwidth (MBW), high resolution anatomical scan (38 slices; TR = 4 s; TE = 64 ms; FOV = 230 mm; matrix = 192 × 192; slice thickness = 3 mm) were also acquired. To maximize brain coverage and reduce drop-out in orbital and temporal regions, MBW and EPI images were acquired at an oblique axial orientation.

fMRI Data Preprocessing and Analysis

Preprocessing steps, utilizing FSL FMRIBs Software Library (FSL v6.0[1]), included the following: skull stripping of all images using BET; slice-to-slice motion correction of EPI images using MCFLIRT; sequential co-registration of EPI images to standard stereotactic space defined by the Montreal Neurological Institute (MNI) and the International Consortium for Brain Mapping through the MBW and MPRAGE images using

[1]https://fsl.fmrib.ox.ac.uk/fsl/

FLIRT; application of a 128 s high-pass temporal filter to remove low frequency drift within the time-series; and spatial smoothing with a 6 mm Gaussian kernel, full-width-at-half maximum. Individual-level independent component analysis (ICA) using MELODIC was applied and combined with an automated component classifier (Tohka et al., 2008; Neyman-Pearson threshold = 0.3) in order to remove artifact signal (e.g., physiological noise, motion) from the functional data. Quality check during preprocessing and analyses ensured adequate signal coverage in our sample.

The task was modeled using an event-related design within the Statistical Parametric Mapping software package (SPM8; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, United Kingdom). Each event was modeled using the onset of the stimulus and a duration equal to the participants' response time (or 750 ms on trials where participants did not respond). Individual fixed-effects models were created for each participant using the general linear model in SPM with regressors for conditions of interest: trials during each emotion block (e.g., neutral, happy, and angry). Consistent with prior work (Perino et al., 2016; Rogers et al., in press), all trials were modeled within a single regressor for a given block of the task, regardless of outcome, in order to capture the neural correlates involved in processing social rewards and social threats. Volumes containing motion in excess of 2 mm slice-to-slice were modeled in a separate junk regressor. However, if the number of volumes that exceeded the threshold was greater than 10% of the total number of trials, then the participant was excluded from the analyses. Jittered inter-trial periods (e.g., fixation) were not explicitly modeled and therefore serve as the implicit baseline for task conditions.

We conducted psychophysiological interaction (PPI) analyses using a generalized form of context-dependent PPI from the automated generalized PPI (gPPI) toolbox in SPM (McLaren et al., 2012). In order to examine amygdala-striatum functional connectivity, we used the bilateral ventral striatum as our seed region, which was defined structurally from WFU pickatlas (Maldjian et al., 2003) using the AAL atlas (Tzourio-Mazoyer et al., 2002) with the following restrictions: $-12 < x < 12$, $4 < y < 8$, $-12 < z < 0$. Time series were extracted from the VS seed region and served as the physiological variable. Each block of trials was then convolved with the canonical HRF to create the psychological regressor. In the final step, the physiological and psychological variables were multiplied in order to create the PPI term. This interaction term was then used to identify regions that covary with the ventral striatum seed region in a task-dependent manner. As such, each participant's individual gPPI model included a deconvolved BOLD signal alongside the psychological and interaction term for each event type.

Random effects, group-level analyses were run using GLMFlex[2]. GLMFlex offers several advantages, including removing outliers and sudden activation changes in brain, corrects for variance-covariance inequality, partitions error terms, and analyzes all voxels containing data. Group-level analyses were performed by entering the number of false alarms committed by participants and self-reported internalizing/externalizing symptoms as continuous covariates in a series of whole-brain regressions, first testing for associations with neural activation followed by our key analysis on analyses on amygdala-VS functional connectivity.

Monte Carlo simulations were used to compute a cluster corrected threshold using the updated (April, 2016) 3dFWHMx and 3dClustSim programs from the AFNI software package (Ward, 2000) and the group-level brain mask for the analyses of interest. Simulations resulted in a voxel-wise threshold of $p < 0.005$ and a minimum cluster size ranging between 117 and 380 voxels for the whole-brain, corresponding to $p < 0.05$, family-wise error (FWE) corrected. For our *a priori* analyses focused on amygdala-VS connectivity, we utilized a small-volume correction, computing a cluster corrected threshold within a structurally defined amygdala mask from the AAL atlas. Simulations resulted in a voxel-wise threshold of $p < 0.005$ and a minimum cluster size of 3 voxels within the amygdala, corresponding to $p < 0.05$ small volume corrected. All reported results are available on NeuroVault[3] (Gorgolewski et al., 2015).

RESULTS

Behavioral Results

False Alarm Rates to Social Rewards and Threats, Study 1

To test for age differences in false alarm rates across happy, angry, and neutral blocks, we conducted a repeated measures analysis of variance with one within subject variable (condition: happy, angry, and neutral) and one between subject variable (age group: adolescents, adults). Results revealed a significant main effect of condition, $F(2,204) = 6.43$, $p = 0.002$, $\eta^2 = 0.059$ and group, $F(1,102) = 13.47$, $p < 0.0001$, $\eta^2 = 0.117$ which was qualified by an age x condition interaction, $F(2,204) = 6.60$, $p = 0.002$, $\eta^2 = 0.061$. To probe this interaction, we conducted paired samples *t*-tests within each age group. As shown in **Figure 2**, adolescents showed more false alarms to happy [$t(52) = 4.37$, $p < 0.0001$, $d = 0.54$] and angry faces [$t(52) = 2.63$, $p = 0.01$, $d = 0.32$] than neutral faces, and more false alarms to happy than angry faces [$t(52) = 2.39$, $p = 0.02$, $d = 0.27$]. Adults did not show any significant differences across conditions. Next, we conducted independent samples *t*-tests across the 2 age groups. Adolescents showed more false alarms than adults to happy [$t(102) = 4.31$, $p < 0.0001$] and angry faces [$t(102) = 2.78$, $p = 0.007$] but did not differ significantly to neutral faces [$t(102) = 1.8$, $p = 0.074$].

False Alarm Rates to Social Rewards and Threats, Study 2

We conducted a repeated measures analysis of variance with one within subject variable (condition: happy, angry, and neutral) to examine differences in false alarm rates across conditions in the adolescent sample. We found a significant effect of condition, $F(2,116) = 3.4$, $p = 0.036$, $\eta^2 = 0.056$. *Post hoc*, paired samples *t*-tests corroborated the findings from study 1 and our prior work

[2]http://mrtools.mgh.harvard.edu/index.php/GLM_Flex

[3]https://neurovault.org/collections/5338/

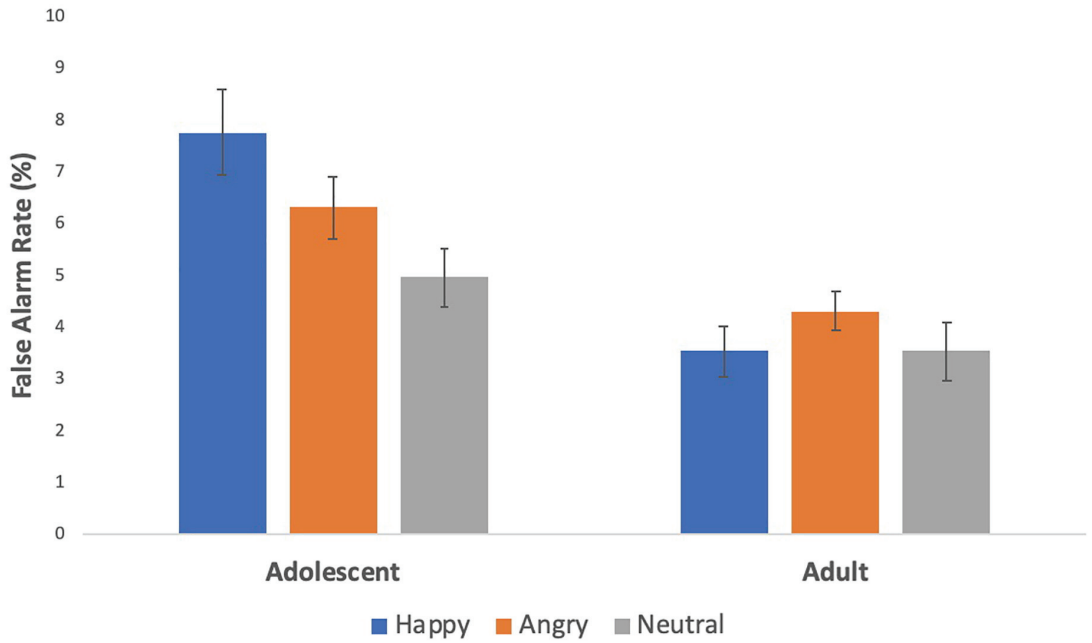


FIGURE 2 | Behavioral effects on the social stop signal task. Adolescents had greater inhibitory failures to social reward and threat cues than to neutral cues, and more so to social reward than threat cues.

(Perino et al., 2016), such that adolescents made significantly more false alarms to happy (M = 19.29%, SE = 0.91%) compared to angry faces (M = 17.46%, SE = 0.91%; [$t(58) = 2.71$, $p = 0.009$, $d = 0.26$)]. However, false alarm rates to happy and angry faces did not differ from neutral faces. The fMRI version of the task includes the SSD, which adapts to participants' behavior ensuring participants perform at a more fixed rate across the task, and so false alarm differences are harder to identify. It is thus not surprising that our behavioral effects are weaker, but it is nonetheless impressive that they still emerged in the expected direction.

False Alarm Rates to Social Rewards and Threats and Links to Internalizing and Externalizing Symptoms

To understand links between disinhibition to social rewards and psychopathology, we examined the relationship between disinhibition to social rewards relative to social threats and internalizing symptoms in adolescents. We calculated a difference score for false alarm rates by subtracting false alarms rates to angry faces from happy faces, where higher scores indicate adolescents make more false alarms to social rewards. Adolescents who had greater false alarm rates to happy relative to angry faces reported greater internalizing symptoms [$r(50) = 0.33$, $p < 0.05$]. There was no significant correlation between false alarm rate to happy relative to angry faces and externalizing symptoms [$r(50) = 0.12$, $p = 0.39$].

fMRI Results

Main Effects of Social Rewards > Social Threats

Given the heightened false alarm rates to happy relative to angry faces, we focused our analyses on this specific contrast. We first conducted a whole-brain t-test that compared happy and angry faces. Next, we investigated functional connectivity for this contrast. Results are shown in **Table 1**.

Neural Correlates of False Alarm Rate to Social Rewards and Threats

Next, we examined how behavioral disinhibition relates to neural activation and amygdala-VS connectivity. Using the same behavioral metric as described above, we regressed the difference in false alarm rates (happy-angry) onto neural activation and neural connectivity for the contrast happy-angry. For neural activation, we found a bilateral amygdala cluster, such that adolescents with greater false alarms to social reward relatives to threat show less activation in bilateral amygdala to social rewards (see **Table 1**).

For neural connectivity, with the ventral striatum as the seed region, PPI analyses yielded coupling with the left amygdala that correlated with greater false alarm rates to happy faces (see **Figure 3A** and **Table 1**). For descriptive purposes, we extracted parameter estimates of functional connectivity. As shown in **Figure 3B**, adolescents who made more false alarms to happy relative to angry faces exhibited greater amygdala-VS connectivity to happy relative to angry faces. To further probe this effect, we examined how differences in false alarm rates are associated with neural connectivity to happy and angry faces separately (happy-neutral and angry-neutral). Using the ventral striatum as the seed region, PPI analyses demonstrated greater coupling with the left amygdala for happy relative to neutral cues that correlated with greater false alarm rates to happy faces. No significant correlation was found for angry relative to neutral cues (see **Table 1**). These findings suggest that failed inhibition to

TABLE 1 | Brain activation patterns for neural activation and functional connectivity.

Anatomical region	*x*	*y*	*z*	*t*	*k*
Social reward > social threat					
PPI (VS seed): Social reward > social threat					
L Middle frontal gyrus	−26	14	46	−4.18	271
L Medial cingulate cortex	−2	−4	40	−3.26	226
Supplementary motor area	10	0	64	−4.09	312
L Inferior parietal lobule	−52	−38	44	−3.52	232
False alarm rate regressed on social reward > social threat					
R Amygdala	26	8	−22	−3.51	83
L Amygdala	−14	0	−18	−3.48	63
PPI (VS seed): False alarm rate regressed on social reward > social threat					
L Amygdala	−24	−4	−14	3.16	34
PPI (VS seed): False alarm rate regressed on social reward > neutral					
L Amygdala	−22	−4	−10	3.43	22
Dorsomedial prefrontal cortex	−10	66	24	4.70	367
Superior temporal sulcus	−60	−24	0	3.76	150
L Cerebelum	−18	−76	−36	3.75	133
PPI (VS seed): False alarm rate regressed on social treat > neutral					
Internalizing regressed on social reward > social threat					
PPI (VS seed): Internalizing regressed on social reward > social threat					
L Amygdala	−24	−6	−12	2.86	7
L Amygdala	−16	0	−16	3.93	76
L Interior frontal gyrus (p. Orbitalis)	−26	26	−12	5.16	179
R Postcentral gyrus	32	−42	70	4.40	669
L Postcentral gyrus	−38	−38	64	3.96	327
L Middle frontal gyrus	−28	−2	66	4.13	374
L Anterior insula	−44	12	−16	4.07	120
R Posterior insula	28	−18	0	3.86	369
R Supramarginal gyrus	64	−24	28	4.00	183
PPI (VS seed): Internalizing regressed on social reward > neutral					
L Amygdala	−22	−2	−14	3.77	68
R Cuneus	20	−84	34	5.10	1208
L Anterior insula	−36	0	10	4.49	356
Supplementary motor area	0	−16	68	4.41	117
Supplementary motor area	6	−8	58	3.68	269
R Caudate	8	2	8	3.88	323
PPI (VS seed): Internalizing regressed on social treat > neutral					
Externalizing regressed on social reward > social threat					
Posterior superior temporal sulcus	−64	−38	−4	−3.89	465
PPI (VS seed): Externalizing regressed on social reward > social threat					
R Angular gyrus	56	−62	36	3.79	136
L Temporoparietal junction	−46	−60	26	3.7	128

PPI refers to psychophysiological interaction. L and R refer to left and right hemispheres, respectively. k refers to the number of voxels within that cluster, t refers to peak activation level within that cluster, and x, y, z refer to MNI coordinates. The amygdala was small-volume corrected. All other regions were based on whole-brain mask (range = 117–380 voxels). All regions are significant at $p < 0.005$.

social rewards relative to threats may be facilitated amygdala-VS connectivity specifically to social reward cues.

Links to Internalizing and Externalizing Symptoms

We examined how amygdala-VS connectivity is associated with internalizing and externalizing symptoms. First, we regressed internalizing symptoms onto neural activation and neural connectivity for the contrast happy-angry. For neural activation, no significant clusters were observed. For neural connectivity, using the ventral striatum as the seed region, the PPI analyses yielded coupling with the left amygdala that correlated with internalizing symptoms (see **Figure 4A** and **Table 1**). This region is nearly identical to that found above for the connectivity analyses regressed with false alarm rate. For descriptive purposes, we extracted parameter estimates of functional connectivity. As shown in **Figure 4B**, adolescents who showed greater connectivity to happy relative to angry faces reported greater internalizing symptoms. To further probe

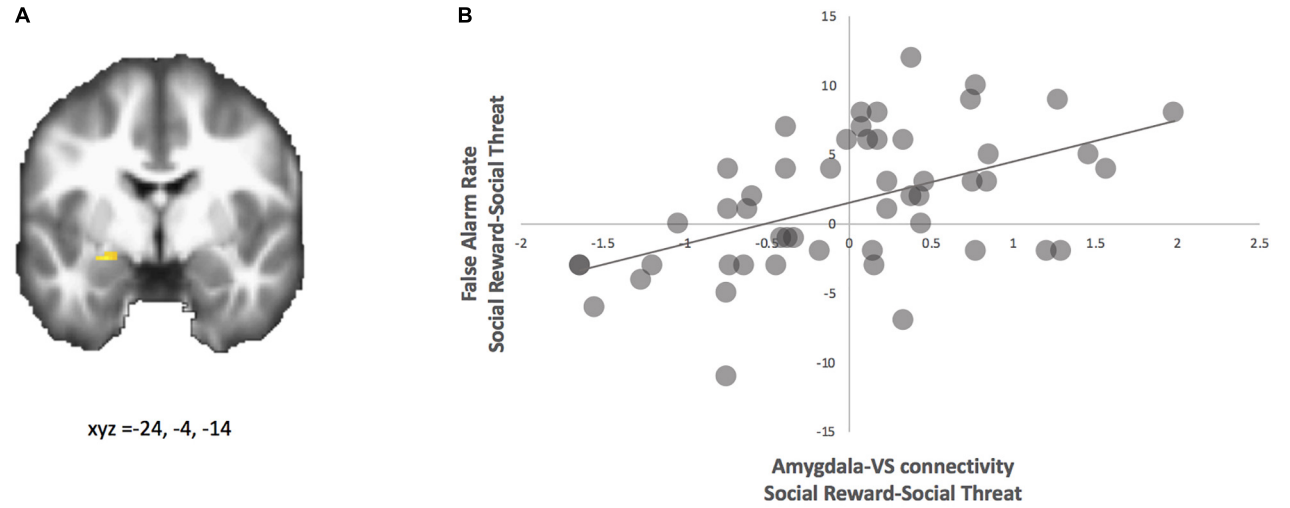


FIGURE 3 | PPI analysis with ventral striatum seed. **(A)** Adolescents with greater false alarm rate to social reward-social threat trials showed greater functional connectivity between the ventral striatum and amygdala (highlighted; MNI coordinates: x, y, z = –24, –4, –14) for social reward > social threat. **(B)** Parameter estimates of connectivity strength were extracted for descriptive purposes and plotted with false alarm rate.

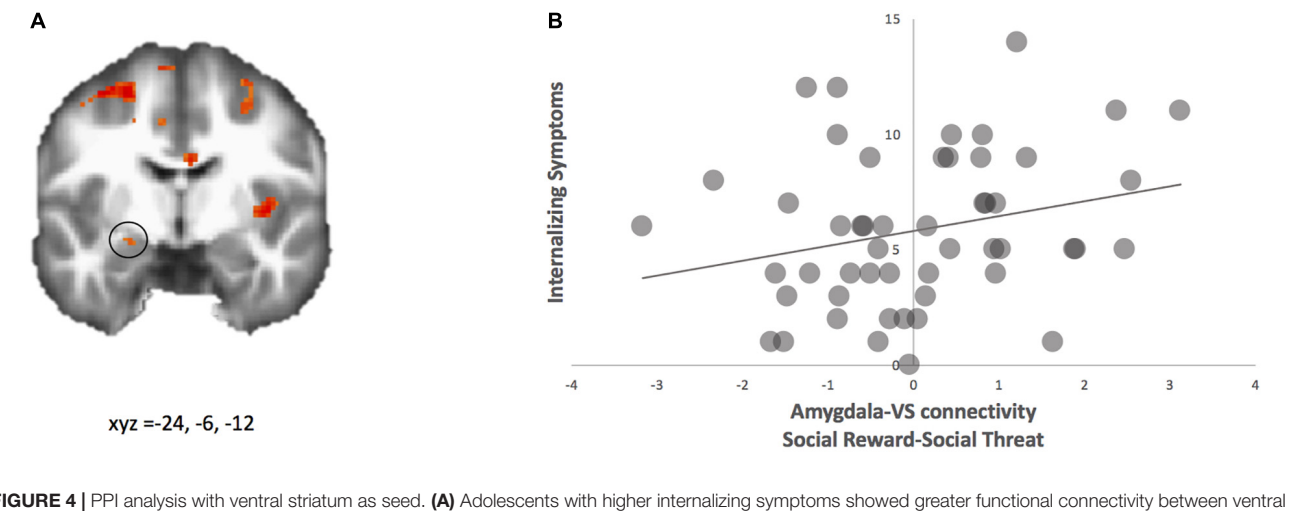


FIGURE 4 | PPI analysis with ventral striatum as seed. **(A)** Adolescents with higher internalizing symptoms showed greater functional connectivity between ventral striatum and amygdala (highlighted; MNI coordinates: x, y, z = –24, –6, –12) for social reward > social threat. **(B)** Parameter estimates of connectivity strength were extracted for descriptive purposes and plotted with internalizing symptom scores.

this effect, we examined how neural connectivity to happy and angry faces separately (happy-neutral and angry-neutral) relate to internalizing symptoms. Using the ventral striatum as the seed region, PPI analyses showed connectivity with the left amygdala for happy relative to neutral cues that correlated with internalizing symptoms. No significant correlation was found for angry relative to neutral cues.

Next, we regressed externalizing symptoms onto neural activation and neural connectivity for the contrast happy-angry. Results for neural activation are shown in **Table 1**. Furthermore, results for neural connectivity using the ventral striatum as the seed region did not yield coupling with the amygdala that correlated with externalizing symptoms (see **Table 1**). We therefore did not continue to analyze whether happy and angry faces separately (happy-neutral and angry-neutral) relate to externalizing symptoms.

DISCUSSION

Adolescents demonstrate a rise in sensitivity to socially affective cues such as social rewards (Guyer et al., 2012), which overlaps with a heightened risk for psychopathology such as internalizing and externalizing symptoms (e.g., Costello et al., 2011). The aim of the current study was to examine neural and behavioral dysregulation to social rewards and links to internalizing and externalizing symptoms in youths. Our results suggest that greater behavioral disinhibition to social

reward cues (i.e., happy peer faces) than to social threat cues (i.e., angry peer faces) is associated with heightened amygdala-VS connectivity in adolescents. Moreover, greater internalizing, but not externalizing, symptoms were associated with greater behavioral disinhibition to social rewards as well as amygdala-VS connectivity. Together, these findings indicate that greater disinhibition to social rewards may render adolescents at greater risk for internalizing symptoms due to their shared amygdala-VS connectivity to social rewards relative to threats.

Behaviorally, adolescents showed greater inhibitory failures in response to socially affective cues – both social reward and social threat cues – than to neutral cues, and even more so to reward than to threat cues. Moreover, there were age-related differences such that adolescents had greater inhibitory failures to socially affective cues than adults who performed relatively uniformly across these various cues. These behavioral findings align with previous research in that adolescents are particularly sensitive to socially appetitive cues such as social rewards (Somerville et al., 2011; Perino et al., 2016), and extend this work by using peers' faces. Given the intensified reward sensitivity in adolescents (Galván, 2013), it is plausible that adolescents demonstrate a stronger bias toward positive than negative cues, resulting in behavioral dysregulation in the presence of social rewards. Socially salient stimuli and information are especially relevant to adolescents, and ultimately shape their behavior (Nelson et al., 2005). Paying closer attention to social information at the cost of inhibitory failures may not necessarily be unfavorable to adolescents. Adolescence is a developmental period of social reformation where there are major changes in one's social network such as forming new, meaningful social connections. For instance, adolescents start to enter romantic relationships (Furman and Wehner, 1997), and non-parental figures or non-family members (e.g., teacher, coach) begin to serve pivotal roles (Wang et al., 2013). Therefore, greater cognitive allocation to social information, such as positive social cues, may facilitate stronger social relationships in youths.

Hyper-sensitivity to socio-affective cues may come at a cost and ultimately place youth at risk for psychopathology. Indeed, greater inhibitory failures to social reward relative to social threat cues were associated with greater internalizing symptoms. Youths with greater internalizing symptoms, but not externalizing symptoms, tend to have better emotion comprehension such as understanding of others' emotions (Göbel et al., 2016). In a social context, adolescents with internalizing symptoms have better identification of happy than angry facial cues (Vanhalst et al., 2017) and have faster reaction times to happy than angry and fearful facial cues in Go/NoGo tasks (Stoycos et al., 2017). This may imply that these youths at risk are particularly more sensitive to socially rewarding stimuli, which corroborate our finding of the relationship between behavioral disinhibition and internalizing symptoms.

Our study did not find a significant link between disinhibition and externalizing symptoms. Previous research on disinhibition and externalizing symptoms in adolescents demonstrates conflicting results. That is, while some research has shown that youth with externalizing symptoms make more false alarms on Go/NoGo tasks (Schulz et al., 2004; Bezdjian et al., 2009), others have found that there is no relationship between externalizing symptoms such as impulsivity and false alarms on Go/NoGo tasks (Brown et al., 2015; Sánchez-Kuhn et al., 2017). To our knowledge, this is the first study to examine the link between externalizing symptoms and behavioral disinhibition using salient peer faces in adolescents. It is possible that adolescents are just as impulsive to socially rewarding cues as they are to socially threatening cues. In other words, adolescents with symptoms of externalizing may be equally impulsive toward emotionally driven cues. However, given inconsistencies in results, further research is needed to better understand disinhibition in youths with symptoms of externalizing within a social context.

At the neural level, we found that adolescents who showed greater disinhibition to social reward cues demonstrated heightened connectivity between the amygdala and ventral striatum. Developmentally, connectivity between the two regions decreases from late childhood to early adolescence (Pfeifer et al., 2011), and continues to decrease in connectivity strength into early adulthood (Heller et al., 2016). Importantly, our findings corroborate a prior study such that adolescents who showed greater behavioral disinhibition to socio-emotional cues demonstrated heightened amygdala-VS connectivity (Heller et al., 2016). Greater connectivity between the amygdala and VS is thought to be a developmentally immature neural phenotype that emerges prior to the development of more mature top-down cortico-subcortical connectivity (Casey et al., 2019). This hierarchical cascade of changes in connectivity patterns (i.e., from subcortico-subcortical connectivity in early adolescence to cortico-subcortical connectivity in late adolescence to cortico-cortical connectivity in adulthood) is proposed to be necessary for emotional brain development (Casey et al., 2019). Together, our findings suggest that amygdala-VS connectivity, particularly in the context of social rewards, may represent a neural marker of emotion regulation difficulties.

Moreover, greater amygdala-VS connectivity was associated with greater internalizing but not externalizing symptoms. This coupling may underline an "unchecked" subcortical system that is characteristic of behavioral dysregulation to social rewards and compromised psychological well-being. While prior studies have examined the relationship between behavioral dysregulation and internalizing symptoms, which underscores connectivity between the cognitive control and affective hubs (e.g., Hare et al., 2008; Stoycos et al., 2017), our findings indicate that subcortico-subcortical connectivity, which is deemed to occur chronologically earlier and thus necessary for subcortico-cortical circuits (Casey et al., 2019), and may serve as an early biomarker for emotion dysregulation and a risk factor for internalizing symptoms. Putting these studies together, it can be reconciled that social context and neurobiology are key contributors to internalizing symptoms in adolescents.

There are several limitations to our study. First, we only had fMRI data for adolescents and therefore do not know whether

these neural patterns are age-specific. Future studies should consider incorporating children and adult comparison groups or utilize longitudinal methods to see how behavioral differences map onto neural differences across development. Second, we used a community sample of adolescents with self-reported internalizing symptoms. Given that these adolescents were not clinically diagnosed, our findings cannot be extended to the community of youths with clinically relevant mood disorders. Nonetheless, we assessed internalizing symptoms in a community sample, suggesting that our findings may be more applicable to adolescents who are classified as healthy, but are not clinically diagnosed. Last, the Emotional and Peer Problems subscale of SDQ cannot be separated into depression and anxiety symptoms, and thus the two cannot be examined in tandem. However, it may be parsimonious to create a composite of internalizing symptoms given that depressive and anxiety symptoms tend to load on a higher-order internalizing symptoms factor. Future research should utilize longitudinal methods to better unpack the cascade of developmental processes that occur at the level of brain connectivity, behavioral disinhibition, and the onset of psychopathology.

In conclusion, the current study corroborates and extends previous work to better understand the contextual effects of disinhibition to social rewards on adolescent well-being. Our findings suggest that greater behavioral disinhibition to social rewards are associated with stronger amygdala-VS connectivity, where amygdala and ventral striatum are classified as "hot" affective nodes. Greater behavioral disinhibition and stronger amygdala-VS connectivity to social rewards are correlated with heightened internalizing symptoms, but not externalizing symptoms. Therefore, a greater orientation to social rewards may have implications for youth's mental health such as depression and anxiety. These behavioral effects were also age-specific to adolescents, thereby confirming that socially salient contexts such as social rewards are especially powerful to youths' motivations, behaviors, and psychological health.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Institutional Review Board at the University of Illinois with written informed consent/assent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

ET and EM designed the research. SI and EM collected the data. SI and ET analyzed the data. All authors wrote the manuscript.

FUNDING

This work was supported by grants from the National Institutes of Health (R01DA039923), the National Science Foundation (SES 1459719), and generous funds from the Department of Psychology at the University of Illinois.

ACKNOWLEDGMENTS

We are greatly appreciate the assistance of the Biomedical Imaging Center at the University of Illinois as well as Elizabeth Lozano, Kathy Do, Michael Perino, Heather Ross, Lynda Lin, Paul Sharp, and Tae-Ho Lee for their assistance in collecting data. We thank Tae-Ho Lee for developing the preprocessing pipeline used for analysis.

REFERENCES

Achenbach, T. M. (1966). The classification of children's psychiatric symptoms: a factor-analytic study. *Psychol. Monogr.* 80, 1–37. doi: 10.1037/h0093906

Albrecht, B., Banaschewski, T., Brandeis, D., Heinrich, H., and Rothenberger, A. (2005). Response inhibition deficits in externalizing child psychiatric disorders: an ERP-study with the Stop-task. *Behav. Brain Funct.* 1:22.

Bezdjian, S., Baker, L. A., Lozano, D. I., and Raine, A. (2009). Assessing inattention and impulsivity in children during the Go/NoGo task. *Br. J. Dev. Psychol.* 27(Pt 2), 365–383. doi: 10.1348/026151008X314919

Blakemore, S. J. (2008). The social brain in adolescence. *Nat. Rev. Neurosci.* 9, 267–277. doi: 10.1038/nrn2353

Bongers, I. L., Koot, H. M., van der Ende, J., and Verhulst, F. C. (2008). Predicting young adult social functioning from developmental trajectories of externalizing behaviour. *Psychol. Med.* 38, 989–999. doi: 10.1017/s0033291707002309

Breiner, K., Li, A., Cohen, A. O., Steinberg, L., Bonnie, R. J., Scott, E. S., et al. (2018). Combined effects of peer presence, social cues, and rewards on cognitive control in adolescents. *Dev. Psychobiol.* 60, 292–302. doi: 10.1002/dev.21599

Brown, B. B., Eicher, S. A., and Petrie, S. (1986). The importance of peer group ("crowd") affiliation in adolescence. *J. Adolesc.* 9, 73–96. doi: 10.1016/s0140-1971(86)80029-x

Brown, M. R. G., Benoit, J. R. A., Juhás, M., Dametto, E., Tse, T. T., MacKay, M., et al. (2015). fMRI investigation of response inhibition, emotion, impulsivity, and clinical high-risk behavior in adolescents. *Front. Syst. Neurosci.* 9:124. doi: 10.3389/fnsys.2015.00124

Casey, B. J., Heller, A. S., Gee, D. G., and Cohen, A. O. (2019). Development of the emotional brain. *Neurosci. Lett.* 693, 29–34.

Casey, B. J., Jones, R. M., and Hare, T. A. (2008). The adolescent brain. *Ann. N. Y. Acad. Sci.* 1124, 111–126. doi: 10.1196/annals.1440.010

Costello, E. J., Copeland, W., and Angold, A. (2011). Trends in psychopathology across the adolescent years: what changes when children become adolescents, and when adolescents become adults? *J. Child Psychol. Psychiatry* 52, 1015–1025. doi: 10.1111/j.1469-7610.2011.02446.x

Cremers, H. R., Veer, I. M., Spinhoven, P., Rombouts, S. A. R. B., and Roelofs, K. (2015). Neural sensitivity to social reward and punishment anticipation in social anxiety disorder. *Front. Behav. Neurosci.* 8:439. doi: 10.3389/fnbeh.2014.00439

Crone, E. A., and Dahl, R. E. (2012). Understanding adolescence as a period of social–affective engagement and goal flexibility. *Nat. Rev. Neurosci.* 13, 636–650. doi: 10.1038/nrn3313

Davey, C. G., Allen, N. B., Harrison, B. J., and Yücel, M. (2011). Increased amygdala response to positive social feedback in young people with major depressive disorder. *Biol. Psychiatry* 69, 734–741. doi: 10.1016/j.biopsych.2010.12.004

Egger, H. L., Pine, D. S., Nelson, E., Leibenluft, E., Ernst, M., Towbin, K. E., et al. (2011). The NIMH child emotional faces picture set (NIMH-ChEFS): a new set of children's facial emotion stimuli. *Int. J. Methods Psychiatr. Res.* 20, 145–156. doi: 10.1002/mpr.343

Everitt, B. J., and Robbins, T. W. (1992). "Amygdala-ventral striatal interactions and reward-related processes," in *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction*, ed. J. P. Aggleton (New York, NY: Wiley-Liss), 401–429.

Fareri, D. S., Gabard-Durnam, L., Goff, B., Flannery, J., Gee, D. G., Lumian, D. S., et al. (2015). Normative development of ventral striatal resting state connectivity in humans. *Neuroimage* 118, 422–437. doi: 10.1016/j.neuroimage.2015.06.022

Fareri, D. S., and Tottenham, N. (2016). Effects of early life stress on amygdala and striatal development. *Dev. Cogn. Neurosci.* 19, 233–247. doi: 10.1016/j.dcn.2016.04.005

Fergusson, D. M., and Woodward, L. J. (2002). Mental health, educational, and social role outcomes of adolescents with depression. *Arch. Gen. Psychiatry* 59, 225–231.

Foulkes, L., and Blakemore, S. J. (2016). Is there heightened sensitivity to social reward in adolescence? *Curr. Opin. Neurobiol.* 40, 81–85. doi: 10.1016/j.conb.2016.06.016

Foulkes, L., McCrory, E. J., Neumann, C. S., and Viding, E. (2014). Inverted social reward: associations between psychopathic traits and self-report and experimental measures of social reward. *PLoS One* 9:e106000. doi: 10.1371/journal.pone.0106000

Furman, W., and Wehner, E. A. (1997). Adolescent romantic relationships: a developmental perspective. *New Dir. Child Dev.* 78, 21–36. doi: 10.1002/cd.23219977804

Galván, A. (2013). The teenage brain. *Curr. Dir. Psychol. Sci.* 22, 88–93.

Göbel, A., Henning, A., Möller, C., and Aschersleben, G. (2016). The relationship between emotion comprehension and internalizing and externalizing behavior in 7- to 10-year-old children. *Front. Psychol.* 7:1917. doi: 10.3389/fpsyg.2016.01917

Goodman, A., Lamping, D. L., and Ploubidis, G. B. (2010). When to use broader internalising and externalising subscales instead of the hypothesised five subscales on the strengths and difficulties questionnaire (SDQ): data from british parents, teachers and children. *J. Abnorm. Child Psychol.* 38, 1179–1191. doi: 10.1007/s10802-010-9434-x

Goodman, R. (1997). The strengths and difficulties questionnaire: a research note. *J. Child Psychol. Psychiatry* 38, 581–586. doi: 10.1111/j.1469-7610.1997.tb01545.x

Gorgolewski, K. J., Varoquaux, G., Rivera, G., Schwarz, Y., Ghosh, S. S., Maumet, C., et al. (2015). NeuroVault.org: a web-based repository for collecting and sharing unthresholded statistical maps of the human brain. *Front. Neuroinform.* 9:8. doi: 10.3389/fninf.2015.00008

Gorno-Tempini, M. L., Pradelli, S., Serafini, M., Pagnoni, G., Baraldi, P., Porro, C., et al. (2001). explicit and incidental facial expression processing: an fMRI study. *Neuroimage* 14, 465–473. doi: 10.1006/nimg.2001.0811

Guyer, A. E., Choate, V. R., Pine, D. S., and Nelson, E. E. (2012). Neural circuitry underlying affective response to peer feedback in adolescence. *Soc. Cogn. Affect. Neurosci.* 7, 81–92. doi: 10.1093/scan/nsr043

Guyer, A. E., Lau, J. Y. F., McClure-Tone, E. B., Parrish, J., Shiffrin, N. D., Reynolds, R. C., et al. (2008). Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. *Arch. Gen. Psychiatry* 65:1303. doi: 10.1001/archpsyc.65.11.1303

Hare, T. A., Tottenham, N., Davidson, M. C., Glover, G. H., and Casey, B. J. (2005). Contributions of amygdala and striatal activity in emotion regulation. *Biol. Psychiatry* 57, 624–632. doi: 10.1016/j.biopsych.2004.12.038

Hare, T. A., Tottenham, N., Galvan, A., Voss, H. U., Glover, G. H., and Casey, B. J. (2008). Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biol. Psychiatry* 63, 927–934. doi: 10.1016/j.biopsych.2008.03.015

Heller, A. S., Cohen, A. O., Dreyfuss, M. F. W., and Casey, B. J. (2016). Changes in cortico-subcortical and subcortico-subcortical connectivity impact cognitive control to emotional cues across development. *Soc. Cogn. Affect. Neurosci.* 11, 1910–1918.

Kerestes, R., Davey, C. G., Stephanou, K., Whittle, S., and Harrison, B. J. (2014). Functional brain imaging studies of youth depression: a systematic review. *Neuroimage* 4, 209–231. doi: 10.1016/j.nicl.2013.11.009

King, S. M., Iacono, W. G., and McGue, M. (2004). Childhood externalizing and internalizing psychopathology in the prediction of early substance use. *Addiction* 99, 1548–1559. doi: 10.1111/j.1360-0443.2004.00893.x

Kohls, G., Peltzer, J., Herpertz-Dahlmann, B., and Konrad, K. (2009). Differential effects of social and non-social reward on response inhibition in children and adolescents. *Dev. Sci.* 12, 614–625. doi: 10.1111/j.1467-7687.2009.00816.x

Ladouceur, C. D., Dahl, R. E., Williamson, D. E., Birmaher, B., Axelson, D. A., Ryan, N. D., et al. (2006). Processing emotional facial expressions influences performance on a Go/NoGo task in pediatric anxiety and depression. *J. Child Psychol. Psychiatry* 47, 1107–1115. doi: 10.1111/j.1469-7610.2006.01640.x

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., and Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 19, 1233–1239. doi: 10.1016/s1053-8119(03)00169-1

Masten, C. L., Eisenberger, N. I., Borofsky, L. A., Pfeifer, J. H., McNealy, K., Mazziotta, J. C., et al. (2009). Neural correlates of social exclusion during adolescence: understanding the distress of peer rejection. *Soc. Cogn. Affect. Neurosci.* 4, 143–157. doi: 10.1093/scan/nsp007

McElhaney, K. B., Antonishak, J., and Allen, J. P. (2008). "They Like Me, They Like Me Not": popularity and adolescents' perceptions of acceptance predicting social functioning over time. *Child Dev.* 79, 720–731. doi: 10.1111/j.1467-8624.2008.01153.x

McLaren, D. G., Ries, M. L., Xu, G., and Johnson, S. C. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *Neuroimage* 61, 1277–1286. doi: 10.1016/j.neuroimage.2012.03.068

Monk, C. S., Klein, R. G., Telzer, E. H., Schroth, E. A., Mannuzza, S., Moulton, J. L., et al. (2008). Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. *Am. J. Psychiatry* 165, 90–98. doi: 10.1176/appi.ajp.2007.06111917

Mullin, B. C., Perks, E. L., Haraden, D. A., Snyder, H. R., and Hankin, B. L. (2018). Subjective executive function weaknesses are linked to elevated internalizing symptoms among community adolescents. *Assessment* doi: 10.1177/1073191118820133 [Epub ahead of print].

Nelson, E. E., Leibenluft, E., McClure, E. B., and Pine, D. S. (2005). The social re-orientation of adolescence: a neuroscience perspective on the process and its relation to psychopathology. *Psychol. Med.* 35, 163–174. doi: 10.1017/s0033291704003915

Olino, T. M., Silk, J. S., Osterritter, C., and Forbes, E. E. (2015). Social reward in youth at risk for depression: a preliminary investigation of subjective and neural differences. *J. Child Adolesc. Psychopharmacol.* 25, 711–721. doi: 10.1089/cap.2014.0165

Ousdal, O. T., Reckless, G. E., Server, A., Andreassen, O. A., and Jensen, J. (2012). Effect of relevance on amygdala activation and association with the ventral striatum. *Neuroimage* 62, 95–101. doi: 10.1016/j.neuroimage.2012.04.035

Perino, M. T., Miernicki, M. E., and Telzer, E. H. (2016). Letting the good times roll: adolescence as a period of reduced inhibition to appetitive social cues. *Soc. Cogn. Affect. Neurosci.* 11, 1762–1771. doi: 10.1093/scan/nsw096

Pfeifer, J. H., Kahn, L. E., Merchant, J. S., Peake, S. J., Veroude, K., Masten, C. L., et al. (2013). Longitudinal change in the neural bases of adolescent social self-evaluations: effects of age and pubertal development. *J. Neurosci.* 33, 7415–7419. doi: 10.1523/JNEUROSCI.4074-12.2013

Pfeifer, J. H., Masten, C. L., Moore, W. E., Oswald, T. M., Mazziotta, J. C., Iacoboni, M., et al. (2011). Entering adolescence: resistance to peer influence. risky behavior, and neural changes in emotion reactivity. *Neuron* 69, 1029–1036. doi: 10.1016/j.neuron.2011.02.019

Pine, D. S., Cohen, P., Gurley, D., Brook, J., and Ma, Y. (1998). The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Arch. Gen. Psychiatry* 55, 56–64.

Rogers, C. R., Perino, M. T., and Telzer, E. H. (in press). Maternal buffering of adolescent dysregulation in socially appetitive contexts: from behavior to the brain. *J. Res. Adolesc.*

Roy, A. K., Fudge, J. L., Kelly, C., Perry, J. S. A., Daniele, T., Carlisi, C., et al. (2013). Intrinsic functional connectivity of amygdala-based networks in adolescent generalized anxiety disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 52, 290–299. doi: 10.1016/j.jaac.2012.12.010

Sánchez-Kuhn, A., León, J. J., Gôngora, K., Pérez-Fernández, C., Sánchez-Santed, F., Moreno, M., et al. (2017). Go/No-Go task performance predicts differences in compulsivity but not in impulsivity personality traits. *Psychiatry Res.* 257, 270–275. doi: 10.1016/j.psychres.2017.07.064

Scheres, A., Milham, M. P., Knutson, B., and Castellanos, F. X. (2007). Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 61, 720–724. doi: 10.1016/j.biopsych.2006.04.042

Schulz, K. P., Fan, J., Tang, C. Y., Newcorn, J. H., Buchsbaum, M. S., Cheung, A. M., et al. (2004). Response inhibition in adolescents diagnosed with attention deficit hyperactivity disorder during childhood: an event-related fMRI study. *Am. J. Psychiatry* 161, 1650–1657. doi: 10.1176/appi.ajp.161.9.1650

Smith, A. R., Steinberg, L., Strang, N., and Chein, J. (2015). Age differences in the impact of peers on adolescents' and adults' neural response to reward. *Dev. Cogn. Neurosci.* 11, 75–82. doi: 10.1016/j.dcn.2014.08.010

Snyder, H. R., and Hankin, B. L. (2016). Spiraling out of control. *Clin. Psychol. Sci.* 4, 1047–1064.

Somerville, L. H., Hare, T., and Casey, B. J. (2011). Frontostriatal maturation predicts cognitive control failure to appetitive cues in adolescents. *J. Cogn. Neurosci.* 23, 2123–2134. doi: 10.1162/jocn.2010.21572

Steinberg, L. (2010). A dual systems model of adolescent risk-taking. *Dev. Psychobiol.* 52, 216–224. doi: 10.1002/dev.20445

Stoycos, S. A., Del Piero, L., Margolin, G., Kaplan, J. T., and Saxbe, D. E. (2017). Neural correlates of inhibitory spillover in adolescence: associations with internalizing symptoms. *Soc. Cogn. Affect. Neurosci.* 12, 1637–1646. doi: 10.1093/scan/nsx098

Telzer, E. H., Fuligni, A. J., Lieberman, M. D., and Galván, A. (2014). Neural sensitivity to eudaimonic and hedonic rewards differentially predict adolescent depressive symptoms over time. *Proc. Natl. Acad. Sci. U.S.A.* 111, 6600–6605. doi: 10.1073/pnas.1323014111

Tohka, J., Foerde, K., Aron, A. R., Tom, S. M., Toga, A. W., and Poldrack, R. A. (2008). Automatic independent component labeling for artifact removal in fMRI. *Neuroimage* 39, 1227–1245. doi: 10.1016/j.neuroimage.2007.10.013

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., et al. (2009). The NimStim set of facial expressions: Judgments from untrained research participants. *Psychiatry Res.* 168, 242–249. doi: 10.1016/j.psychres.2008.05.006

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the mni mri single-subject brain. *Neuroimage* 15, 273–289. doi: 10.1006/nimg.2001.0978

Vanhalst, J., Gibb, B. E., and Prinstein, M. J. (2017). Lonely adolescents exhibit heightened sensitivity for facial cues of emotion. *Cogn. Emot.* 31, 377–383. doi: 10.1080/02699931.2015.1092420

Vuontela, V., Carlson, S., Troberg, A.-M., Fontell, T., Simola, P., Saarinen, S., et al. (2013). Working memory, attention, inhibition, and their relation to adaptive functioning and behavioral/emotional symptoms in school-aged children. *Child Psychiatry Hum. Dev.* 44, 105–122. doi: 10.1007/s10578-012-0313-2

Wang, M.-T., Brinkworth, M., and Eccles, J. (2013). Moderating effects of teacher–student relationship in adolescent trajectories of emotional and behavioral adjustment. *Dev. Psychol.* 49, 690–705. doi: 10.1037/a0027916

Ward, B. D. (2000). *Simultaneous Inference for FMRI Data*. Available at: https://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf (accessed June 13, 2019).

Zimmer–Gembeck, M. J., Hunter, T. A., and Pronk, R. (2007). A model of behaviors, peer relations and depression: perceived social acceptance as a mediator and the divergence of perceptions. *J. Soc. Clin. Psychol.* 26, 273–302. doi: 10.1521/jscp.2007.26.3.273

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 29 July 2019
doi: 10.3389/fnbeh.2019.00171

Age and Gender Effects in Sensitivity to Social Rewards in Adolescents and Young Adults

Sibel Altikulaç[1,2,3], Marieke G. N. Bos[1,2], Lucy Foulkes[4], Eveline A. Crone[1,2] and Jorien van Hoorn[1,2]*

[1] Department of Developmental and Educational Psychology, Faculty of Social and Behavioural Sciences, Institute of Psychology, Leiden University, Leiden, Netherlands, [2] Leiden Institute for Brain and Cognition, Leiden, Netherlands, [3] Department of Clinical, Neuro and Developmental Psychology, Faculty of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam, Netherlands, [4] Department of Education, University of York, York, United Kingdom

Adolescence is a sensitive period for socio-cultural processing and a vast literature has established that adolescents are exceptionally attuned to the social context. Theoretical accounts posit that the social reward of social interactions plays a large role in adolescent sensitivity to the social context. Yet, to date it is unclear how sensitivity to social reward develops across adolescence and young adulthood and whether there are gender differences. The present cross-sectional study (N = 271 participants, age 11–28 years) examined age and gender effects in self-reported sensitivity to different types of social rewards. In order to achieve this aim, the Dutch Social Reward Questionnaire for Adolescents was validated. Findings revealed that each type of social reward was characterized by distinct age and gender effects. Feeling rewarded by gaining positive attention from others showed a peak in late adolescence, while enjoying positive reciprocal relationships with others showed a linear increase with age. Enjoying cruel behavior toward others decreased with age for girls, while boys showed no changes with age and reported higher levels across ages. Reward from giving others control showed a mid-adolescent dip, while enjoying group interactions did not show any changes with age. Taken together, the results imply that the social reward of social interactions is a nuanced and complex construct, which encompasses multiple components that show unique effects with age and gender. These findings enable us to gain further traction on the ubiquitous effects of the social context on decision-making in adolescent's lives.

Keywords: social reward, social context, age, gender, adolescence, SRQ-A

OPEN ACCESS

Edited by:
Amanda E. Guyer, University of California, Davis, United States

Reviewed by:
Luigia Trabace, University of Foggia, Italy
Anna Weinberg, McGill University, Canada

***Correspondence:**
Eveline A. Crone
ECrone@fsw.leidenuniv.nl

Received: *26 February 2019*
Accepted: *12 July 2019*
Published: *29 July 2019*

Citation:
Altikulaç S, Bos MGN, Foulkes L, Crone EA and van Hoorn J (2019) Age and Gender Effects in Sensitivity to Social Rewards in Adolescents and Young Adults. Front. Behav. Neurosci. 13:171. doi: 10.3389/fnbeh.2019.00171

INTRODUCTION

Adolescence is the period between childhood and adulthood often characterized by heightened sensitivity to rewards, especially in a social context (Crone and Dahl, 2012; Blakemore and Mills, 2014; van Hoorn et al., 2019). Indeed, studies of non-social rewards in adolescence show greater reward sensitivity in risk-taking tasks involving immediate reward (Weigard et al., 2014), greater sensation seeking in self-report questionnaires (Martin et al., 2002; Steinberg et al., 2017), and more approach behavior toward rewards (Urošević et al., 2012). In the social domain, adolescents are exceptionally attuned to social rejection (Sebastian et al., 2010), quickly embarrassed when

observed by peers (Somerville et al., 2013), and susceptible to peer influence (e.g., Chein et al., 2011). Theoretical accounts postulate that adolescents may be highly attuned to the social context because they are more sensitive to *social rewards* (for a review, see Foulkes and Blakemore, 2016). Social reward can be defined as "the motivational and pleasurable aspects of interactions with other people" (Foulkes et al., 2014a, p. 1). Yet to date, the development of sensitivity to social rewards across adolescence and into adulthood is unclear. In addition, few studies have examined the effect of different *types* of social reward across adolescence (Foulkes et al., 2017). The current study aimed to fill this gap by examining age and gender effects in self-reported sensitivity to a range of social rewards in a cross-sectional design including adolescence to young adulthood (ages 11–28 years).

The social world of adolescence encompasses many challenges, and fitting in with the peer group is a key developmental task. During this time, both the quality and the quantity of time spent with peers increases (Somerville, 2013; Lam et al., 2014). Previous work shows that social interactions with peers are experienced as more rewarding for adolescents relative to adults. For example, adolescents feel more rewarded when talking to their peers compared to talking with adults (Csikszentmihalyi et al., 1977), and show a faster response toward smiling faces and "likes"/thumbs up than adults (Demurie et al., 2012; Cromheeke and Mueller, 2016). Neuroimaging research has shown that adolescents, but not (young) adults, make more risky decisions in the presence of peers, which is supported by activation in reward-related neural circuitry (Chein et al., 2011). Together, these studies provide empirical evidence for an adolescent peak in sensitivity to a range of positive types of social rewards (i.e., likes, smiling faces, and potential approval from friends), yet few studies have examined age differences in the *subjective value* of social interactions (except Csikszentmihalyi et al., 1977).

Individual differences in sensitivity to social rewards have reliably been assessed using self-report in adolescents and adults with the Social Reward Questionnaire (SRQ; Foulkes et al., 2014b; SRQ-A; Foulkes et al., 2017). This questionnaire assesses five different types of social rewards, including the enjoyment of being flattered, liked, and gaining positive attention (*Admiration*), being cruel, callous, and using others for personal gains (*Negative Social Potency*), giving others control and allowing them to make decisions (*Passivity*), having kind, reciprocal relationships (*Prosocial Interactions*); and engaging in group interactions (*Sociability*). Thus, the SRQ assesses a broad set of social rewards that may underlie sensitivity to the social context. Prior work using the SRQ has shown meaningful differences in sensitivity to social rewards between adolescents with autism spectrum disorders and typically developing adolescents (i.e., enjoying passivity, but not engaging in group interactions; Van Hoorn et al., 2017) as well as a distinctive inverse pattern for adolescents high in callous-unemotional traits such that they enjoy being cruel, but not having kind relationships (Foulkes et al., 2017). To examine sensitivity to social rewards, the secondary aim of this paper was to validate our Dutch version of the SRQ-A and to examine test–retest reliability as well as construct validity using the Resistance to Peer Influence questionnaire (RPI; Steinberg and Monahan, 2007) and Behavior Inhibition Scale-Behavior Activation Scale (BIS-BAS; Carver and White, 1994) as a measure of sensitivity to non-social reward.

We expected a peak in sensitivity to all types of social rewards during adolescence, except for the rewarding feeling from giving others control (Passivity). For this more passive type of social reward, we expected a linear decrease given the importance of becoming independent from parents in adolescence into young adulthood (Crone and Dahl, 2012). In line with theory and empirical work, we expected that feeling rewarded when gaining positive attention (Admiration), enjoying kind relationships (Prosocial Interactions), as well as enjoying group interactions (Sociability) peak during adolescence and decrease again in young adulthood (Csikszentmihalyi et al., 1977; Chein et al., 2011; Demurie et al., 2012; Somerville, 2013; Cromheeke and Mueller, 2016). Finally, antisocial behaviors are also uniquely heightened during adolescence (Fairchild et al., 2013) and have been associated with feeling rewarded from cruel behavior toward others (Foulkes et al., 2014b; Craker and March, 2016). Therefore, we expected a peak in feeling rewarded from cruel behaviors toward others (Negative Social Potency) during adolescence.

With regards to gender, we expected specific differences in sensitivity to reward from prosocial behavior (Prosocial Interactions) and cruel behavior toward others (Negative Social Potency). Girls behave more prosocially across age and tend to be more supportive in their friendships compared to boys (Eisenberg et al., 1995, 2005; De Goede et al., 2009; Luengo Kanacri et al., 2013) whereas adolescent boys show more overt antisocial behavior compared to girls (Snyder et al., 2012). Thus, we expected that females would also be more sensitive to social rewards from prosocial interactions and that males would be more sensitive to rewards from cruel behaviors toward others.

MATERIALS AND METHODS

Participants and Procedure

Participants were recruited from a large longitudinal brain imaging study with three time points called BrainTime. Recruitment for the BrainTime study occurred via high schools and advertisements in local newspapers in and around Leiden, the Netherlands. As part of the larger study, participants completed several online questionnaires, took part in a MRI study, and were compensated €10 per hour. Further recruitment details can be found in previous publications (e.g., Peters et al., 2016). The current cross-sectional study used the third time point of BrainTime, which consisted of 277 typically developing adolescents and young adults between 11 and 28 years old. Six participants from the BrainTime sample were excluded because of missing data for the SRQ-A. Hence, the final sample of the current study [called time point 1 (T1) for this paper] consisted of N = 271 participants [M_{age} = 17.84 years; SD_{age} = 3.67; $range_{age}$ = 11.90–28.60 years; 144 females (53%)]. The sample consisted of 90% Caucasian participants, 6% non-Caucasian participants [Turkish (n = 1), Latin-American (n = 7), North-African (n = 1), African (n = 3), and Asian (n = 5)], and 4% of participants whose ethnicity was unknown. Participants in the

sample had an average of 1.51 siblings (SD = 0.874, range = 0–5 siblings). There was no information about social economic status available for our participants.

A subset of 146 participants (52% of T1) also completed a follow up test–retest reliability session 6 months later, including several other questionnaires unrelated to this study (see e.g., Becht et al., 2018). Six participants were excluded because of incomplete data. Therefore, the final sample for the test–retest session [called time point 2 (T2) for this paper] included N = 140 participants [M_{age} = 18.48 years, SD_{age} = 4.07; $range_{age}$ = 12.30–29.50 years; 79 females (56%)]. Of this sample, 94% of the participants were Caucasian, 6% of the participants was non-Caucasian [Latin-American (n = 2), North-African (n = 1), African (n = 2), and Asian (n = 3)], and the ethnicity of 1% of the participants was unknown.

To determine whether our sample was a normative Dutch sample, the intelligence of participants was estimated using subscales *Picture Completion* and *Vocabulary* of the WISC-III (11–16 year olds; Kort et al., 2002) or WAIS-III (16+ year olds; Uterwijk, 2000), at the second time point of the original BrainTime study. The estimated IQ scores fell within the average range (N_{IQ} = 239; M_{IQ} = 108.4; SD_{IQ} = 10.4). Prior to the study, all participants and/or parents of participants under 18 years old provided informed consent. For T1 of the current study, the Leiden University Medical Ethical Committee approved all procedures under the project name "Brain development between ages 8 and 25: A longitudinal study" with approval number P10.191. For the follow-up (T2), all procedures were approved by the Leiden University Ethical Committee under the name of "Braintime questionnaires" with approval number CEP16-0308/122.

Questionnaire Development

Social Reward Questionnaire – Adolescent (SRQ-A) Version (Foulkes et al., 2017)

Participants aged 11–17 years completed the Dutch translation of the SRQ-A version (Foulkes et al., 2017) and participants aged 18+ years completed the Dutch translation of the adult SRQ (Brazil et al., in preparation). The two versions of the measure are highly similar (see the following paragraph). Similar to the original, the Dutch translation of the adult SRQ (Foulkes et al., 2014b; Brazil et al., in preparation) includes six subscales with a total of 23 questions: *Admiration* (enjoyment of being flattered, liked, and gaining positive attention, e.g., "I enjoy achieving recognition from others"); *Negative Social Potency* (enjoyment of being cruel, callous, and using others for personal gains, e.g., "I enjoy embarrassing others"); *Passivity* (enjoyment of giving others control over decisions, e.g., "I enjoy following someone else's rules"); *Prosocial Interactions* (enjoyment of having kind, reciprocal relationships, e.g., "I enjoy treating others fairly"); *Sexual Relationships* (enjoyment of having frequent sexual experiences, e.g., "I enjoy having an active sex life"); and *Sociability* (enjoyment of engaging in group interactions, e.g., "I enjoy going to parties").

The Dutch translation of the adolescent SRQ (SRQ-A) was translated by a bilingual Dutch-English speaker using the forward–backwards method (Bracken and Barona, 1991). The last author checked with Foulkes and Brazil to make sure that the translated items reflected the content of the original items, and that the adolescent and adult version used similar wording. In line with the English SRQ-A, the *Sexual Relationship* subscale was removed, and minor word changes were made to improve clarity for younger participants. Care was taken that all participants understood the instructions of the questionnaire. Responses to the adult and adolescent questionnaires were coded on a seven-point Likert scale, ranging from 1 = strongly disagree to 7 = strongly agree. Mean scores for each subscale are calculated, but no overall mean score is computed due to the contrasting meaning of some of the subscales (cf. Foulkes et al., 2014b, 2017).

Measures to Assess Construct Validity of Dutch SRQ-A

Resistance to Peer Influence (RPI; Steinberg and Monahan, 2007)

This questionnaire provided a general measure of resistance to peer influence (RPI). In 10 pairs of statements, participants indicated which of the two statements applied to them the most, e.g., "Some people go along with friends just to keep their friends happy" but "Other people refuse to go along with what their friends want to do, even though they know it will make their friends unhappy." After selecting a statement, participants decided whether it was "really true" or "sort of true" for them. Afterward, responses were coded on a four-point scale and averaged, with a high RPI score indicating high RPI. Prior research shows that adolescents with lower scores on the RPI (more susceptible to peer influences) are more impulsive and take more risks (Steinberg and Monahan, 2007). Therefore, we expected that adolescents who are more resistant to peer influence (high RPI scores) would have higher Prosocial Interactions scores and lower Sociability scores, since they may place more value on the opinions of others and use these opinions to guide their behavior.

Behavioral Inhibition System–Behavioral Activation System (BIS–BAS; Carver and White, 1994)

This is a 24-item questionnaire that measures both the Behavioral Inhibition System (BIS) and Behavioral Activation System (BAS). It consists of four subscales; *BIS* (reactions to the anticipation of punishment), *BAS Drive* (the persistent pursuit of desired goals), *BAS Fun Seeking* (desire for new rewards and willingness to approach a potentially rewarding event), and *BAS Reward Responsiveness* (sensitivity to pleasant reinforcers in the environment). Items consist of several statements and participants had to indicate to what extent they agreed with each statement on a four-point scale (1 = strongly agree, 4 = strongly disagree). We expected that BAS Reward Responsiveness would only be related to more positive types of social reward, including feelings of reward from getting positive attention (Admiration), Prosocial Interactions, and engaging in group interactions (Sociability). Moreover, we expected that BAS Drive and BAS Fun Seeking would be related to all SRQ-A subscales, because they measure trait-like sensitivity to rewards, which may underlie

sensitivity to social rewards. We did not expect any relationships between BIS and social rewards.

Statistical Analyses

Validity and Reliability of SRQ-A

To validate the Dutch SRQ-A for both adolescents and young adults, we used R studio with the Lavaan package to run a confirmatory factor analysis (CFA; Rosseel, 2012). At T1 (N = 271), 157 adolescents completed the 20-item SRQ-Adolescent and 114 adults completed the 23-item adult SRQ. Given that the "Sexual Relationships" scale is only included in the adult version, these questions were excluded from current analyses. Therefore, our model consisted of 50 parameters (i.e., 20 factor loadings, 20 error variances, 10 factor correlations). Given that the subjects-to-parameters ratio should be at least 5:1 (Bentler and Chou, 1987) our sample was adequate to test this model (ratio 5.4:1). The SRQ-A consists of ordinal items and therefore the mean and variance adjusted weighted least squares (WLSMV) estimation procedure was used (Flora and Curran, 2004). A comparative fit index (CFI) of 0.95 or higher and a root mean square error of approximation (RMSEA) of 0.08 or lower were used to determine a good model fit (Hu and Bentler, 1999), as in the original validation papers.

Internal consistency was assessed using Cronbach's alpha. However, given the limitation that Cronbach's alpha is not an indicator of scale unidimensionality (Schmitt, 1996), we relied most on mean inter-item correlations (MICs) to assess homogeneity and internal consistency of the scales (cf. Foulkes et al., 2017). For the sake of completeness, we also report Cronbach's alphas and MICs split for age groups in **Supplementary Table 1**. Construct validity was tested with the additional questionnaires (RPI and BIS-BAS) completed by all participants at T1, using Pearson's correlations in IBM SPSS Statistics 23. Test–retest reliability was assessed by correlating the subscale scores of the follow-up session at T2 with the subscale scores of the initial session for each participant. To control for errors resulting from multiplicity, the false discovery rate (FDR) was used (Benjamini and Hochberg, 1995).

Age and Gender Effects

We expected nonlinear age effects for all types of social reward assessed with the SRQ-A, except Passivity for which we expected a linear decrease with age. Therefore, we used a regression analysis with the enter method in SPSS for each subscale separately, and included effects of gender in model 1, adding linear and quadratic age effects in model 2, and finally the interaction effects of gender × linear age, and gender × quadratic age in model 3.[1] The social reward subscales were utilized as the dependent variable, and age, gender, and the interaction terms of age × gender were added as independent variables. Age was centered because we included interaction terms in our models (Aiken and West, 1991).

[1]We also ran regression models controlling for self-reported psychopathology (N = 18; coded as 0 = no psychopathology; 1 = psychopathology). These analyses yielded the same results with age and gender as those without psychopathology. For the subscale Sociability, we found a small main effect of psychopathology ($\beta = -1.84$, $R^2_{adj} = 0.03$, $p = 0.002$).

RESULTS

Validation of Dutch SRQ-A

In order to ensure that the Dutch version of the SRQ-A was a valid and reliable measure of social rewards we tested a five-factor model using a CFA, based on the five-factor model of the original SRQ-A. The items and factors used in the CFA corresponded with the original SRQ-A. The CFA-model fit the data well [$\chi^2_{(160)} = 375.05$, $p < 0.001$; CFI = 0.96; RMSEA = 0.065, 90% CI = 0.067-0.087]. The ranges of the factor loadings were between 0.44 and 0.90 ($M_{loadings} = 0.67$, $SD_{loadings} = 0.11$). All factor loadings are shown in **Table 1**.

SRQ-A Reliability

In **Tables 2**, **3**, an overview of correlations, descriptive statistics, Cronbach's alphas, and MICs for each of the five subscales is displayed. At T1, internal consistency of four out of five subscales was reasonable, with Cronbach's alphas between 0.67 to 0.78

TABLE 1 | Standardized factor loadings from the five-factor CFA.

Factor	Loading	Item number
Prosocial interaction	0.65	2
	0.65	6
	0.54	16
	0.65	19
	0.68	22
Passivity	0.85	12
	0.76	21
	0.72	23
Admiration	0.66	1
	0.69	7
	0.73	11
	0.62	18
Sociability	0.61	4
	0.58	10
	0.90	15
Negative social potency	0.70	3
	0.44	5
	0.77	8
	0.47	14
	0.62	17

Item numbers are based on the adult SRQ. Items 9, 13, and 20 correspond with the sexual relationships subscale and are not included.

TABLE 2 | Correlations of each subscale at T1 (n = 271), and Pearson's correlations between mean subscale scores at T1 and T2 (n = 140).

	1	2	3	4	T1–T2
1. Admiration					0.63***
2. Negative social potency	**0.18****				0.69***
3. Passivity	−0.03	−0.08			0.56***
4. Prosocial interactions	**0.40****	**−0.19****	<0.01		0.58***
5. Sociability	**0.47****	0.07	−0.02	**0.28****	0.65***

*Factor correlations with $p < 0.05$ are shown in bold. **$p < 0.01$, ***$p < 0.001$.*

TABLE 3 | Descriptive statistics (minimum, maximum, mean, and SD), mean inter-item correlations (MICs), and Cronbach's alphas of each subscale at T1, as well as MICs and Cronbach's alphas at T2.

	Minimum T1	Maximum T1	Mean+ (*SD*) T1	MIC T1	MIC T2	Cronbach's alpha T1	Cronbach's alpha T2
Social Reward Questionnaire – Adolescents (SRQ-A)							
Admiration	1.25	7.00	5.18 (*1.04*)	0.34	0.41	0.69	0.73
Negative social potency	1.00	4.80	2.08 (*0.77*)	0.21	0.33	0.55	0.67
Passivity	1.00	6.00	2.84 (*1.17*)	0.55	0.63	0.78	0.84
Prosocial interactions	3.00	7.00	6.04 (*0.68*)	0.31	0.38	0.67	0.74
Sociability	1.00	7.00	5.61 (*1.07*)	0.41	0.49	0.68	0.74

+, *Mean item score in each factor.*

(Taber, 2018), and Negative Social Potency had a slightly lower alpha ($\alpha = 0.55$, $SD = 0.07$). At T2, internal consistency for all five subscales was reasonable, with Cronbach's alphas between 0.67 and 0.84. The MICs fell in the acceptable range for all subscales for T1 and T2 (T1: range = 0.21-0.55; T2: range = 0.33–0.49) conform guidelines from Clark and Watson (1995) for subscales that measure relatively narrow constructs.

SRQ-A Test–Retest Reliability

Test–retest reliability was assessed with Pearson correlations (cf. Foulkes et al., 2017) based on 140 participants who completed the SRQ-A again roughly 6 months after the initial assessment ($M_{T1-T2} = 6.96$ months, $SD_{T1-T2} = 1.92$ months, range = 3.36–12.00 months). Pearson correlations were in the moderate range (Mukaka, 2012) for each subscale ($M = 0.62$, $SD = 0.05$, all $ps < 0.001$), which indicates that the questionnaire is relatively stable across 6-months' time (**Table 2**).

SRQ-A Construct Validity

To examine the associations between social rewards and sensitivity to social context and non-social reward, we conducted Pearson correlation analyses. FDR-corrected *p*-values are presented in **Table 4**. Both *Admiration* and *Sociability* were positively correlated with all BAS subscales. *Sociability* was also negatively correlated with RPI. *Negative Social Potency* was positively correlated with BAS Drive and BAS Fun Seeking. *Passivity* was negatively correlated with BAS Drive and BAS Fun Seeking. Finally, *Prosocial Interactions* was positively correlated with all measures. Findings were in the expected direction and imply an acceptable construct validity of the Dutch SRQ-A.

Age and Gender Effects in Sensitivity to Social Reward

To examine age and gender effects on sensitivity to social reward, separate regression analyses were conducted for each SRQ-A subscale. Analyses included gender in model 1 as a baseline, linear and quadratic age effects in model 2, and interaction effects of gender × linear age and gender × quadratic age in model 3 (see **Table 5** for an overview of all models per subscale).

For *Admiration*, the second and third model were significant ($p < 0.01$ and $p = 0.02$, respectively), but only the second model predicted significantly more variance than the baseline model [$F(3,267) = 4.49$, $p < 0.01$, $R^2_{adj} = 0.04$, $R^2_{change} = 0.05$], hence we picked the most parsimonious model. The results showed a quadratic age effect ($\beta = -0.16$, $t = -2.36$, $p = 0.02$), indicating an adolescent peak in late adolescence which fell at 21.34 years old (**Figure 1A**). This suggests that the enjoyment of *Admiration* increases for both boys and girls until young adulthood, and levels off after the age of approximately 21.34 years old.

The regression analysis for *Negative Social Potency* resulted in three significant models (all $p < 0.001$). The third model explained significantly more variance than the baseline model [$F(5,265) = 6.77$, $p < 0.01$, $R^2_{adj} = 0.10$, $R^2_{change} = 0.03$], with main effects of age ($\beta = -0.27$, $t = -3.11$, $p < 0.01$) and gender ($\beta = 0.27$, $t = 3.60$, $p < 0.01$) which were qualified by an interaction of linear age × gender ($\beta = 0.27$, $t = 2.88$, $p < 0.01$).

TABLE 4 | Pearson correlations between SRQ-A subscales and external measures.

	SRQ-A subscale				
	Admiration	**Negative social potency**	**Passivity**	**Prosocial interactions**	**Sociability**
RPI					
Mean RPI	−0.01	−0.08	−0.08	**0.22****	**−0.24****
BISBAS					
BAS drive	**0.38****	**0.19****	**−0.25****	**0.23****	**0.15****
BAS fun seeking	**0.35****	**0.17****	**−0.18****	**0.24****	**0.26****
BAS reward responsiveness	**0.41****	0.00	−0.04	**0.35****	**0.32****
BIS	0.09	−0.11	0.10	**0.21****	0.05

*Significant correlations after FDR correction for multiple comparisons (with alpha level 0.05) in in bold. *p < 0.05; **p < 0.01.*

TABLE 5 | Regression analysis (enter method) per subscale separately.

	SRQ-A subscale														
	Admiration			**Negative social potency**			**Passivity**			**Prosocial interactions**			**Sociability**		
	B	***SE.B***	β	***B***	***SE.B***	β	***B***	***SE.BB***	β	***B***	***SE.B***	β	***B***	***SE.B***	β
Model 1															
Constant	5.20	0.09		1.91	0.06		2.80	0.10		6.24	0.05		5.70	0.09	
Gender	−0.04	0.13	−0.02	0.36	0.09	0.23**	0.09	0.14	0.04	−0.43	0.08	−0.32**	−0.20	0.13	−0.09
R^2_{adj}		−0.00			0.05			−0.00			0.10			0.01	
Model 2															
Constant	**5.32**	**0.10**		1.96	0.07		**2.70**	**0.11**		**6.26**	**0.06**		5.73	0.10	
Gender	**−0.05**	**0.12**	**−0.03**	0.37	0.09	0.24**	**0.07**	**0.14**	**0.03**	**−0.44**	**0.08**	**−0.32****	−0.20	0.13	−0.09
Age (linear)	**0.07**	**0.02**	**0.25****	−0.02	0.01	−0.11	**0.04**	**0.02**	**0.12**	**0.04**	**0.01**	**0.23****	−0.01	0.02	−0.03
Age (quadratic)	**−0.01**	**0.00**	**−0.16***	−0.00	0.00	−0.09	**0.01**	**0.00**	**0.14***	**−0.00**	**0.00**	**−0.04**	−0.00	0.00	−0.04
R^2_{adj}		**0.04**			0.07			**0.04**			**0.14**			0.00	
Model 3															
Constant	5.33	0.11		**1.95**	**0.08**		2.66	0.13		6.29	0.07		5.74	0.12	
Gender	−0.07	0.16	−0.03	**0.41**	**0.11**	**0.27****	0.11	0.18	0.05	−0.49	0.10	−0.36**	−0.19	0.17	−0.09
Age (linear)	0.06	0.03	0.20*	**−0.06**	**0.02**	**−0.27****	0.06	0.03	0.19	0.04	0.02	0.22*	−0.02	0.03	−0.08
Age (quadratic)	−0.01	0.01	−0.19	**−0.00**	**0.00**	**−0.09**	0.01	0.01	0.20	−0.00	0.00	−0.11	−0.00	0.01	−0.05
Gender × age (linear)	0.03	0.04	0.07	**0.08**	**0.03**	**0.27****	−0.05	0.04	−0.11	0.00	0.02	0.01	0.03	0.04	0.08
Gender × age (quadratic)	0.00	0.01	0.02	**−0.00**	**0.01**	**−0.07**	−0.00	0.01	−0.05	0.00	0.01	0.10	0.00	0.01	−0.00
R^2_{adj}		0.03			**0.10**			0.04			0.13			0.00	

*Best-fitted models are displayed in bold. No effects are found for sociability, and therefore, no model is displayed in bold. Age is centered (mean = 17.84 years old). Gender is coded 0 = female, 1 = male. *$p < 0.05$; **$p < 0.01$.*

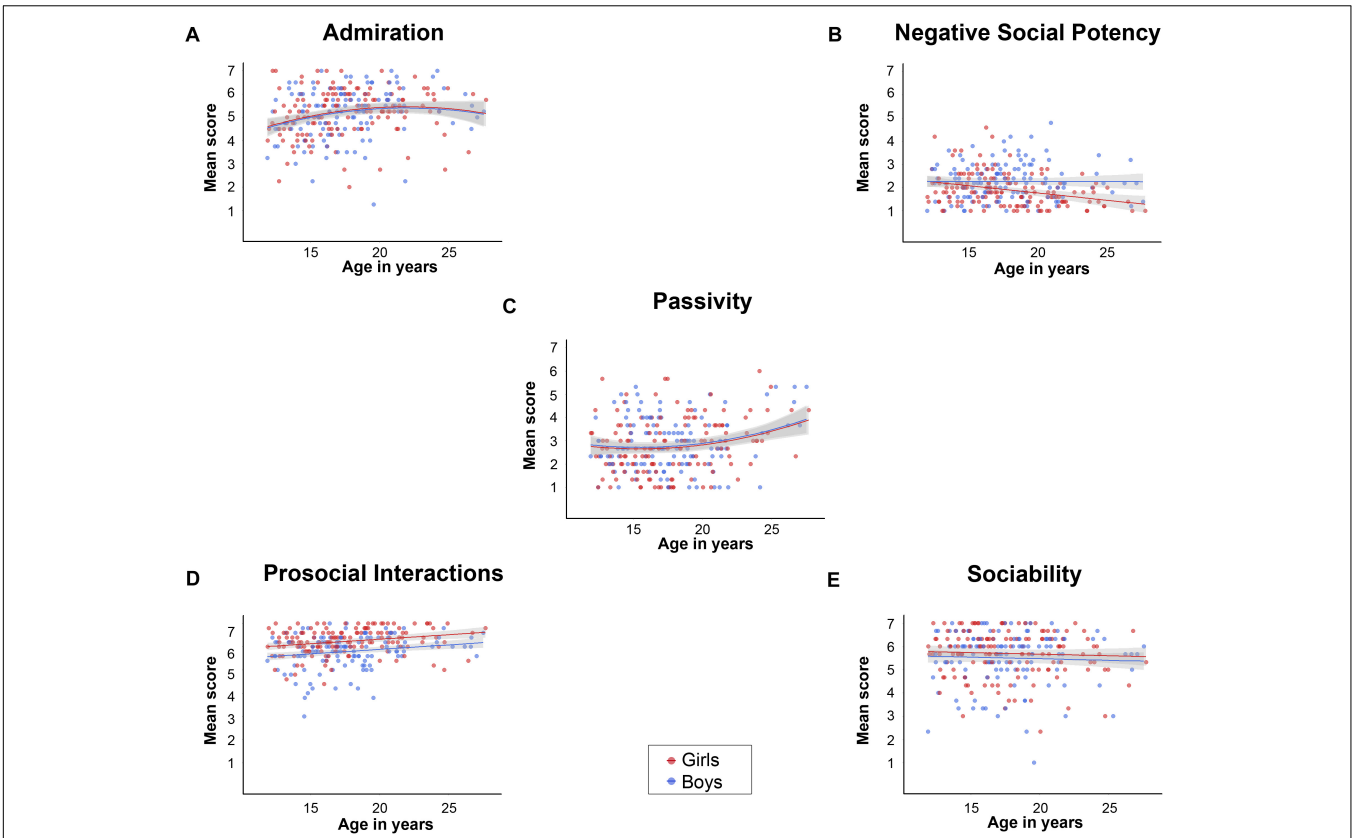


FIGURE 1 | Mean scores on each SRQ-A subscale of adolescents and young adults between ages 11–28 years. **(A)** Mean scores of *Admiration* showing a quadratic age effect, with a peak at 21.34 years old. **(B)** Mean scores of *Negative Social Potency* showing an interaction effect of gender and age. **(C)** Mean scores of *Passivity* showing a quadratic age effect, with a dip at 15.40 years old. **(D)** Mean scores of *Prosocial Interactions* showing a main effect for gender and a main effect of age, and **(E)** mean scores of *Sociability* showing no main nor interaction effects.

The interaction revealed that boys and girls show similar levels of *Negative Social Potency* in early adolescence, with patterns diverging later in adolescence when girls show a decrease, while boys show no changes over time (**Figure 1B**).

For *Passivity*, all three models were significant, with the second model predicting significantly more variance than the baseline model [$F(3,267) = 4.99$, $p < 0.01$, $R^2_{adj} = 0.04$, $R^2_{change} = 0.05$]. The results showed a quadratic effect of age ($\beta = 0.14$, $t = 2.05$, $p = 0.04$), revealing an adolescent dip in mid-adolescence at 15.40 years old (**Figure 1C**). This suggests that the enjoyment of *Passivity* decreases until approximately age 15.40 years, and increases again with age, for both boys and girls.

The regression analysis for *Prosocial Interactions* resulted in three significant models, with the second model explaining significantly more variance [$F(3,267) = 15.06$, $p < 0.01$, $R^2_{adj} = 0.14$, $R^2_{change} = 0.05$], by a main effect of linear age ($\beta = 0.23$, $t = 3.54$, $p < 0.01$) and gender ($\beta = -0.32$, $t = -5.70$, $p < 0.01$). These findings show that girls enjoy *Prosocial Interactions* more across all ages, and in addition, that both boys and girls have higher levels of *Prosocial Interactions* with age (**Figure 1D**).

Finally, the regression analysis for *Sociability* revealed no significant model, indicating neither significant main effects nor interaction effects of age and gender (all *ps* > 0.13). This suggests that enjoyment of engaging in group interactions is stable across adolescence and into young adulthood (**Figure 1E**).

DISCUSSION

The main goal of the present study was to examine age and gender differences in sensitivity to different types of social rewards in a sample of adolescents and young adults between the ages of 11 and 28 years. Understanding sensitivity to social reward as an underlying neurocognitive mechanism for social influence processes is vital to further delineate why and under what conditions adolescents are affected by their social context (Somerville et al., 2018). Our key finding is that the reward from being liked and gaining positive attention showed a late adolescent peak. Gender differences were in the expected direction, as girls felt more rewarded by kind interactions and this increased with age, whereas enjoying being cruel to others was stable for boys and decreased for girls with age. However, contrary to our expectations, social reward from engaging in group interactions was stable across the entire age range, and letting others make decisions showed a mid-adolescent dip. Thus, sensitivity to social reward is a nuanced

and complex phenomenon, which reveals differential age-related patterns for each type of social reward. These findings are further unpacked below.

Social Reward as an Underlying Neurocognitive Mechanism for Social Influence Processes

The present study was the first to study the *subjective value* of a broad range of social rewards in a cross-sectional sample that spanned early adolescence to adulthood. Our findings revealed that the reward from being liked and gaining positive attention showed a higher hedonic value during late adolescence (at approximately age 21 years). Given that previous work provides empirical evidence for an early to mid-adolescent peak in neural reward sensitivity (approximately age 16–17 years; e.g., Braams et al., 2015; Silverman et al., 2015), peer influence on risk perception and prosocial behavior (age 12–14 years; Knoll et al., 2015; age 12–13 years; Van Hoorn et al., 2016a) as well as sensitivity to peer influence (age 10–14 years; Steinberg and Monahan, 2007), this peak fell somewhat later than expected.

Sensitivity to social evaluation is thought to be central throughout adolescence (Somerville et al., 2013), but younger adolescents are found to be most sensitive to social exclusion (Sebastian et al., 2010). As such, social signals of positive attention may be particularly important during early adolescence because this is a period of rapid social development, without necessarily increasing in hedonic value (Foulkes and Blakemore, 2016). Possibly, early adolescents' sensitivity to social influences are guided by greater motivations to avoid social punishment or risk (i.e., social exclusion), rather than an orientation to social reward (Blakemore, 2018). Speculatively, the "balance" between *avoiding* social risk and *gaining* social approval as processes that predict sensitivity to the social context changes with age. The increase in hedonic value of social approval during late adolescence fits with the epidemiological literature on morbidity and mortality from risk taking which peaks in late adolescence (Willoughby et al., 2013). Together, this work illustrates that the emergence of reward-related behaviors such as risk taking likely depends on age, and also on opportunities and characteristics of the social context (Willoughby et al., 2013).

Next, our findings revealed that early adolescents *and* young adults felt more rewarded when giving others control over decisions (i.e., passive behavior), compared to mid-adolescents (approximately age 15 years). While the decrease during adolescence corroborates previous research emphasizing that adolescents seek independence and strive to become more autonomous (Zimmer-Gembeck and Collins, 2003), it was somewhat surprising that our findings revealed an adolescent dip rather than a linear decrease with age. Interestingly, Foulkes et al. (2017) noticed a similar pattern in the relationship between psychopathic traits and passivity, which were positively related in adults, but negatively related in adolescents. Young adults tend to have control over most of their life decisions, possibly resulting in more enjoyment when giving others control over decisions, as this means less effort for the individual. However, passivity in adolescents may be experienced as submission to authority figures such as parents, which is undesirable in the context of establishing their independence (Foulkes et al., 2017).

Moreover, late adolescents and young adults experienced being in positive, reciprocal relationships as more rewarding compared to younger adolescents. Gradual improvement in mentalizing skills across adolescence into young adulthood may facilitate positive interactions with others (Frith and Frith, 2006), and these positive experiences may in turn feel rewarding. These findings are partly consistent with prior research showing that prosocial behavior (i.e., behavior that benefits others) increases during young adulthood after a dip during adolescence (although note that prosocial *behavior* is different from *enjoying* prosocial relations; Eisenberg et al., 2005; Luengo Kanacri et al., 2013). Hence, prosocial behavior observed in late adolescence and adulthood may perhaps in part be driven by experiencing more reward from this behavior than younger adolescents. In line with our expectations, we found gender differences in social reward from experiencing kind relationships as well as being cruel toward others. Across adolescence and young adulthood, girls feel more rewarded from having intimate, reciprocal interactions than boys. This resonates with previous work indicating that girls behave more prosocially and show more intimacy and support in their friendships (Eisenberg et al., 1995; De Goede et al., 2009).

Further, we observed that the rewarding feeling from engaging in group interactions does not show age-related changes in hedonic value. Previous studies have shown that different social actors within the social context have different effects on adolescent decision-making (van Hoorn et al., 2019). For example, peers can create vulnerabilities and opportunities for adolescents (Van Hoorn et al., 2016b), and the presence of a mother or other adult differentially modulates reward-related neural circuits in the brain than peers (Chein et al., 2011; Guassi Moreira and Telzer, 2016; van Hoorn et al., 2018). The SRQ-A does not distinguish between reward value from interacting with peers, strangers, and parents, as it measures reward value from social interactions in general. This likely contributed to the differences in the current findings relative to work from Csikszentmihalyi et al. (1977), who reported increased reward in adolescence specifically during conversations with peers relative to adults.

Finally, we examined one relatively negative type of social reward, i.e., feeling reward from being cruel to others. Both males and females in our typically developing sample reported a limited sense of reward when being cruel, callous, and using others for personal gains, which decreased with age for females while it was stable for males. Although adolescence is a time during which antisocial behavior peaks (Fairchild et al., 2013), the current findings do not provide evidence for a heightened feeling of reward from being cruel and using others for personal gains during this period. As such, the increase in antisocial behavior during adolescence may not due to more enjoyment of behaving antisocially, at least not in a normative sample,

highlighting the importance of social context in which these types of behavior occur.

Validation of the Dutch SRQ-A and Relation With Non-social Reward

Our analyses indicated that the Dutch translation of the SRQ-A is a valid and reliable measure of sensitivity to social reward in adolescence. We further examined the relationship between social rewards and RPI (Steinberg and Monahan, 2007) as well as non-social rewards (BIS-BAS; Carver and White, 1994). RPI was associated with two types of social rewards that are most directly related to friendships and being part of a group. Feeling more rewarded from engaging in group interactions was associated with less RPI, which likely reflects a higher tendency to conform to the peer group if an adolescent highly values the (opinions from) the peer group (Telzer et al., 2018). On the other hand, feeling more rewarded from prosocial interactions was related to greater RPI. Speculatively, adolescents who enjoy prosocial and kind interactions potentially have more of these positive friendships, which are known to provide a buffer against negative behaviors such as risk taking (Telzer et al., 2015).

In terms of non-social reward, sensitivity to pleasant reinforcers in the environment (BAS Reward Responsiveness) was only related to more positive types of social reward, including feelings of reward from getting positive attention, prosocial interactions, and engaging in group interactions. Across the entire range of social rewards that we measured, each subtype was related to the drive or persistent pursuit of seeking out rewards (BAS Drive) and the motivation to find novel rewards spontaneously (BAS Fun Seeking). This is in line with our expectations, and serves to support the idea that the SRQ-A measures reward value. The underlying construct for sensitivity to social reward may be the tendency to seek out rewards, both in more spontaneous and persistent ways (Carver and White, 1994), rather than the avoidance of punishment (BIS), which did not show this consistent (reverse) association with social rewards. Taken together, the relations between social reward and non-social reward as well as RPI are in the expected direction and provide interesting avenues for future research.

Limitations and Future Directions

It is important to acknowledge the limitations of our study. Sensitivity to social reward may be affected by earlier experiences, such as early stressful life events (see e.g., Coker et al., 2011). While this was beyond the scope of the current paper, it would be an interesting future direction. Moreover, the SRQ-A does not distinguish between reward value from interacting with different actors such as peers and parents, as it was designed to measure reward value from social interactions in general. A promising avenue for future research is to examine social reward from specific others (peers, parents, strangers, best friends, etc.) in a wide adolescent age range (also see Güroğlu et al., 2014). These results will be important to better understand adolescent-specific behavior for each type of social rewards within different social contexts. Finally, our results are based on cross-sectional data and did not include a younger comparison group of children younger than age 11 years. Given potential issues associated with lower internal consistency in younger adolescents, it will be important to develop additional items that are suitable for children and young adolescents. To further understand the developmental pattern of the different social rewards, future studies should employ a longitudinal design with children, adolescents, and adults.

CONCLUSION

Theoretical and empirical work characterizes adolescence as a time of uniquely heightened sensitivity to (non-social) reward, social stimuli, and peer influence (Galvan, 2010; Chein et al., 2011; Blakemore and Mills, 2014). The present study was the first to examine subjective sensitivity to social rewards in a cross-sectional sample between early adolescence and adulthood. Our findings revealed that reward from being liked and gaining positive attention showed a higher hedonic value during late adolescence, which corroborates the idea that sensitivity to the social context may at least partly due to the social reward of getting approval from others. However, at the same time the results highlight that social reward is more nuanced and complex (cf. Foulkes and Blakemore, 2016), because this pattern was not apparent in other types of social rewards that were examined. The SRQ-A provides an important individual differences measure in typically developing samples as well as atypical samples where social reward may go awry, such as autism spectrum disorders.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Prior to the study, all participants and/or parents of participants under 18 years old provided written informed consent in accordance with the Declaration of Helsinki. For the first time point (T1) of the current study, the Leiden University Medical Ethical Committee approved all procedures under the project name "Brain development between ages 8 and 25: A longitudinal study" with approval number P10.191. For the follow-up (T2), all procedures were approved by the Leiden University Ethical Committee under the name of "Braintime questionnaires" with approval number CEP16-0308/122.

AUTHOR CONTRIBUTIONS

JvH and EC contributed to the conception and design of the study with input from LF on questionnaire design. SA and

JvH performed the statistical analyses with input from MB. SA and JvH wrote the manuscript. LF, MB, and EC provided important intellectual content to the manuscript. All authors contributed to the manuscript revision, and read and approved the submitted version of the manuscript.

FUNDING

This research was supported by an ERC Starting Grant (ERC 2010-StG-263234 to EC) and ERC Consolidator Grant (ERC CoG PROSOCIAL 681632 to EC).

ACKNOWLEDGMENTS

We are very grateful to the entire research team for their help in data collection. We gratefully thank Eva Collins and her family for their help in translating the Social Reward Questionnaire.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2019.00171/full#supplementary-material

REFERENCES

Aiken, L. S., and West, S. G. (1991). *Multiple Regression: Testing and Interpreting Interactions*. Newbury Park, CA: Sage Publications.

Becht, A. I., Bos, M. G. N., Nelemans, S. A., Peters, S., Vollebergh, W. A. M., Brantje, S. J. T., et al. (2018). Goal-directed correlates and neurobiological underpinnings of adolescent identity: a multimethod multisample longitudinal approach. *Child Dev.* 89, 823–836. doi: 10.1111/cdev.13048

Benjamini, Y., and Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. Ser. B* 57, 289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x

Bentler, P. M., and Chou, C. P. (1987). Practical issues in structural modeling. *Sociol. Methods Res.* 16, 78–117. doi: 10.1177/0049124187016001004

Blakemore, S. J. (2018). Avoiding social risk in adolescence. *Curr. Dir. Psychol. Sci.* 27, 116–122. doi: 10.1177/0963721417738144

Blakemore, S. J., and Mills, K. L. (2014). Is adolescence a sensitive period for sociocultural processing? *Annu. Rev. Psychol.* 65, 187–207. doi: 10.1146/annurev-psych-010213-115202

Braams, B. R., van Duijvenvoorde, A. C., Peper, J. S., and Crone, E. A. (2015). Longitudinal changes in adolescent risk-taking: a comprehensive study of neural responses to rewards, pubertal development, and risk-taking behavior. *J. Neurosci.* 35, 7226–7238. doi: 10.1523/jneurosci.4764-14.2015

Bracken, B. A., and Barona, A. (1991). State of the art procedures for translating, validating and using psychoeducational tests in cross-cultural assessment. *Sch. Psychol. Int.* 12, 119–132. doi: 10.1177/0143034391121010

Carver, C. S., and White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment. *J. Pers. Soc. Psychol.* 67, 319–333. doi: 10.1037//0022-3514.67.2.319

Chein, J., Albert, D., O'Brien, L., Uckert, K., and Steinberg, L. (2011). Peers increase adolescent risk taking by enhancing activity in the brain's reward circuitry. *Dev. Sci.* 14, F1–F10. doi: 10.1111/j.1467-7687.2010.01035.x

Clark, L. A., and Watson, D. (1995). Constructing validity: basic issues in objective scale development. *Psychol. Assess.* 7, 309–319. doi: 10.1037/1040-3590.7.3.309

Coker, T. R., Elliott, M. N., Wallander, J. L., Cuccaro, P., Grunbaum, J. A., Corona, R., et al. (2011). Association of family stressful life-change events and health-related quality of life in fifth-grade children. *Arch. Pediatr. Adolesc. Med.* 165, 354–359. doi: 10.1001/archpediatrics.2011.13

Craker, N., and March, E. (2016). The dark side of Facebook®: the dark tetrad, negative social potency, and trolling behaviours. *Pers. Individ. Differ.* 102, 79–84. doi: 10.1016/j.paid.2016.06.043

Cromheeke, S., and Mueller, S. C. (2016). The power of a smile: stronger working memory effects for happy faces in adolescents compared to adults. *Cogn. Emot.* 30, 288–301. doi: 10.1080/02699931.2014.997196

Crone, E. A., and Dahl, R. E. (2012). Understanding adolescence as a period of social–affective engagement and goal flexibility. *Nat. Rev. Neurosci.* 13, 636–650. doi: 10.1038/nrn3313

Csikszentmihalyi, M., Larson, R., and Prescott, S. (1977). The ecology of adolescent activity and experience. *J. Youth Adolesc.* 6, 281–294. doi: 10.1007/BF02138940

De Goede, I. H. A., Branje, S. J. T., and Meeus, W. H. J. (2009). Developmental changes and gender differences in adolescents' perceptions of friendships. *J. Adolesc.* 32, 1105–1123. doi: 10.1016/j.adolescence.2009.03.002

Demurie, E., Roeyers, H., Baeyens, D., and Sonuga-Barke, E. (2012). The effects of monetary and social rewards on task performance in children and adolescents: liking is not enough. *Int. J. Methods Psychiatr. Res.* 21, 301–310. doi: 10.1002/mpr.1370

Eisenberg, N., Carlo, G., Murphy, B., and Court, P. (1995). Prosocial development in late adolescence: a longitudinal study. *Child Dev.* 66, 1179–1197. doi: 10.1111/j.1467-8624.1995.tb00930.x

Eisenberg, N., Cumberland, A., Guthrie, I. K., Murphy, B. C., and Shepard, S. A. (2005). Age changes in prosocial responding and moral reasoning in adolescence and early adulthood. *J. Res. Adolesc.* 15, 235–260. doi: 10.1111/j.1532-7795.2005.00095.x

Fairchild, G., van Goozen, S. H. M., Calder, A. J., and Goodyer, I. M. (2013). Research review: evaluating and reformulating the developmental taxonomic theory of antisocial behaviour. *J. Child Psychol. Psychiatry* 54, 924–940. doi: 10.1111/jcpp.12102

Flora, D. B., and Curran, P. J. (2004). An empirical evaluation of alternative methods of estimation for confirmatory factor analysis with ordinal data. *Psychol. Methods* 9, 466–491. doi: 10.1037/1082-989X.9.4.466

Foulkes, L., and Blakemore, S. J. (2016). Is there heightened sensitivity to social reward in adolescence? *Curr. Opin. Neurobiol.* 40, 81–85. doi: 10.1016/j.conb.2016.06.016

Foulkes, L., McCrory, E. J., Neumann, C. S., and Viding, E. (2014a). Inverted social reward: associations between psychopathic traits and self-report and experimental measures of social reward. *PLoS One* 9:e106000. doi: 10.1371/journal.pone.0106000

Foulkes, L., Viding, E., McCrory, E., and Neumann, C. S. (2014b). Social reward questionnaire (SRQ): development and validation. *Front. Psychol.* 5:201. doi: 10.3389/fpsyg.2014.00201

Foulkes, L., Neumann, C. S., Roberts, R., McCrory, E., and Viding, E. (2017). Social reward questionnaire-adolescent version and its association with callous–unemotional traits. *R. Soc. Open Sci.* 4:160991. doi: 10.1098/rsos.160991

Frith, C. D., and Frith, U. (2006). How we predict what other people are going to do. *Brain Res.* 1079, 36–46. doi: 10.1016/j.brainres.2005.12.126

Galvan, A. (2010). Adolescent development of the reward system. *Front. Hum. Neurosci.* 4:6. doi: 10.3389/neuro.09.006.2010

Guassi Moreira, J. F., and Telzer, E. H. (2016). Mother still knows best: maternal influence uniquely modulates adolescent reward sensitivity during risk taking. *Dev. Sci.* 21:e12484. doi: 10.1111/desc.12484

Güroğlu, B., Van den Bos, W., and Crone, E. A. (2014). Sharing and giving across adolescence: an experimental study examining the development of prosocial behavior. *Front. Psychol.* 5:291. doi: 10.3389/fpsyg.2014.00291

Hu, L., and Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. *Struct. Equ. Model* 6, 1–55. doi: 10.1080/10705519909540118

Knoll, L. J., Magis-Weinberg, L., Speekenbrink, M., and Blakemore, S. J. (2015). Social influence on risk perception during adolescence. *Psychol. Sci.* 26, 583–592. doi: 10.1177/0956797615569578

Kort, W., Schittekatte, M., Compaan, E. L., Bosmans, M., Bleichrodt, N., Vermeir, G., et al. (2002). *WISC-III NL. Handleiding. Nederlandse bewerking*. London: The Psychological Corporation.

Lam, C. B., McHale, S. M., and Crouter, A. C. (2014). Time with peers from middle childhood to late adolescence: developmental course and adjustment correlates. *Child Dev.* 85, 1677–1693. doi: 10.1111/cdev.12235

Luengo Kanacri, B. P., Pastorelli, C., Eisenberg, N., Zuffianò, A., and Caprara, G. V. (2013). The development of prosociality from adolescence to early adulthood: the role of effortful control. *J. Pers.* 81, 302–312. doi: 10.1111/jopy.12001

Martin, C. A., Kelly, T. H., Rayens, M. K., Brogli, B. R., Brenzel, A., Smith, W. J., et al. (2002). Sensation seeking, puberty, and nicotine, alcohol, and marijuana use in adolescence. *J. Am. Acad. Child Adolesc. Psychiatry* 41, 1495–1502. doi: 10.1097/00004583-200212000-00022

Mukaka, M. M. (2012). A guide to appropriate use of correlation coefficient in medical research. *Malawi Med. J.* 24, 69–71.

Peters, S., Peper, J. S., Van Duijvenvoorde, A. C. K., Braams, B. R., and Crone, E. A. (2016). Amygdala-orbitofrontal connectivity predicts alcohol use two years later: a longitudinal neuroimaging study on alcohol use in adolescence. *Dev. Sci.* 28:e12448. doi: 10.1111/desc.12448

Rosseel, Y. (2012). Lavaan: an R package for structural equation modeling. *J. Stat. Softw.* 48, 1–36. doi: 10.3389/fpsyg.2014.01521

Schmitt, N. (1996). Uses and abuses of coefficient alpha. *Psychol. Assess.* 8, 350–353. doi: 10.1037/1040-3590.8.4.350

Sebastian, C., Viding, E., Williams, K. D., and Blakemore, S. J. (2010). Social brain development and the affective consequences of ostracism in adolescence. *Brain Cogn.* 72, 134–145. doi: 10.1016/j.bandc.2009.06.008

Silverman, M. H., Jedd, K., and Luciana, M. (2015). Neural networks involved in adolescent reward processing: an activation likelihood estimation meta-analysis of functional neuroimaging studies. *Neuroimage* 122, 427–439. doi: 10.1016/j.neuroimage.2015.07.083

Snyder, J. J., Schrepferman, L. P., Bullard, L., McEachern, A. D., and Patterson, G. R. (2012). Covert antisocial behavior, peer deviancy training, parenting processes, and sex differences in the development of antisocial behavior during childhood. *Dev. Psychopathol.* 24, 1117–1138. doi: 10.1017/S0954579412000570

Somerville, L. H. (2013). The teenage brain: sensitivity to social evaluation. *Curr. Dir. Psychol. Sci.* 22, 121–127. doi: 10.1177/0963721413476512

Somerville, L. H., Haddara, N., Sasse, S. F., Skwara, A. C., Moran, J. M., and Figner, B. (2018). Dissecting "peer presence" and "decisions" to deepen understanding of peer influence on adolescent risky choice. *Child Dev.* doi: 10.1111/cdev.13081 [Epub ahead of print].

Somerville, L. H., Jones, R. M., Ruberry, E. J., Dyke, J. P., Glover, G., and Casey, B. J. (2013). The medial prefrontal cortex and the emergence of self-conscious emotion in adolescence. *Psychol. Sci.* 24, 1554–1562. doi: 10.1177/0956797613475633

Steinberg, L., Icenogle, G., Shulman, E. P., Breiner, K., Chein, J., Bacchini, D., et al. (2017). Around the world, adolescence is a time of heightened sensation seeking and immature self-regulation. *Dev. Sci.* 21:e12532. doi: 10.1111/desc.12532

Steinberg, L., and Monahan, K. C. (2007). Age differences in resistance to peer influence. *Dev. Psychol.* 43, 1531–1543. doi: 10.1037/0012-1649.43.6.1531.Age

Taber, K. S. (2018). The use of Cronbach's alpha when developing and reporting research instruments in science education. *Res. Sci. Educ.* 48, 1273–1296. doi: 10.1007/s11165-016-9602-2

Telzer, E. H., Fuligni, A. J., Lieberman, M. D., Miernicki, M. E., and Gaìlvan, A. (2015). The quality of adolescents' peer relationships modulates neural sensitivity to risk taking. *Soc. Cogn. Affect. Neurosci.* 10, 389–398. doi: 10.1093/scan/nsu06

Telzer, E. H., van Hoorn, J., Rogers, C. R., and Do, K. T. (2018). Social influence on positive youth development: a developmental neuroscience perspective. *Adv. Child Dev. Behav.* 54, 215–258. doi: 10.1016/bs.acdb.2017.10.003

Urošević, S., Collins, P., Muetzel, R., Lim, K., and Luciana, M. (2012). Longitudinal changes in behavioral approach system sensitivity and brain structures involved in reward processing during adolescence. *Dev. Psychol.* 48, 1488–1500. doi: 10.1037/a0027502

Uterwijk, J. (2000). *WAIS-III Nederlandstalige Bewerking. Technische Handleiding*. Lisse: Swets & Zeitlinger.

Van Hoorn, J., Van Dijk, E., Güroglu, B., and Crone, E. A. (2016a). Neural correlates of prosocial peer influence on public goods game donations during adolescence. *Soc. Cogn. Affect. Neurosci.* 11, 923–933. doi: 10.1093/scan/nsw013

Van Hoorn, J., Van Dijk, E., Meuwese, R., Rieffe, C., and Crone, E. A. (2016b). Peer influence on prosocial behavior in adolescence. *J. Res. Adolesc.* 26, 90–100. doi: 10.1111/jora.12173

van Hoorn, J., McCormick, E. M., Rogers, C. R., Ivory, S., and Telzer, E. H. (2018). Differential effects of parent and peer presence on neural correlates of risk taking in adolescence. *Soc. Cogn. Affect. Neurosci.* 9, 945–955. doi: 10.1093/scan/nsy071

van Hoorn, J., Shablack, H., Lindquist, K., and Telzer, E. H. (2019). Incorporating the social context into neurocognitive models of adolescent decision-making: a neuroimaging meta-analysis. *Neurosci. Biobehav. Rev.* 101, 129–142. doi: 10.1016/j.neubiorev.2018.12.024

Van Hoorn, J., Van Dijk, E., Crone, E. A., Stockmann, L., and Rieffe, C. (2017). Peers influence prosocial behavior in adolescent males with autism spectrum disorders. *J. Autism Dev. Disord.* 47, 2225–2237. doi: 10.1007/s10803-017-3143-z

Weigard, A., Chein, J., Albert, D., Smith, A., and Steinberg, L. (2014). Effects of anonymous peer observation on adolescents' preference for immediate rewards. *Dev. Sci.* 17, 71–78. doi: 10.1111/desc.12099

Willoughby, T., Good, M., Adachi, P. J. C., Hamza, C., and Tavernier, R. (2013). Examining the link between adolescent brain development and risk taking from a social–developmental perspective. *Brain Cogn.* 83, 315–323. doi: 10.1016/j.bandc.2013.09.008

Zimmer-Gembeck, M. J., and Collins, W. A. (2003). "Autonomy development during adolescence," in *Blackwell Handbook of Adolescence*, eds G. R. Adams and M. D. Berzonsky (Malden, MA: Blackwell Publishing), 175–204.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling Editor declared a past co-authorship with one of the authors EC.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 07 August 2019
doi: 10.3389/fnbeh.2019.00178

Blunted Social Reward Responsiveness Moderates the Effect of Lifetime Social Stress Exposure on Depressive Symptoms

*Samantha Pegg[1], Paige Ethridge[2], Grant S. Shields[3], George M. Slavich[4], Anna Weinberg[2] and Autumn Kujawa[1]**

[1] Department of Psychology and Human Development, Vanderbilt University, Nashville, TN, United States, [2] Department of Psychology, McGill University, Montreal, QC, Canada, [3] Center for Mind and Brain, University of California, Davis, Davis, CA, United States, [4] Department of Psychiatry and Biobehavioral Sciences, Cousins Center for Psychoneuroimmunology, University of California, Los Angeles, Los Angeles, CA, United States

Exposure to social stress is a well-established risk factor for the development and recurrence of depression. Reduced neural responsiveness to monetary reward has been associated with greater symptoms following stress exposure. However, it remains unclear whether reduced reward responsiveness serves as a mediator or moderator of the effects of stress on internalizing symptoms or whether similar patterns emerge with responses to social reward. We addressed this issue by measuring lifetime stress exposure and event-related potentials (ERPs) to social reward in 231 emerging adults (M = 18.16, SD = 0.41 years old). Participants completed the Stress and Adversity Inventory (STRAIN) to assess severity of lifetime stressors and self-report measures of current internalizing symptoms. In addition, participants completed the Island Getaway task in which the reward positivity (RewP) ERP was recorded in response to social acceptance, adjusting for responses to rejection (RewP residual). In this task, participants vote to accept or reject peers and receive reward/acceptance and rejection feedback. Stressors were divided into social and non-social stress severity scores. Analyses were conducted to test social reward responsiveness as a mediator or moderator of the effects of social and non-social stress on internalizing symptoms. Both social and non-social stress exposure over the life course predicted symptoms of depression ($ps < 0.001$) and social anxiety ($ps < 0.002$). The effect of social stress on depression was moderated by the residual RewP to social reward, adjusting for responses to social rejection (p =0.024), such that greater lifetime social stress exposure and a relatively blunted RewP to social reward were associated with greater depressive symptoms. Social reward responsiveness did not mediate effects of stress on internalizing symptoms. Reduced processing of social reward may be a vulnerability for depression that increases risk for symptoms following exposure to social stress. Blunted social reward responsiveness appears to be a relatively unique vulnerability for

OPEN ACCESS

Edited by:
Johanna M. Jarcho, Temple University, United States

Reviewed by:
Sunny Dutra, William James College, United States
Jesse Kaye, University of Wisconsin School of Medicine and Public Health, United States

***Correspondence:**
Autumn Kujawa
autumn.kujawa@vanderbilt.edu

Received: 28 March 2019
Accepted: 17 July 2019
Published: 07 August 2019

Citation:
Pegg S, Ethridge P, Shields GS, Slavich GM, Weinberg A and Kujawa A (2019) Blunted Social Reward Responsiveness Moderates the Effect of Lifetime Social Stress Exposure on Depressive Symptoms. Front. Behav. Neurosci. 13:178. doi: 10.3389/fnbeh.2019.00178

depression, rather than social anxiety. Results support the utility of ERP measures in measuring individual differences in social reward processing that can be applied to better understand neural processes involved in the development of depression, and highlight the importance of considering specific dimensions of stressful life experiences.

Keywords: reward responsiveness, social reward, life stress, neurophysiology, event-related potentials, electroencephalogram, depression

INTRODUCTION

Life stress exposure is a well-established risk factor for depression (Kendler et al., 1999; Hammen, 2005; Kessler et al., 2010; Slavich, 2016). Experiencing more stressful life events in childhood is associated with increased risk for both recent and lifetime history of depressive disorders (Chapman et al., 2004). In fact, exposure to stressful life events during the past year is a strong risk factor for and precursor to the development of major depression (Kendler et al., 2002, 2006). In this context, interpersonal stress has been shown to have particularly strong effects on depression risk (Hammen, 2009). For example, depressive episodes have been related to humiliating life events, characterized by situations in which a person is devalued in an important role (Kendler et al., 2003). Additionally, individuals diagnosed with major depressive disorder (MDD) who experienced a severe targeted rejection life event prior to onset have been found to develop depression three times faster than persons experiencing other types of severe, pre-onset life stress (Slavich et al., 2009).

Despite these strong associations between exposure to life stress and the development of depression, many people who experience even major life stressors during their lives do not develop depression. Therefore, there is a need to identify processes that make some people more likely than others to develop depression following exposure to stress. These vulnerabilities likely depend in part on genes and brain function. For example, genetic factors related to neural response to rejection have been shown to differentiate individuals diagnosed with MDD from those who are not following a targeted rejection stressful event (Slavich et al., 2014). In terms of brain function, neuroscience research has been shown to have the potential to elucidate alterations in brain function that make some people more susceptible to develop depression in response to stress (Kujawa and Burkhouse, 2017). Overactivation of threat circuits, including the amygdala, has been shown to predict response to stress, including stress related to natural disasters, terrorist attacks, and more typical life stress (McLaughlin et al., 2014; Swartz et al., 2015; Kujawa et al., 2016).

There is also growing evidence that deficits in positive valence systems, which include reward responsiveness, play a key role in pathways from stress to depression. For example, one study found that life stress over the past year was associated with low positive affect only in persons with low ventral striatum activity – a key subcortical brain region involved in reward processing and motivation – in response to monetary reward (Nikolova et al., 2012). Additionally, reduced activity in the ventral striatum is related to increased risk for anhedonia in individuals exposed to early life stress (Corral-Frías et al., 2015). These data suggest that low reward responsiveness – typically assessed in response to monetary reward – might be a vulnerability factor that moderates the effects of stress on the emergence of depression.

Other research has suggested a more mechanistic relationship between stress and neural response to reward – namely, that stress may reduce reward responsiveness, which in turn leads to depressive symptoms. For example, some types of early life stress have been associated with reduced striatal activation, which predicts depressive symptoms later in life (Goff et al., 2013; Hanson et al., 2015). In addition to striatal activation, research has examined neurophysiological indicators of activation of reward learning systems such as the reward positivity (RewP), an event-related potential (ERP) enhanced in response to positive feedback and rewards (Holroyd and Coles, 2002, 2008; Carlson et al., 2011). In monetary reward tasks, RewP is associated with activation in brain regions involved in reward processing, including the ventral striatum and medial prefrontal cortex (Carlson et al., 2011). Similar to findings from neuroimaging studies examining brain regions involved in reward processing, research investigating RewP has found that a reduced RewP to monetary rewards prospectively predicts depressive symptoms across childhood and adolescence (Bress et al., 2015; Nelson et al., 2016; Kujawa et al., 2019). Additionally, recent research has shown that RewP to monetary reward measured in childhood interacts with acute stressful events to predict depressive symptoms in early adolescence (Goldstein et al., 2019). However, it remains unclear how this manifests with regard to social reward and to specific types of stressful experiences, as well as the extent to which reduced reward responsiveness as measured by RewP reflects a moderator or mechanism of the effects of stress on depressive symptoms.

Critically, prior reward responsiveness research has primarily focused on monetary reward. Although this work has shown that alterations in reward responsiveness are associated with the development of depressive symptoms (e.g., Kujawa et al., 2019), measuring reward responsiveness only in response to monetary rewards has limitations. For example, individuals vary in the extent to which they value the same amount of money. In addition, laboratory-based monetary reward tasks typically offer relatively small amounts of money, and tasks vary from one another in the amount they offer, which may have an impact on task engagement and reward valuation. Social reward, instead, may be a stronger or more consistent predictor of social behaviors and clinical symptoms (Davey et al., 2008; Forbes and Dahl, 2012; Silk et al., 2012). In addition, alterations in response to social reward may be particularly relevant for examining how different individuals fare under interpersonal stress. For example, individuals at risk for depression may not

be as responsive to or less motivated to participate in positive social activities (Setterfield et al., 2016), particularly when they experience stress. However, little is known about the relationship between *social* reward responsiveness, *social* stress exposure, and internalizing symptoms, even though social stress is the strongest psychosocial precipitant of MDD (e.g., Hammen, 2009). Compared to monetary reward, responses to social rewards might be more relevant when considering response to interpersonal experiences and/or predict specific features of depression (e.g., social withdrawal/anhedonia). Additionally, we may be able to better predict response to specific types of stressors by examining relations between distinct types of reward, specific types of stress, and the development of depressive symptoms.

One ERP task that has been developed to examine neural reactivity to social reward is the Island Getaway task (Kujawa et al., 2014). In this game, participants interact with perceived peers and give and receive positive and negative social feedback in the form of votes to stay in or get kicked out of the game across several rounds. This task consistently elicits a RewP enhanced in response to social reward/acceptance feedback, maximal over frontocentral sites, and with similar timing as observed in monetary reward tasks (Ethridge et al., 2017). RewP can be reliably assessed across development (Kujawa et al., 2018), including in response to social reward using the Island Getaway task (Ethridge and Weinberg, 2018). Yet, relatively little is known about the RewP in the context of social reward, including the extent to which social reward responsiveness might serve as a mediator or moderator of the effects of stress on depressive symptoms.

In addition, much of the research on reward responsiveness and stress has focused on subjective experiences of stress, the measurement of which is often confounded with the assessment of depressive symptoms (Slavich, 2019). Measures of stress can also vary in numerous ways, including in how comprehensively they assess stressors, their consideration of chronic vs. acute stressors, the types of stressors assessed (e.g., minor vs. severe stressors), the timeframe assessed, and the frequency and duration of stressor exposure assessed (Epel et al., 2018; Slavich, 2019). The Stress and Adversity Inventory (STRAIN; Slavich and Shields, 2018) was developed to address these issues by providing investigators with a standardized system for assessing lifetime stress exposure across a number of different stressor types (acute vs. chronic), timespans (childhood, adulthood), life domains, and social-psychological characteristics. In the present study, we employed the STRAIN to characterize participants' total lifetime severity of stressors experienced across these categories.

More specifically, we examined associations between lifetime exposure to social and non-social stressors, neurophysiological response to social reward, and internalizing symptoms in a large sample of emerging adults. We sought to provide a preliminary examination of the utility of social reward responsiveness in understanding links between stress exposure and internalizing symptoms. To extend the existing literature on monetary reward responsiveness, we tested competing theories of the role of reward responsiveness in depression by investigating whether social reward responsiveness moderated (e.g., Nikolova et al., 2012; Corral-Frías et al., 2015) or mediated (e.g., Goff et al., 2013; Hanson et al., 2015) the effects of social and non-social stress on symptoms of depression. In addition, we tested these associations for both social and non-social stress exposure to examine whether interpersonal aspects of reward processing mediate or moderate the effects of social stress specifically. Although we were primarily motivated by models of reward responsiveness in depression, we explored similar models predicting symptoms of social anxiety in order to test whether observed associations were specific to depression or also present for other internalizing symptoms. Social anxiety represents a logical comparison in this context, as social stressors – including problems in peer relationships – have been found to predict both social anxiety and depressive symptoms (La Greca and Harrison, 2005; Starr and Davila, 2008). Alterations in social reward responsiveness could reflect a relatively specific neural process underlying symptoms of depression in particular (e.g., Bress et al., 2015; Nelson et al., 2016) or could underlie both depression and anxiety symptoms more broadly.

MATERIALS AND METHODS

Participants

A total of 268 emerging adults were recruited at the start of their first year of college and completed the Island Getaway task for a larger study examining neural mediators and moderators of the effects of stress on internalizing symptoms. In this larger study, we aimed to recruit up to 100 first-year students per year for 3 years for a total sample size with adequate power to detect generally modest associations between neural and clinical measures. Following written informed consent in accordance with the Declaration of Helsinki, participants completed a series of EEG tasks in a counterbalanced order, the results of which have been previously reported (Ethridge and Weinberg, 2018; Sandre et al., 2019), along with measures of stress exposure and clinical symptoms. Of this sample, 13 were excluded due to a computer error during data collection, 3 for not completing the measure of clinical symptoms, 20 for not completing the STRAIN, and 1 due to excessive noise in EEG data. The final sample thus included 231 emerging adults (M = 18.16, SD = 0.41 years). Most participants identified as female (71.9%) and Caucasian (51.3%). All study procedures were approved by the McGill University research ethics board. All data exclusions, measures, and conditions have been disclosed in the present manuscript.

Measures

Lifetime Stress Exposure

To assess the frequency and subjective severity of participants' exposure to different stressors across the life course, individuals completed the STRAIN online (Slavich and Shields, 2018). The STRAIN assesses stressors occurring across several life domains, including: Housing, Education, Work, Treatment/Health, Marital/Partner, Reproduction, Financial, Legal/Crime, Other Relationships, Death, Life Threatening Situation, and Possessions. Participants first respond to introductory questions for stressors in each life domain; then, if a stressor was endorsed,

they were asked additional questions about the severity, frequency, timing, and duration of the stressor.

To differentiate lifetime social and non-social stress severity, all items that were related to interpersonal or social situations/interactions (i.e., that had a primary underlying social-psychological characteristic that was social) were binned into the social stress variable. Social items included questions such as, "Have you ever had ongoing arguments with a spouse or partner?", "Were you ever bullied by other kids at school?", and "Did moving to college make you lose contact with friends?" All remaining items were binned into the non-social variable. Non-social items included questions such as, "Have you ever looked for a job for at least 6 months?", "Have you ever been hospitalized because of a health problem?", and "Have you failed a class or been in danger of failing a class in college?" The resulting lifetime social stress severity composite had 51 total items, and the non-social stress severity composite had 30 items.

Internalizing Symptoms

Both depression and social anxiety were investigated in the present study using the Inventory of Depression and Anxiety Symptoms (IDAS), a 99-item, validated measure of current (i.e., past 2 weeks) anxiety and depressive symptoms (Watson et al., 2007). The IDAS is comprised of 10 specific symptom scales, including social anxiety, and broader scales, including dysphoria, which is composed of single items that assess depressed mood, anhedonia, worry, worthlessness, guilt, psychomotor agitation, psychomotor retardation, and hopelessness, as well as two items assessing cognitive problems (Watson et al., 2007). The rating scales range from 1 (*Not at all*) to 5 (*Extremely*). We used the dysphoria subscale to measure depressive symptoms, the primary outcome of interest. We also tested models including social anxiety symptoms to evaluate specificity of these effects for depression vs. internalizing symptoms more broadly.

EEG Task

Participants completed the Island Getaway task while EEG data were collected (Kujawa et al., 2014; Ethridge et al., 2017). Task code for prior versions of Island Getaway are available here: http://arfer.net/projects/survivor. In this task, participants were told that they would be playing a "Survivor"-style computer game with other students their age where they would travel along the Hawaiian Islands with co-players, trying to make it to the final island without being voted off along the way. Co-players included 11 confederate peers, whom participants were led to believe were other college students completing the task not necessarily as part of the same experiment or in the same building as the participant. Prior to beginning the task, a photograph was taken for the participant's game profile picture. They were then told about the overall concept and goal of the game. They first answered several questions to create a profile, including questions about their name, age, hometown, and general interests and reviewed the profile information of their co-players. Hometowns of the co-players included cities in Canada and the United States, usually close to large universities (e.g., Toronto, New York City).

Each round, participants were presented with the profile information of the other players and decided to vote to either accept (i.e., "Keep") or reject (i.e., "Kick out") each co-player, while led to believe that co-player was simultaneously voting to accept or reject the participant. Each profile was presented until the participant voted. To make the task more realistic, a statement appeared on the screen saying, "Waiting for [co-player name] to vote. . .," if participants voted faster than the simulated voting time assigned to the co-player for that round (based on actual voting speeds from pilot testing). Following the vote, a fixation cross was presented for 1000 ms, followed by feedback indicating how the co-player voted for the participant. A green thumbs up was shown on the screen indicating social reward/acceptance feedback, and a red thumbs down was presented indicating social rejection. Feedback was displayed for 2000 ms. This was followed by a screen that had two scales for participants to rate how much they liked the co-player and how much they thought other people would like the co-player, ranging from 1 (*Not at all*) to 9 (*Extremely*). Participants then saw a blank screen for 1500 ms before the next co-player profile within the round was presented. At the end of each round, participants were shown the picture of the co-player that was voted off during that round. All participants reached the final island at the end of the sixth and final round. Over the course of the 51 trials across the six rounds, participants were presented with roughly equal acceptance and rejection feedback, but ultimately "won" the game without being voted out by peers.

To increase believability, members of study staff acted as though they were in communication with other labs during the study setup and introduced pauses in the experiment to "wait" for other labs to be ready to begin. At the end of the task, prior to being debriefed, participants were asked to verbally indicate whether they believed that the task that they were playing was real in that they were playing against other live players. This was assessed with a 1-item question on a scale from 1 to 5, with higher scores indicating stronger belief in the task. On average, participants reported that they moderately believed that the task was real (M = 3.35, SD = 1.36), and belief ratings were not correlated with the residual RewP measure obtained from this task (p = 0.804).

EEG Data Collection and Processing

EEG data were recorded with a 32-electrode cap BrainProducts actiCHamp system (Munich, Germany) based on a standard 10/20 layout. Facial electrodes were placed approximately 1 cm above and below the left eye and 1 cm from the outer corners of the eyes to measure electrooculogram (EOG) from eye movements. Bipolar electrodes were referenced to an electrode placed on the back of the neck of the participant. Mastoid references were electrodes TP9 and TP10. Impedances were reduced to approximately 10 kΩ. A 24 bit resolution and sampling rate of 1000 Hz were used to digitize the recordings.

BrainVision Analyzer software (Brain Products, Munich, Germany) was used to process the EEG data. Data were re-referenced to an average of the two mastoids and band-pass filtered with 0.01 and 30 Hz as cutoffs with 24 db/oct slopes. Data were segmented 500 ms prior to and 1000 ms after acceptance/rejection feedback. Ocular correction was conducted using a modification of Gratton's algorithm (Gratton et al., 1983).

Automatic artifact rejection criteria were a voltage step greater than 50.0 μV between sample points, maximum voltage difference of 175.0 μV within trials, and minimum voltage difference of 0.5 μV within 100 ms intervals. Data were then inspected visually to reject any remaining artifacts. Following artifact rejection procedures, participants had on average 26.61 (*SD* = 1.44) trials for the accept condition and 24.06 (*SD* = 1.32) trials for the reject condition at Cz. The 200 ms prior to feedback was set as the baseline.

ERPs were averaged across participants for both acceptance/social reward and rejection/non-reward. ERP components were scored using the time window approach based on visual assessment. To examine RewP, data were extracted between 250 and 350 ms at Cz, consistent with RewP research using monetary reward tasks (Ethridge et al., 2017). We calculated unstandardized residual RewP to acceptance adjusting for RewP to rejection for analysis (Meyer et al., 2017). More positive values indicate greater responses to social reward. The RewP residual score has been shown to be reliably measured in this task (Ethridge and Weinberg, 2018).

Data Analysis

To examine the associations between variables, bivariate correlation analyses were first conducted between residual RewP to social reward (i.e., RewP to acceptance adjusting for responses to rejection), clinical symptoms (depression, social anxiety), and social and non-social lifetime stress exposure. Next, both simple mediation and moderation analyses were conducted to examine the extent to which social reward responsiveness (residual RewP) mediated or moderated relationships between social and non-social stress exposure, and participants' depressive and anxiety symptoms. To conduct these analyses, the PROCESS v3.1 macro for SPSS was used (Hayes, 2017).

RESULTS

Preliminary Analyses

Participants' lifetime social stress severity scores ranged from 0 to 71 (*M* = 25.62, *SD* = 15.59). Lifetime non-social stress scores ranged from 0 to 46 (*M* = 9.81, *SD* = 8.54). Participants' depression scores (i.e., IDAS dysphoria symptoms) ranged from 10 to 42 out of a possible 50 (*M* = 21.86, *SD* = 7.51). Participants' social anxiety scores ranged from 6 to 30 out of a possible 30 (*M* = 13.18, *SD* = 5.55). The IDAS dysphoria and social anxiety subscales had high internal consistency (Cronbach's αs = 0.86 for each measure). With clinical cutoffs for IDAS identified by Stasik-O'Brien et al. (2018), 21.6% of participants were in the clinical range for symptoms of depression (clinical cut-offs for the social anxiety scale from the 99-item IDAS were not available).

ERP waveforms for acceptance and rejection conditions and corresponding scalp distribution for the difference of acceptance minus rejection conditions are presented in **Figure 1**. RewP to acceptance and rejection feedback had high split-half reliability at Cz (Spearman-Brown coefficients = 0.87 and 0.86, respectively).

To examine associations between participants' symptoms, social and non-social lifetime stress exposure, and residual RewP, bivariate correlation analyses were first conducted (see **Table 1**). As expected, greater lifetime social stress exposure was positively associated with depression ($r = 0.37$, $p < 0.001$) and social anxiety ($r = 0.26$, $p < 0.001$). Non-social stress exposure was also positively correlated with symptoms of depression ($r = 0.38$, $p < 0.001$) and social anxiety ($r = 0.20$, $p = 0.002$). Social and non-social stress exposure were not significantly correlated with the RewP residual score. The RewP residual score was not significantly correlated with either social anxiety or depressive symptoms, suggesting that social reward responsiveness did not mediate the association between lifetime stress exposure and participants' symptom levels. Indeed, bootstrapped confidence intervals of tests of indirect effects of social and non-social lifetime stress exposure on internalizing symptoms through residual RewP all included 0 (see **Table 2**).

Moderation Analyses

Four moderation analyses were conducted to investigate relationships between social and non-social lifetime stress exposure, RewP residual scores, and depressive and anxiety symptoms. Specifically, we examined residual RewP as a moderator of associations between social and non-social lifetime stress exposure and depressive and social anxiety symptoms. Main effects of social stress or non-social stress and residual RewP were entered into each model. Then the interaction between either social or non-social stress and residual RewP was entered (see **Table 3**).

The overall model for lifetime social stress exposure predicting depressive symptoms was significant, $R^2 = 0.17$, $F(3, 227) = 15.01$, $p < 0.001$. The significant main effect of social stress exposure in predicting symptoms of depression was qualified by an interaction between social stress exposure and RewP residual scores (see **Figure 2A**), $t(227) = -2.28$, $p = 0.024$. Decomposing this interaction using simple slopes revealed that greater lifetime social stress exposure predicted more depressive symptoms at low (-1 SD), mean, and high (+1 SD) levels of residual RewP. The magnitude of the relationship between social stress and depression was relatively stronger at low [simple slope = 0.24, $SE = 0.04$, $t(227) = 5.96$, $p < 0.001$] as compared to mean [simple slope = 0.18, $SE = 0.03$, $t(227) = 6.10$, $p < 0.001$], and high levels of residual RewP [simple slope = 0.11, $SE = 0.04$, $t(227) = 2.85$, $p = 0.005$]. To further understand this relationship, we also examined the effects of RewP at high and low levels of social stress. A reduced residual RewP predicted more depressive symptoms only at a high (+1 SD) level of social stress exposure [simple slope = -0.44, $SE = 0.17$, $t(227) = -2.64$, $p = 0.009$]. The simple slopes at low (-1 SD) and mean levels of social stress exposure were not significant (*ps* = 0.642 and 0.125, respectively; see **Figure 2B**).

For illustrative purposes, we divided the social stress variable into thirds. We then split these participants based on their depressive symptoms into high and low depressive symptom groups via a median split. As depicted in **Figure 3**, RewP was

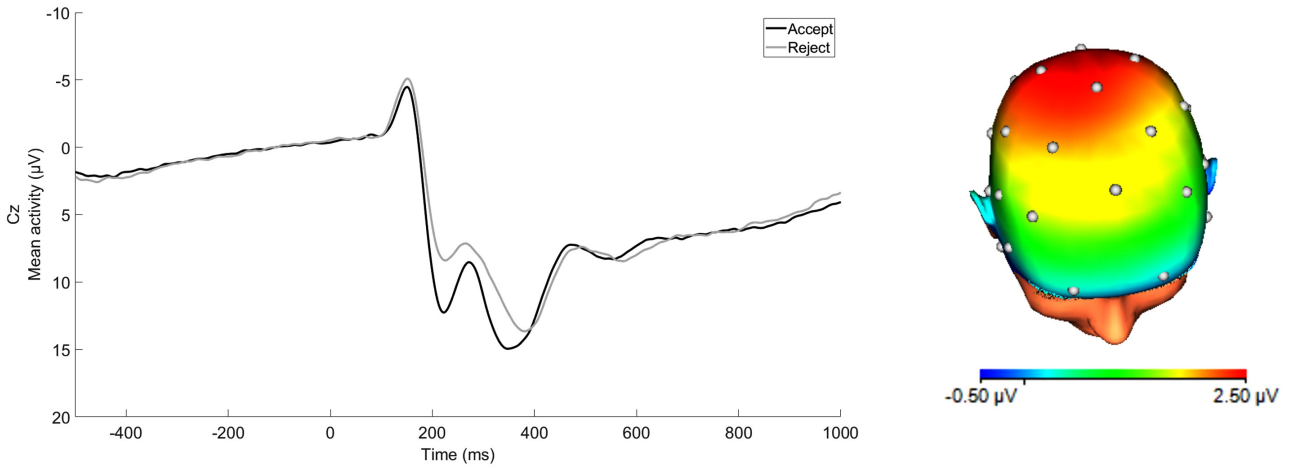


FIGURE 1 | ERP waveform at Cz and scalp distribution at the 250–350 ms time window for average response to acceptance and rejection feedback corresponding to RewP. Scalp distribution reflects the response to acceptance minus rejection difference score. (32-channel montage with linked mastoid reference.)

TABLE 1 | Bivariate correlations between clinical symptoms, life stress variables, and social reward responsiveness.

Variables	*M* (*SD*)	1	2	3	4	5
1. Depression	21.86 (7.51)	–				
2. Social anxiety	13.18 (5.55)	0.62**	–			
3. Residual RewP	0.00 (3.83)	−0.10	−0.09	–		
4. Lifetime social stress severity	25.62 (15.59)	0.37**	0.26**	−0.04	–	
5. Lifetime non-social stress severity	9.81 (8.54)	0.38**	0.20*	−0.04	0.57**	–

*$p < 0.01$, **$p < 0.001$; *RewP, Reward positivity.*

TABLE 2 | Model coefficients for simple mediation models testing effects of lifetime social and non-social stress severity and residual RewP on clinical symptoms.

	Consequent			
	M (Residual RewP)		Y (Depression)	
Antecedent	***b***	***SE***	***b***	***SE***
X (Social stress severity)	−0.01	0.02	0.18**	0.03
M (Residual RewP)	–	–	−0.17	0.12
Constant	0.26	0.49	170.31**	0.88
	R^2 = 0.00, F(1, 229) = 0.40		R^2 = 0.15, F(2, 228) = 19.57**	
X (Non-social stress severity)	−0.02	0.03	0.33**	0.05
M (Residual RewP)	–	–	−0.17	0.12
Constant	0.18	0.38	18.63**	0.70
	R^2 = 0.00, F(1, 229) = 0.40		R^2 = 0.15, F(2, 228) = 20.33**	
X (Social stress severity)	−0.01	0.02	0.09**	0.02
M (Residual RewP)	–	–	−0.12	0.09
Constant	0.26	0.49	10.83**	0.68
	R^2 = 0.00, F(1, 229) = 0.40		R^2 = 0.07, F(2, 228) = 9.18**	
X (Non-social stress severity)	−0.02	0.03	0.13*	0.04
M (Residual RewP)	–	–	−0.12	0.09
Constant	0.18	0.38	11.91**	0.55
	R^2 = 0.00, F(1, 229) = 0.40		R^2 = 0.05, F(2, 228) = 5.79*	

*$p < 0.01$, **$p < 0.001$; *RewP, Reward positivity; b, unstandardized regression coefficients; SE, standard error.*

TABLE 3 | Regression analyses testing the main and interaction effects of lifetime social and non-social stress severity and residual RewP on depressive symptoms (IDAS dysphoria subscale).

Depressive Symptoms		
Lifetime Social Stress Severity	**Unstandardized *b (SE)***	***p***
Social stress severity	0.18 (0.03)	<0.001
Residual RewP	0.24 (0.22)	0.268
Social stress severity X residual RewP	−0.02 (0.01)	0.024
	Change R^2 = 0.02, F(1,227) = 5.19	
Total model	R^2 = 0.17, F(3,227) = 15.01	<0.001
Lifetime Non-social Stress Severity	**Unstandardized *b (SE)***	***p***
Non-social stress severity	0.33 (0.05)	<0.001
Residual RewP	−0.02 (0.18)	0.929
Non-social stress severity X residual RewP	−0.02 (0.01)	0.251
	Change R^2 = 0.01, F(1,227) = 1.33	
Total model	R^2 = 0.16, F(3,227) = 14.01	<0.001
Social Anxiety Symptoms		
Lifetime Social Stress Severity	**Unstandardized *b (SE)***	***p***
Social stress severity	0.09 (0.02)	<0.001
Residual RewP	0.07 (0.17)	0.695
Social stress severity X residual RewP	−0.01 (0.01)	0.188
	Change R^2 = 0.01, F(1,227) = 1.74	
Total model	R^2 = 0.08, F(3,227) = 6.72	<0.001
Lifetime Non-social Stress Severity	**Unstandardized *b (SE)***	***p***
Non-social stress severity	0.13 (0.04)	0.00
Residual RewP	−0.10 (0.14)	0.502
Non-social stress severity X residual RewP	−0.00 (0.01)	0.791
	Change R^2 = 0.00, F(1,227) = 0.07	
Total model	R^2 = 0.05, F(3,227) = 3.86	0.010

RewP = Reward positivity.

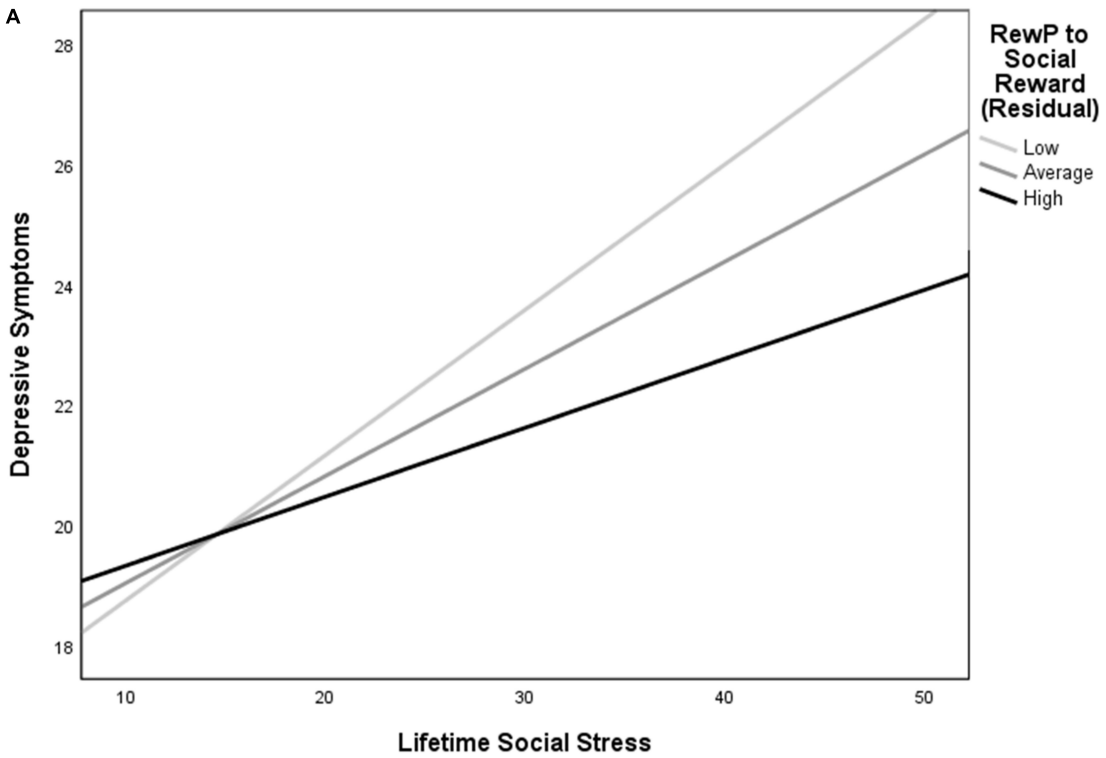
relatively reduced in the high lifetime social stress exposure/high depressive symptom group as compared to the high lifetime social stress exposure/low depression group.

The overall models for lifetime social stress exposure predicting social anxiety symptoms, non-social stress exposure predicting depressive symptoms, and non-social stress exposure predicting social anxiety symptoms were all significant (see **Table 3**). However, only social and non-social lifetime stress exposure were significant predictors of clinical symptoms. The interactions between social or non-social stress exposure and participants' residual RewP were not significant in these models, suggesting that residual RewP may be a relatively specific moderator of the impact of lifetime social stress exposure on symptoms of depression rather than social anxiety.

DISCUSSION

The present study examined associations between social and non-social lifetime stress exposure, social reward responsiveness as measured by RewP using the Island Getaway task, and symptoms of depression and social anxiety in a sample of emerging adults. Both social and non-social stress exposure were related to depressive symptoms. Additionally, social and non-social stress exposure were associated with social anxiety symptoms. In contrast, we did not find significant bivariate associations between the RewP residual score and participants' symptoms, and results did not support social reward responsiveness (as measured by RewP) as a mediator of the effect of lifetime stress exposure on symptom levels. Instead, a significant interaction emerged between social stress and RewP to acceptance (adjusting for RewP to rejection via residual score) predicting depressive symptoms, such that the combination of greater lifetime social stress exposure and a reduced RewP to social reward was associated with greater depressive symptoms. Moreover, social reward responsiveness only predicted depressive symptoms at high levels of social stress. Finally, this moderation effect of RewP on symptom outcomes was unique to symptoms of depression and did not extend to symptoms of social anxiety.

Although preliminary and in need of replication, these results suggest that reduced social reward responsiveness may constitute a vulnerability for depressive symptoms following exposure to social stress, specifically. It is also possible that having greater reward responsiveness to social



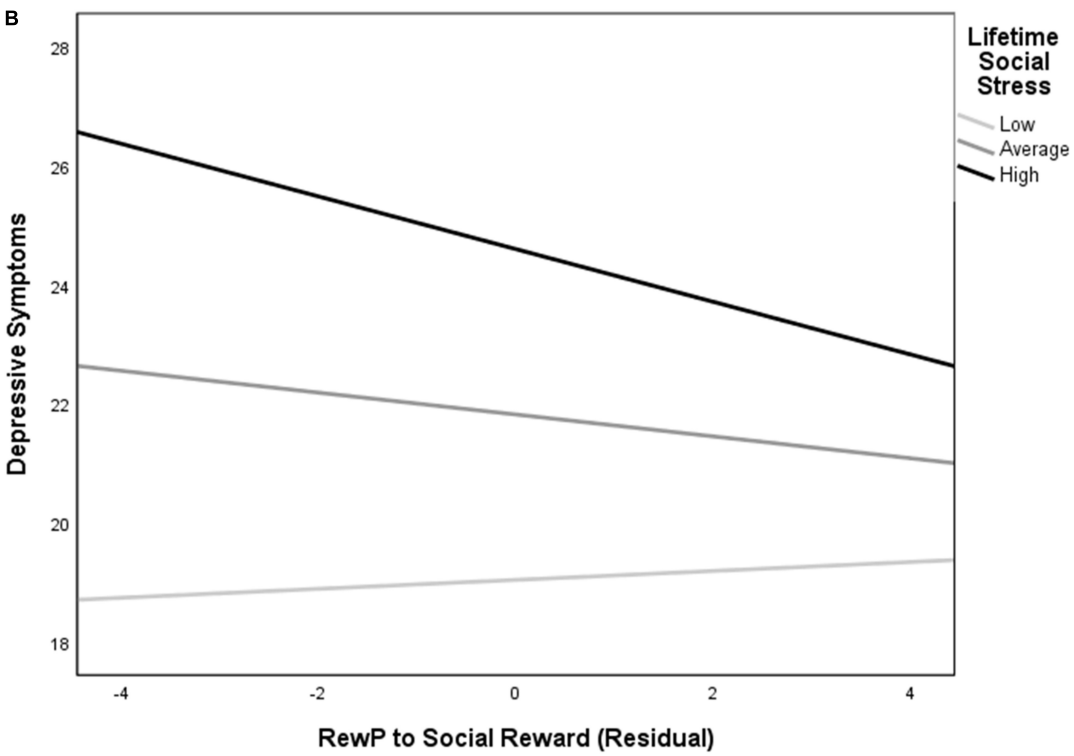


FIGURE 2 | Simple slopes depicting **(A)** the relationship between social stress exposure and depression at low (-1 SD), mean, and high (+1 SD) residual RewP to social reward, and **(B)** the relationship between residual RewP to social reward and depression at low (-1 SD), mean, and high (+1 SD) social stress. Lifetime social stress exposure was positively associated with symptoms of depression at all levels of RewP, but with a relatively stronger magnitude of association at low compared to mean and high levels of residual RewP. Reduced RewP residual predicted more depressive symptoms only at a high level of social stress.

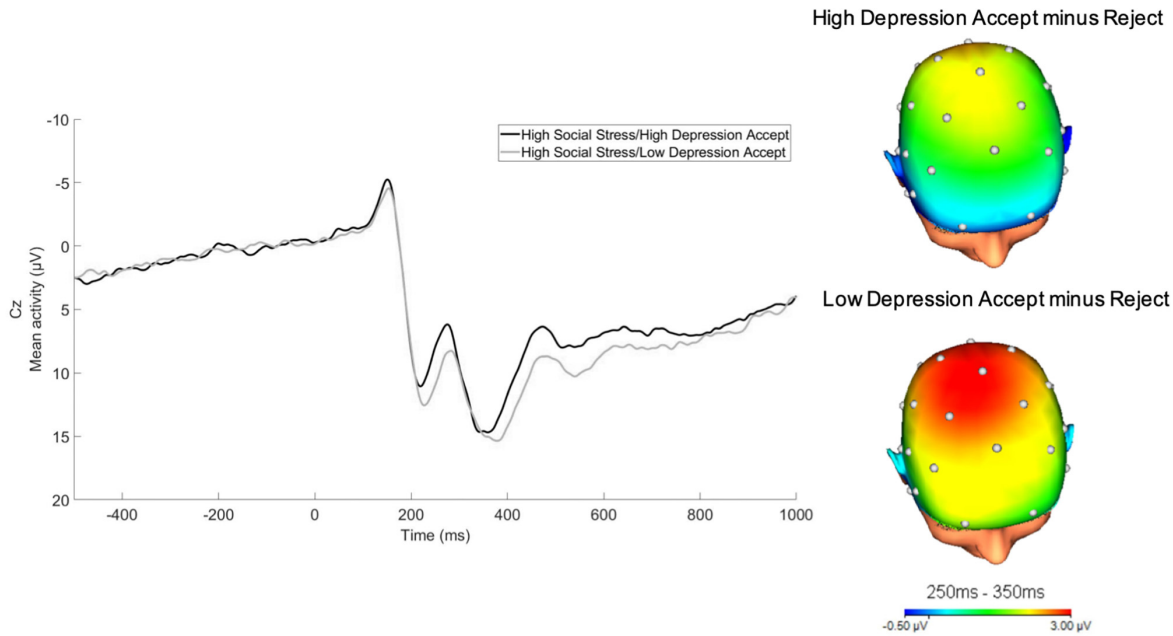


FIGURE 3 | RewP to acceptance feedback at Cz in participants who experienced high lifetime social stress exposure (top 1/3). For illustrative purposes, a median split was computed to depict participants at high vs. low levels of depressive symptoms as measured by the IDAS dysphoria subscale following social stress exposure (32-channel montage with linked mastoid reference).

reward may help to protect against the impact of stress, particularly stress in interpersonal relationships. Individuals with blunted social reward responsiveness may be less likely to seek out and benefit from positive social interactions, which could inhibit their ability to cope with stress (Setterfield et al., 2016). As such, RewP to social feedback might predict more specific depressive symptom presentations, such as social withdrawal or social anhedonia. As RewP is relatively stable throughout development (Kujawa et al., 2018), identifying these specific symptom manifestations may improve understanding of depression onset and potential avenues for intervention before symptoms manifest (i.e., examining reduced social reward responsiveness and targeting these alterations early on).

More broadly, these findings emphasize the importance of examining social reward, in addition to monetary reward, in developmental trajectories of depression. Additional research should be conducted examining responses to multiple types of reward, including social reward, within the same sample to investigate whether particular types of reward responsiveness have unique predictive utility for depression. In addition, the current results emphasize the importance of considering specific dimensions of stressful experiences in clinical neuroscience research. That is, despite growing evidence that alterations in neural systems involved in positive emotions likely reflect a vulnerability that increase risk for later depression (for a review, see Kujawa and Burkhouse, 2017), little research has examined the possibility that a specific neural process might predict responses to specific types of stress. Despite the exploratory nature of the scoring of social and non-social stress scales used herein, the present study has taken a preliminary step to fill this gap.

Our results are broadly consistent with prior research showing that reduced activity in brain regions involved in reward processing may pose a potential increased risk for the development of depression in individuals exposed to stress (e.g., Nikolova et al., 2012; Corral-Frías et al., 2015). Despite a growing body of literature on the effects of stress and monetary reward responsiveness on depression, the present study is among the first to examine the effects of both life stress exposure and social reward responsiveness on depressive symptoms, and is the first to examine *lifetime* stress exposure. Our results suggest that, rather than directly explaining the relationship between life stress and depressive symptoms, reduced responsiveness to social reward may be a vulnerability factor specifically when people are exposed to social stress, a key risk factor for the development of depression. This suggests that individual differences in social reward responsiveness may be one factor that influences likelihood of developing depression following exposure to social stress, and, as such, individuals low in social reward responsiveness might benefit from targeted prevention.

Strengths of the current study include evaluation of competing hypotheses with regard to reward responsiveness as a mediator or moderator of the effects of stress on psychiatric symptoms, extension to the social reward domain, assessment of lifetime stress exposure, and tests of specificity of associations for depression or internalizing symptoms more broadly. A few limitations should be considered when interpreting these results. First, the study design was cross-sectional. For this reason, causality and the directionality cannot be determined.

In particular, although mediation analyses can be performed with cross-sectional data, results should be replicated with longitudinal data. Second, given prior work linking reduced RewP and activation of ventral striatum to monetary reward to the later emergence of depressive symptoms (Kujawa and Burkhouse, 2017; Keren et al., 2018), we interpreted RewP as an indicator of a potential vulnerability for depression in the context of lifetime social stress exposure. However, the study design did not enable us to examine whether reduced RewP to social reward emerges prior to exposure to social stress or to increases in symptoms of depression. Future longitudinal research must be conducted to examine associations between social reward responsiveness and stress exposure across time and development, and to assess social reward responsiveness across levels of analysis, including behavior and circuit measures (National Institute of Mental Health [NIMH], 2019). Third, although the items that comprised the STRAIN social and non-social stress subscales were binned based on whether they were related to social situations or interactions, the present study is limited in its ability to test the validity of this scoring approach. The analyses of social vs. non-social stress scales of the STRAIN are exploratory and should be interpreted as such. Further work examining the extent to which these subscales converge with other indicators of social and non-social strain is needed. Fourth, although subthreshold depressive symptoms are a strong predictor of subsequently developing MDD (e.g., Keenan et al., 2008), this was a non-clinical sample and future research is needed to examine whether the present results generalize to clinical populations. Likewise, future studies could sample adolescents and adults from the community who have greater lifetime stress exposure burdens to examine the associations described here in other, more generally representative, populations. Fifth, we employed a self-report measure of current depression and anxiety symptoms in the present study, and it will be important for future studies to utilize interview-based assessments of participants' symptoms and current and past history. Finally, given the number of models tested and relatively modest effect sizes, the current results must be interpreted cautiously, and replication is needed.

It is also worth noting that we only measured responses to social acceptance and rejection feedback, as opposed to neutral feedback for a few reasons. First, measuring acceptance/social reward and rejection feedback is consistent with a commonly used monetary reward paradigm to elicit RewP (Proudfit, 2015). In this task, the relative response to reward vs. loss has consistently been linked cross-sectionally and prospectively with depressive symptoms (Bress et al., 2015; Nelson et al., 2016; Kujawa et al., 2019). Second, evidence suggests that RewP presents as a relative positivity to monetary reward or the best possible outcome in a task and is less sensitive to differences between neutral and loss feedback (e.g., Kujawa et al., 2013). Finally, given the nature of social interaction tasks, "neutral" feedback is difficult to manipulate, as there would likely be individual differences in how people process feedback that is more ambiguous. The inclusion of a third condition would lengthen the task considerably. Nonetheless, additional research is needed to examine neural responses to neutral feedback in social vs. monetary reward tasks.

Notwithstanding these limitations, the present study is the first to examine how social reward processing is associated with lifetime stress exposure and depression and anxiety symptoms in a large sample of emerging adults – a developmental period when rates of depression increase dramatically (Kessler et al., 2001). The results highlight the potential utility of ERP measures of social reward responsiveness for clarifying pathways to the emergence of depression. In addition, they elucidate a pathway that appears to be relatively specific for lifetime social (vs. non-social) stress exposure in predicting depressive (vs. anxiety) symptoms. These findings may thus have implications for designing preventions targeting those low in social reward responsiveness, with the possibility of buffering against the negative effects of social stress before symptoms emerge.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the supplementary files (doi: 10.6084/m9.figshare.9033842).

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Declaration of Helsinki with written informed consent from all participants. All participants gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved b the McGill University research ethics board.

AUTHOR CONTRIBUTIONS

SP, PE, AW, and AK contributed to the design of this research study. PE and AW oversaw the conduct of the research study, data collection, and management. AK designed the original Island Getaway task. GMS created the STRAIN and oversaw the preparation of the stress data for inclusion, which was led by GSS. SP and AK analyzed and interpreted the data by consulting with all co-authors. SP and AK drafted the manuscript, which was subsequently revised by all co-authors. All authors read and approved the final version of the manuscript.

FUNDING

Implementation of the STRAIN in this study was supported by a Society in Science—Branco Weiss Fellowship, NARSAD Young Investigator Grant #23958 from the Brain and Behavior Research Foundation, and National Institutes of Health grant K08 MH103443 to GMS.

REFERENCES

Bress, J. N., Meyer, A., and Proudfit, G. H. (2015). The stability of the feedback negativity and its relationship with depression during childhood and adolescence. *Dev. Psychopathol.* 17, 1285–1294. doi: 10.1017/S0954579414001400

Carlson, J. M., Foti, D., Mujica-Parodi, L. R., Harmon-Jones, E., and Hajcak, G. (2011). Ventral striatal and medial prefrontal BOLD activation is correlated with reward-related electrocortical activity: a combined ERP and fMRI study. *Neuroimage.* 57, 1608–1616. doi: 10.1016/j.neuroimage.2011.05.037

Chapman, D. P., Whitfield, C. L., Felitti, V. J., Dube, S. R., Edwards, V. J., and Anda, R. F. (2004). Adverse childhood experiences and the risk of depressive disorders in adulthood. *J. Affect. Disord.* 82, 217–225. doi: 10.1016/j.jad.2003.12.013

Corral-Frías, N. S., Nikolova, Y. S., Michalski, L. J., Baranger, D. A., Hariri, A. R., and Bogdan, R. (2015). Stress-related anhedonia is associated with ventral striatum reactivity to reward and transdiagnostic psychiatric symptomatology. *Psychol. Med.* 45, 2605–2617. doi: 10.1017/S0033291715000525

Davey, C., Yücel, M., and Allen, N. (2008). The emergence of depression in adolescence: development of the prefrontal cortex and the representation of reward. *Neurosci. Biobehav. Rev.* 32, 1–19. doi: 10.1016/j.neubiorev.2007.04.016

Epel, E., Crosswell, A., Mayer, S., Prather, A., Slavich, G., Puterman, E., et al. (2018). More than a feeling: a unified view of stress measurement for population science. *Front. Neuroendocrinol.* 49:146–169. doi: 10.1016/j.yfrne.2018.03.001

Ethridge, P., Kujawa, A., Dirks, M. A., Arfer, K. B., Kessel, E. M., Klein, D. N., et al. (2017). Neural responses to social and monetary reward in early adolescence and emerging adulthood. *Psychophysiology* 54, 1786–1799. doi: 10.1111/psyp.12957

Ethridge, P., and Weinberg, A. (2018). Psychometric properties of neural responses to monetary and social rewards across development. *Int. J. Psychophysiol.* 132, 311–322. doi: 10.1016/j.ijpsycho.2018.01.011

Forbes, E. E., and Dahl, R. E. (2012). Altered reward function in adolescent depression: what, when, and how? *J. Child Psychol. Psychiatry.* 53, 3–15. doi: 10.1111/j.1469-7610.2011.02477.x

Goff, B., Gee, D. G., Telzer, E. H., Humphreys, K. L., Gabard-Durnam, L., Flannery, J., et al. (2013). Reduced nucleus accumbens reactivity and adolescent depression following early-life stress. *Neuroscience* 249, 129–138. doi: 10.1016/j.neuroscience.2012.12.010

Goldstein, B. L., Kessel, E. M., Kujawa, A., Finsaas, M. C., Davila, J., Hajcak, G., et al. (2019). Stressful life events moderate the effect of neural reward responsiveness in childhood on depressive symptoms in adolescence. *Psychol. Med.* [Epub ahead of print].

Gratton, G., Coles, M. G., and Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalogr. Clin. Neurophysiol.* 55, 468–484. doi: 10.1016/0013-4694(83)90135-9

Hammen, C. (2005). Stress and depression. *Annu. Rev. Clin. Psychol.* 1, 293–319. doi: 10.1146/annurev.clinpsy.1.102803.143938

Hammen, C. (2009). Adolescent depression: stressful interpersonal contexts and risk for recurrence. *Curr. Dir. Psychol. Sci.* 18, 200–204. doi: 10.1111/j.1467-8721.2009.01636.x

Hanson, J. L., Hariri, A. R., and Williamson, D. E. (2015). Blunted ventral striatum development in adolescence reflects emotional neglect and predicts depressive symptoms. *Biol. Psychiatr.* 78, 598–605. doi: 10.1016/j.biopsych.2015.05.010

Hayes, A. (2017). *Introduction to Mediation, Moderation, and Conditional Process Analysis*, 2nd Edn. New York, NY: Guilford Press.

Holroyd, C. B., and Coles, M. G. H. (2002). The neural basis of human error processing: reinforcement learning, dopamine, and error-related negativity. *Psychol. Rev.* 109, 679–709. doi: 10.1037/0033-295X.109.4.679

Holroyd, C. B., and Coles, M. G. H. (2008). Dorsal anterior cingulate cortex integrates reinforcement history to guide voluntary behavior. *Cortex.* 44, 548–559. doi: 10.1016/j.cortex.2007.08.013

Keenan, K., Hipwell, A., Feng, X., Babinski, D., Hinze, A., Rischall, M., et al. (2008). Subthreshold symptoms of depression in preadolescent girls are stable and predictive of depressive disorders. *J. Am. Acad. Child Adolesc. Psychiatr.* 47, 1433–1442. doi: 10.1097/CHI.0b013e3181886eab

Kendler, K. S., Gardner, C. O., and Prescott, C. A. (2002). Toward a comprehensive developmental model for major depression in women. *Am. J. Psychiatr.* 159, 1133–1145. doi: 10.1176/appi.ajp.159.7.1133

Kendler, K. S., Gardner, C. O., and Prescott, C. A. (2006). Toward a comprehensive developmental model for major depression in men. *Am. J. Psychiatr.* 163, 115–124. doi: 10.1176/appi.ajp.163.1.115

Kendler, K. S., Hettema, J. M., Butera, F., Gardner, C. O., and Prescott, C. A. (2003). Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalized anxiety. *Arch. Gen. Psychiatr.* 60, 789–796. doi: 10.1001/archpsyc.60.8.789

Kendler, K. S., Karkowski, L. M., and Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *Am. J. Psychiatr.* 156, 837–841. doi: 10.1176/ajp.156.6.837

Keren, H., Callaghan, G. O., Vidal-Ribas, P., Buzzell, G. A., Brotman, M. A., Leibenluft, E., et al. (2018). Reward processing in depression: a conceptual and meta-analytic review across fMRI and EEG studies. *Am. J. Psychiatr.* 175, 1111–1120. doi: 10.1176/appi.ajp.2018.17101124

Kessler, R. C., Avenevoli, S., and Merikangas, K. R. (2001). Mood disorders in children and adolescents: an epidemiologic perspective. *Biol. Psychiatr.* 49, 1002–1014. doi: 10.1016/s0006-3223(01)01129-5

Kessler, R. C., McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., et al. (2010). Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *Br. J. Psychiatr.* 197, 378–385. doi: 10.1192/bjp.bp.110.080499

Kujawa, A., Arfer, K. B., Klein, D. N., and Proudfit, G. H. (2014). Electrocortical reactivity to social feedback in youth: a pilot study of the Island getaway task. *Dev. Cogn. Neurosci.* 10, 140–147. doi: 10.1016/j.dcn.2014.08.008

Kujawa, A., and Burkhouse, K. L. (2017). Vulnerability to depression in youth: advances from affective neuroscience. *Biol. Psychiatry. Cogn. Neurosci. Neuroimaging.* 2, 28–37. doi: 10.1016/j.bpsc.2016.09.006

Kujawa, A., Carroll, A., Mumper, E., Mukherjee, D., Kessel, E. M. M., Olino, T., et al. (2018). A longitudinal examination of event-related potentials sensitive to monetary reward and loss feedback from late childhood to middle adolescence. *Int. J. Psychophysiol.* 132, 323–330. doi: 10.1016/j.ijpsycho.2017.11.001

Kujawa, A., Hajcak, G., Danzig, A. P., Black, S. R., Bromet, E. J., Carlson, G. A., et al. (2016). Neural reactivity to emotional stimuli prospectively predicts the impact of a natural disaster on psychiatric symptoms in children. *Biol. Psychiatry.* 80, 381–389. doi: 10.1016/j.biopsych.2015.09.008

Kujawa, A., Hajcak, G., and Klein, D. N. (2019). Reduced reward responsiveness moderates the effect of maternal depression on depressive symptoms in offspring: evidence across levels of analysis. *J. Child. Psychol. Psychiatr.* 60, 82–90. doi: 10.1111/jcpp.12944

Kujawa, A., Smith, E., Luhmann, C., and Hajcak, G. (2013). The feedback negativity reflects favorable compared to nonfavorable outcomes based on global, not local, alternatives. *Psychophyiology* 50, 134–138. doi: 10.1111/psyp.12002

La Greca, A., and Harrison, H. (2005). Adolescent peer relations, friendships, and romantic relationships: do they predict social anxiety and depression? *J. Clin. Child Adolesc. Psychol.* 34, 49–61. doi: 10.1207/s15374424jccp3401_5

McLaughlin, K. A., Busso, D. S., Duys, A., Green, J. G., Alves, S., Way, M., et al. (2014). Amygdala response to negative stimuli predicts PTSD symptom onset following a terrorist attack. *Depress. Anxiety.* 31, 834–842. doi: 10.1002/da.22284

Meyer, A., Lerner, M., De Los Reyes, A., Laird, R., and Hajcak, G. (2017). Considering ERP difference scores as individual difference measures: issues with subtraction and alternative approaches. *Psychophysiology* 54, 114–122. doi: 10.1111/psyp.12664

National Institute of Mental Health. [NIMH] (2019). *RDoC Matrix*. Available at: http://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml (accessed February 28, 2019).

Nelson, B. D., Perlman, G., Klein, D. N., Kotov, R., and Hajcak, G. (2016). Blunted neural response to rewards as a prospective predictor of the development of depression in adolescent girls. *Am. J. Psychiatr.* 173, 1223–1230. doi: 10.1176/appi.apj.2016.15121524

Nikolova, Y. S., Bogdan, R., Brigidi, B. D., and Hariri, A. R. (2012). Ventral striatum reactivity to reward and recent life stress interact to predict positive affect. *Biol. Psychiatr.* 72, 157–163. doi: 10.1016/j.biopsych.2012.03.014

Proudfit, G. H. (2015). The reward positivity: from basic research on reward to a biomarker for depression. *Psychophysiology* 50, 449–459. doi: 10.1111/psyp.12370

Sandre, A., Bagot, R. C., and Weinberg, A. (2019). Blunted neural response to appetitive images prospectively predicts symptoms of depression, and not anxiety, during the transition to university. *Biol. Psychol.* 145, 31–41. doi: 10.1016/j.biopsycho.2019.04.001

Setterfield, M., Walsh, M., Frey, A., and McCabe, C. (2016). Increased social anhedonia and reduced helping behaviour in young people with high depressive symptomatology. *J. Affect. Disord.* 15, 372–377. doi: 10.1016/j.jad.2016.08.020

Silk, J. S., Davis, S., McMakin, D. L., Dahl, R. E., and Forbes, E. E. (2012). Why do anxious children become depressed teenagers? the role of social evaluative threat and reward processing. *Psychol. Med.* 42, 2095–2107. doi: 10.1017/S0033291712000207

Slavich, G. M. (2016). Life stress and health: a review of conceptual issues and recent findings. *Teach. Psychol.* 43, 346–355. doi: 10.1177/0098628316662768

Slavich, G. M. (2019). Stressnology: the primitive (and problematic) study of life stress exposure and pressing need for better measurement. *Brain. Behav. Immun.* 75, 3–5. doi: 10.1016/j.bbi.2018.08.011

Slavich, G. M., Thornton, T., Torres, L., Monroe, S., and Gotlib, I. (2009). Targeted rejection predicts hastened onset of major depression. *J. Soc. Clin. Psychol.* 28, 223–243. doi: 10.1521/jscp.2009.28.2.223

Slavich, G. M., and Shields, G. S. (2018). Assessing lifetime stress exposure using the stress and adversity inventory for adults (Adult STRAIN): an overview and initial validation. *Psychosom. Med.* 80, 17–27. doi: 10.1097/PSY.0000000000000534

Slavich, G. M., Tartter, M. A., Brennan, P. A., and Hammen, C. (2014). Endogenous opioid system influences depressive reactions to socially painful targeted rejection life events. *Psychoneuroendocrinology* 49, 141–149. doi: 10.1016/j.psyneuen.2014.07.009

Starr, L. R., and Davila, J. (2008). Differentiating interpersonal correlates of depressive symptoms and social anxiety in adolescence: implications for models of comorbidity. *J. Clin. Child. Adolesc. Psychol.* 37, 337–349. doi: 10.1080/15374410801955854

Stasik-O'Brien, S. M., Brock, R. L., Chmielewski, M., Naragon-Gainey, K., Koffel, E., McDade-Montez, E., et al. (2018). Clinical utility of the inventory of depression and anxiety symptoms (IDAS). *Assessment* 26, 944–960. doi: 10.1177/1073191118790036

Swartz, J. R., Knodt, A. R., Radtke, S. R., and Hariri, A. R. (2015). A neural biomarker of psychological vulnerability to future life stress. *Neuron* 85, 505–511. doi: 10.1016/j.neuron.2014.12.055

Watson, D., O'Hara, M. W., Simms, L. J., Kotov, R., Chmielewski, M., McDade-Montez, E. A., et al. (2007). Development and validation of the inventory of depression and anxiety symptoms (IDAS). *Psychol. Assess.* 19, 253–268. doi: 10.1037/1040-3590.19.3.253

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer JK declared a past collaboration with one of the authors AW to the handling Editor.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 23 August 2019
doi: 10.3389/fnbeh.2019.00177

Social and Non-social Reward: A Preliminary Examination of Clinical Improvement and Neural Reactivity in Adolescents Treated With Behavioral Therapy for Anxiety and Depression

Karen T. G. Schwartz[1], Maria Kryza-Lacombe[1], Michael T. Liuzzi[2], V. Robin Weersing[1,2] and Jillian Lee Wiggins[1,2]*

[1] San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, United States, [2] Department of Psychology, San Diego State University, San Diego, CA, United States

Background: Pediatric anxiety and depression are highly prevalent and debilitating disorders that often co-occur. Neural circuitry of reward processing has been shown to be implicated in both, and there is an emerging evidence base linking treatment response to brain patterns of reward processing. The current study aimed to add to this literature by investigating the association between clinical improvement and social and non-social reward in youth previously treated for anxiety and depression.

Methods: The current study leveraged clinical improvement data from a successful randomized controlled trial testing the efficacy of a transdiagnostic, brief behavioral treatment for youth diagnosed with anxiety or depression. Participants (N = 15) interested in engaging in a neuroimaging follow-up underwent an fMRI scan, during which they completed social (i.e., Face Task) and non-social (i.e., Piñata Task, a youth-friendly monetary incentive delay task) reward tasks. Whole-brain activation and functional connectivity analyses identified neural responses to the tasks separately; a third set of analyses directly compared clinical improvement-related findings to understand the impact of task context on neural reactivity to reward.

Results: Activation-based findings were sparse; however, connectivity as a function of degree of treatment response was apparent and robust. Within the context of social reward, significant clusters within frontal and temporal regions driven by happy face contrasts, the social reward stimulus, were observed. This supports connectivity between these regions and both amygdala and ventral striatum seeds as a function of degree of clinical improvement. Connectivity within the context of non-social reward also yielded significant clusters in temporal and parietal regions. Here too, the magnitude and direction of region coupling depended on the degree of clinical improvement and the task conditions. No differences in connectivity by task type as a function of clinical improvement were found.

OPEN ACCESS

Edited by:
Amanda E. Guyer, University of California, Davis, United States

Reviewed by:
Autumn Kujawa, Vanderbilt University, United States
Thomas M. Olino, Temple University, United States

****Correspondence:***
Karen T. G. Schwartz
kgarelik@gmail.com

Received: *31 March 2019*
Accepted: *16 July 2019*
Published: *23 August 2019*

Citation:
Schwartz KTG, Kryza-Lacombe M, Liuzzi MT, Weersing VR and Wiggins JL (2019) Social and Non-social Reward: A Preliminary Examination of Clinical Improvement and Neural Reactivity in Adolescents Treated With Behavioral Therapy for Anxiety and Depression. Front. Behav. Neurosci. 13:177. doi: 10.3389/fnbeh.2019.00177

Conclusion: Findings serve as preliminary evidence that neural regions found to be related to clinical improvement within the context of social and non-social reward are similar to regions that have been shown to support reward processing in normative samples. Implications for treatment and future work are discussed.

Keywords: reward, behavioral therapy, fMRI, adolescents, anxiety, depression

INTRODUCTION

Pediatric anxiety and depression are highly prevalent, debilitating, and associated with a chronic course and long-term impairment (e.g., Merikangas et al., 2010). They frequently co-occur, both concurrently and sequentially (Garber and Weersing, 2010), and data suggest shared genetic risk (Thapar and McGuffin, 1997). Anxiety and depression also respond to the same classes of psychosocial (e.g., cognitive and behavioral therapies) and pharmacological (e.g., SSRIs) interventions (Compton et al., 2004), and treatment of one target disorder may lead to cross-over effects on the other disorder (e.g., interventions that target depression may reduce non-targeted anxiety symptoms; Garber et al., 2016).

This work has served as the rationale for the development of transdiagnostic interventions designed to target core processes across anxiety and depression and treat them as a unified problem area. In adults, unified protocols have demonstrated superior symptom improvement across clinical domains, both compared to control conditions and disorder-specific care (see McEvoy et al., 2009 for a review). The few studies that have tested transdiagnostic protocols in pediatric samples have also documented the efficacy in targeting internalizing disorders (Chu et al., 2016; Ehrenreich-May et al., 2017; Weersing et al., 2017), suggesting shared processes of disorder and recovery across anxiety and depression. However, such findings are in contrast to evidence that anxiety and depression differ in their responses to intervention. For instance, interventions targeting anxiety have the largest intervention effect sizes in the pediatric literature; in contrast, depression treatment effects are the smallest in the field (Weisz et al., 2017). Furthermore, pediatric unified protocols have evidenced better effects on anxiety, compared to depression outcomes, despite success overall (Queen et al., 2014; Weersing et al., 2017). Thus, additional work must be done to examine underlying dimensional factors that cross diagnostic boundaries and may more effectively account for observed differences in response to care in internalizing youth. Such efforts are aligned with the priorities of the National Institutes of Health (NIH) in an effort to improve the efficacy of treatments (e.g., Insel et al., 2010).

One neurobiological mechanism that has been implicated across anxiety and depression is reward processing, in both social and non-social contexts. Reward processing encompasses neural reactivity associated with anticipation and consumption of positive gains, such as monetary winnings or social approval, as well as behavioral learning that motivates future actions. Studies of reward processing in pediatric samples have included tasks based on monetary incentives or tasks focused on social appraisal. The former maps onto the adult literature, as money is an ecologically valid incentive that is easily manipulated and distributed by study personnel. Social reward is a relatively new area of interest relevant to pediatric samples, given the developmental alterations in social valuation during adolescence (Steinberg and Morris, 2001). Indeed, adolescence is a period of substantial neural maturation in areas associated with reward (e.g., Ernst et al., 2006; Galvan, 2010). Concurrent developmental changes include enhanced need for social inclusion and peer acceptance (e.g., Choudhury et al., 2006). Thus, happy faces may be particularly rewarding during this developmental period (Scherf et al., 2012). Furthermore, happy faces are utilized to signal success on achievement-oriented tasks, such as academic assignments; therefore, happy faces are emotionally salient and socially relevant cues that can be reasonably expected to probe reward processing neural circuitry in youth.

Anhedonia, or the motivation and ability to seek and experience rewarding activities, is a core diagnostic feature of depression, though not anxiety. Anhedonia has been shown to serve as a phenotype of aberrant integration of reward and arousal, above and beyond other symptoms of internalizing disorders in youth (Pornpattananangkul et al., 2019). Generally, youth with or at risk for depression evidence blunted patterns of response in areas associated with reward, and signals appear to be further diminished by intensified cognitive control (e.g., Forbes et al., 2006, 2009; Chantiluke et al., 2012; Wiggins et al., 2017). Four treatment trials targeting depression in youth included task-based neuroimaging components prior to treatment, only (i.e., baseline; Forbes et al., 2010), or at both pre- and post-treatment timepoints (i.e., baseline and follow-up; Straub et al., 2015; Chuang et al., 2016; Mori et al., 2016); three studies probed non-social (i.e., monetary) reward processing (Forbes et al., 2010; Straub et al., 2015; Mori et al., 2016). Pre- to post-treatment changes in brain patterns suggested that aberrant responses to reward conditions "normalized" in youth as a function of treatment (i.e., mirrored patterns observed in healthy controls; Mori et al., 2016). Pre-post signal reductions in areas associated with emotion regulation were observed as a function of treatment engagement and related significantly to larger depression symptom reductions at post and follow-up (Straub et al., 2015).

The conceptual connection between anhedonia, depression and reward processing is clear; however, reward processing has also be implicated in anxiety in a different fashion. Anxiety disorders are characterized by avoidance of anxiety-provoking stimuli, escape behaviors when exposed to anxiety triggers, and negative "reward" of avoidance and escape through the reduction of anxious distress. In adolescence, avoidance of social interactions becomes particularly prevalent due to intensified concerns regarding peer approval and acceptance. Though

smaller than the depression literature, neuroimaging findings on reward processing in pediatric anxiety have begun to accrue. fMRI studies enrolling anxious vs. non-anxious youth evidenced increased striatal, frontal, and limbic reactivity during social and non-social reward tasks (e.g., Guyer et al., 2012; Benson et al., 2015; Jarcho et al., 2015); of note, these studies did not include a treatment component. To date, five reports citing data from four independent trials serve as the current literature base on neural predictors of response to psychosocial interventions targeting pediatric anxiety (McClure et al., 2007; Maslowsky et al., 2010; Kujawa et al., 2016; Burkhouse et al., 2017; White et al., 2017). Three studies incorporated fMRI data from baseline and follow-up (McClure et al., 2007; Maslowsky et al., 2010; White et al., 2017), while two representing the same trial utilized baseline data only (Kujawa et al., 2016; Burkhouse et al., 2017). However, no investigations examined reward processing, specifically, as a neural predictor or mechanism of treatment response in this population.

It is notable that none of the published findings tested a transdiagnostic protocol, yet the majority of samples evidenced substantial diagnostic comorbidity. Furthermore, changes in striatal reactivity in response to a depression-focused intervention was associated with cross-over effects, such that changes of greater magnitude predicted a faster rate of decline in anxiety symptoms across time (Forbes et al., 2010). Thus, work within the transdiagnostic realm is warranted. Moreover, given the relevance of social processing in anxiety and depression, disorders frequently characterized by interpersonal difficulties, focusing on social in addition to non-social reward is necessary.

In sum, the literature base on neural mechanisms of treatment response in internalizing youth is in its infancy. Studies are few, segregated by diagnosis, and lack replication within treatment modality across independent teams. Additionally, treatment paradigms employed were diagnosis-specific, despite high rates of comorbidity within samples, and typically focused on only one aspect of reward (i.e., non-social reward). To address these gaps in the literature, the current study leveraged resources from a successful randomized controlled trial (RCT) to examine neural mechanisms within the context of a treatment trial in a comorbid sample of anxious-depressed youth. Specifically, we sought to examine both social and non-social reward processing as promising neural mechanisms of clinical improvement in a subsample of youth, ages 8−16 years, enrolled in a multi-site RCT investigating the effectiveness of a transdiagnostic brief behavioral therapy (BBT) for pediatric anxiety and depression (Weersing et al., 2017). BBT may be a particularly relevant treatment paradigm to evaluate the relationship between both social and non-social reward processing and treatment response due to the behavioral target of intervention. That is, both anxiety and depression are characterized by avoidance of negative affect and behavioral withdrawal, including from social situations. Behavioral interventions directly target avoidance by increasing reinforcement in response to engagement and decreasing reinforcement for avoidance behaviors. Furthermore, behavioral interventions are developmentally appropriate for youth, as behavioral tasks are active, concrete, and cognitively straightforward (Martin and Oliver, 2018). So, we re-contacted this sample to collect neuroimaging data post-treatment with the aim of relating imaging data to variables defined during the original RCT participation, such as baseline characteristics of youth and BBT treatment response.

The original BBT trial evidenced statistically significant positive effects across measures. Youth who received BBT were more likely to be categorized as treatment responders by the post-treatment assessment [i.e., Clinical Global Impressions, Improvement Scale (CGI-I; Guy, 1976) $\leq$2] and evidenced improved functioning compared to those receiving assisted referral to care (ARC; control condition). Furthermore, the rate of functional improvement among those who received BBT was significantly faster than improvements reported by those in the ARC condition (see Weersing et al., 2017 for full methods and CONSORT). The BBT intervention targeted avoidance across anxiety and depression by promoting graded engagement in important life tasks, providing participants with concrete, alternate experiences meant to be rewarding (Weersing et al., 2008). Some of the targeted tasks were social in nature while others were based on success experiences, as youth have a number of difficulties with achievement-oriented activities. We thus took the opportunity to probe the distinction between social (i.e., happy face) and non-social (i.e., monetary) reward tasks, as a comparison like this in the same sample has yet to be published. Additionally, the developmental maturation of reward processing circuitry in adolescence suggests differences in salience and associated neural reactivity in response to social and monetary reward cues can be expected.

To our knowledge, this study is the first to (a) evaluate social reward in internalizing youth within the context of treatment (b) inform the relationship between reward processing and clinical improvement in response to a youth-focused transdiagnostic psychosocial intervention, and (c) analyze data from one sample of youth who each performed two tasks. Planned statistical analyses represent secondary analyses of data from a completed clinical trial (Weersing et al., 2017), combined with original neuroimaging data collection. Scans were performed post-treatment to generate hypotheses regarding the long-term role of treatment response in reward processing. These efforts are exploratory in nature to contribute to the establishment of a literature base of neural mechanisms of treatment response in internalizing youth and bolster future research.

MATERIALS AND METHODS

The protocol for the neuroimaging follow-up was reviewed and approved by the University of California, San Diego Institutional Review Board. Secondary approval was obtained from San Diego State University's Institutional Review Board. Written informed consent was obtained from all participating caregivers and adolescents over 18 years of age, prior to the administration of any study materials, in accordance with the Declaration of Helsinki. Adolescents younger than 18 provided assent, in addition to their caregiver's written informed consent to participate. Consent forms included a specific clause allowing

data from initial BBT participation to be linked to current data collection.

Participants

Neuroimaging and clinical improvement data from 15 youth were analyzed for the current study. All BBT families initially recruited from the San Diego site (October 2010 to December 2014) who consented to being contacted in the future regarding additional opportunities for research were considered for participation in this neuroimaging follow-up (N = 49). Recruitment targeted participants randomized to the BBT arm to allow for inferences to be made regarding the association between treatment response to BBT and reward processing circuitry, as well as to control for treatment type and dose received. BBT caregivers of record were contacted via phone between August 2016 and November 2017 to assess interest as well as youth contraindications for undergoing an fMRI scan.

Of the 49 participants randomized to receive BBT through the San Diego site, 44 were contacted to assess interest in the current investigation (i.e., consented to further contact, not lost to follow-up by the RCT final assessment). Of those 44, four were lost to follow-up (e.g., contact information was out of date) and one participant had died since RCT study completion. We connected by phone with the remaining 39 participants to assess eligibility; 10 declined to participate, while 29 completed the phone screen. Of those screened, 21 met eligibility requirements for the neuroimaging follow-up (e.g., expressed interest in completing study activities, denied contraindications for the fMRI environment). Post-screen, three eligible participants were lost to follow-up and one declined to participate, prior to consenting to the current study. Thus, the current study enrolled 17 youth. Of the 17 consented to participate in the neuroimaging follow-up, one individual refused to complete the fMRI scan and one individual yielded an unusable dataset due to technical error. **Table 1** reports sample characteristics of the 15 youth included in the current study's analyses.

Participants enrolled in the neuroimaging follow-up were initially randomized at a mean age of 11.43 years (SD = 1.61; range: 8−14 years); at the time of scan, participants had a mean age of 15.29 years (SD = 2.42; range: 9−19 years). Primary diagnostic complaints at initial RCT enrollment were predominantly within the anxiety spectrum [n = 15; 35% (n = 6) Generalized Anxiety Disorder, 35% (n = 6) Separation Anxiety Disorder, 18% (n = 3) Social Phobia]; 29% (n = 5) had clinically elevated depression in addition to anxiety. In terms of treatment response, 41% (n = 7) of the participants engaged in the neuroimaging follow-up were characterized as BBT treatment responders at post-treatment.

Those enrolled in the neuroimaging follow-up did not significantly differ from those recruited in San Diego who were randomized to BBT but ineligible for the follow-up on any demographic or clinical indicators at baseline or post-treatment, with the exception of baseline clinical severity of internalizing symptoms. Those who did not engage in the neuroimaging follow-up had higher average severity scores at baseline (M = 4.44, SD = 0.88) compared to those who participated [M = 4.00, SD = 0.61; $t(43.34)$ = 2.04, p = 0.048].

TABLE 1 | Sample demographics.

N	15
Age	
Baseline	11.42 (1.64)
Time of scan	15.29 (2.42)
Gender (% Female)	7 (47%)
Race	
White	10 (67%)
Multiracial	4 (27%)
Other	1 (7%)
Ethnicity (% Hispanic)	5 (33%)
Days between post-treatment and scan	
Face Task	1284.20 (565.48)
Piñata Task	1325.93 (562.94)
Face Task accuracy	93.58% (6.35%)
Face Task bias	
Happy (ranged from −44.52 to 55.81)	5.80 (26.73)
Sad (ranged from −29.80 to 46.28)	2.80 (21.47)
Threatening (ranged from −57.37 to 27.26)	−7.11 (20.43)
CGI-I	
Clinical improvement	2.53 (1.13)
Treatment response (% Responders)	6 (40%)
SCARED	15.73 (10.24)
MFQ	11.99 (13.48)

Continuous variables are displayed as M (SD); categorical variables are displayed as N (%). CGI-I: Clinical Global Impressions, Improvement Scale assigned post-treatment (Treatment Response: CGI-I ≤2); SCARED, Screen for Child Anxiety and Related Disorders completed at time of scan; MFQ, Mood and Feelings Questionnaire completed at time of scan.

However, this difference, though statistically significant, does not reflect practical differences in clinical presentation. It is also notable that a smaller proportion of the neuroimaging sample was categorized as treatment responders at post (41%), versus rates of response observed in the BBT sample as a whole [57%; $\chi^2(1)$ = 3.41, p = 0.065]. This difference was not statistically significant.

Measures

Demographics

Caregivers provided updated demographic information at the time of scan (e.g., age, gender; see **Table 1**).

Clinical Characteristics

Clinical improvement was measured by the Clinical Global Impressions, Improvement Scale (CGI-I; Guy, 1976). The CGI-I is a 7-point, single item indicator of clinical change, such that lower scores represent improvement (1 = *very much improved*), while higher scores reflect clinical deterioration (7 = *very much worse*). Trained and reliable independent evaluators unaware of the participant's treatment condition assigned a CGI-I score at the post-treatment assessment, capturing change in symptoms of anxiety and/or depression since the baseline assessment. The original trial utilized the CGI-I as an indicator of treatment response; participants with a score of 1 (very much improved) or 2 (much improved) were categorized as treatment responders,

while those with a score of ≥3 (minimally improved) were categorized as non-responders (Weersing et al., 2017). The current study included the CGI-I dimensionally, as the main predictor of interest, to evaluate the association between clinical improvement and brain function.

The Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version (Kaufman et al., 1997) was used to determine eligibility at baseline (i.e., the presence of a primary anxiety or depression diagnosis). At the time of scan, caregivers completed the Screen for Child Anxiety and Related Disorders (SCARED; Birmaher et al., 1997) and the Mood and Feelings Questionnaire (MFQ; Angold et al., 1987) to inform severity of current anxiety and depression symptoms in youth, respectively, with higher scores indicating increased symptom severity (see **Table 1**). This study utilized the SCARED and MFQ in Additional Analyses intended to identify the impact of current symptoms on the observed pattern of fMRI findings.

Neuroimaging Paradigms

Youth completed two tasks that elicited neural activation within the context of social or non-social reward. Scans occurred 568−2317 days after the post-treatment assessment (see **Table 1** and "Additional Analyses"). Participants completed the social reward task prior to the non-social reward task. This determination was made due to the social reward task lasting longer with greater potential for cognitive fatigue than the non-social reward task. As two participants provided data collected in the inverted order, task order was included as a potential confound (see section "Additional Analyses").

Social reward task (Face Task)

Participants performed a jittered, event-related task with emotional face stimuli, including happy (i.e., social reward) faces, using a dot probe paradigm adapted from the Tel Aviv University/National Institute of Mental Health paradigm (Abend et al., 2014) during fMRI data acquisition. This task was modified to include four valence categories: happy, angry, sad, and neutral faces (see **Supplementary Figure S1**). Emotional faces were from the NimStim Set of Facial Expressions[1] (Tottenham et al., 2009). Each trial began with a fixation cross for 500 ms. Next, neutral-neutral or neutral-emotional face pairs were presented on the screen for 500 ms, followed by a probe (< or >) presented for 1000 ms. The probe was positioned either in place of the emotional face (congruent condition) or the neutral face (incongruent condition). Participants were instructed to respond quickly and accurately by pressing the button that corresponded to the direction in which the probe was pointing (left or right). Inter-trial intervals were jittered (250−1180 ms, $M = 715$ ms).

The faces dot-probe paradigm was advantageous to control for potential differences in attention and to present social reward faces, in addition to faces reflecting other valences (angry, sad, neutral). These benefits allowed for the examination of specificity of response to the social reward faces. The inclusion of faces in dot-probe paradigms has been shown to probe areas implicated in reward processing in prior research in anxious (Shechner et al., 2012) and depressed (Forbes, 2011) youth.

[1]http://www.macbrain.org/resources.htm

Participants completed three runs of the Face Task (7 min. 27 s. per run). There were eight total conditions included in the task: happy-neutral/congruent, happy-neutral/incongruent, angry -neutral/congruent, angry-neutral/incongruent, sad-neutral/ congruent, sad-neutral/incongruent, neutral-neutral/congruent, and neutral-neutral/incongruent. Neutral-neutral pairs were randomly split into "congruent" and "incongruent" groups for analysis purposes. Due to lack of jitter between face and probe displays, presentation could not be separated for analysis. There were 48 trials per condition. All participants had >65% accuracy and were therefore included in analyses (see **Table 1**). Of the 15 participants included in the Face Task analyses, 14 participants had three usable runs and one had two usable runs (excessive motion in the third run; see fMRI Data Processing).

Non-social reward task (Piñata Task)

A child-friendly monetary incentive delay task was utilized to assess neural functioning within the context of non-social reward (i.e., Piñata Task; see **Supplementary Figure S2**; Helfinstein et al., 2013; Wiggins et al., 2017; Dougherty et al., 2018). The Piñata Task is an event-related task (Helfinstein et al., 2013) previously used to reliably elicit reward-related brain activation in children (Wiggins et al., 2017). Each trial began with a variable length anticipation period consisting of a 2000 ms indicator of whether or not the participant had the opportunity to receive a reward during that round, followed by a 2500−5500 ms jittered delay period (together, referred to as the Cue Period). Then, the participant was presented with a target (i.e., turtle-shaped piñata) that they were instructed to "hit" (i.e., push a button to simulate striking the piñata). The fMRI operator explicitly instructed participants to attempt to hit the piñata during each trial, independent of reward condition. On reward trials, participants earned stars that translated into money earned (≤ $15), if they struck the piñata within the time limit. The time to hit the piñata was automatically adjusted in real time (+/−50 ms), based on the participant's performance, to promote approximately 2/3 hit trials and 1/3 miss trials. If the participant pressed the button within the time allotted, the piñata broke, indicating a hit. Missed targets swung away (1500 ms). A basket was then shown displaying stars (reward/hit condition) or empty (reward/miss or no reward conditions; referred to as the Feedback Period, 1500 ms). Inter-trial intervals were jittered.

Participants completed three runs with a total of 60 trials across all runs (30 reward, 30 no reward conditions). Task runs spanned 4 min and 52 s. Non-social analyses included all available data from 14 participants, all of whom completed three runs of the task. The fifteenth participant was excluded from analyses due to data acquisition error.

ANALYTIC PLAN

Three sets of analyses were completed: (a) evaluation of the association between clinical improvement and neural reactivity within the context of social reward (i.e., in the Face Task); (b) evaluation of improvement and neural reactivity within the context of non-social reward (i.e., monetary; Piñata Task); (c) direct comparison of social and non-social reward findings.

Each set included group-level models that evaluated whole-brain activation, as well as seed-based functional connectivity. Although full factorial models were planned and executed, we focused on contrasts that included clinical improvement, given our interest in understanding that association between clinical improvement and neural processes. As such, direct comparisons of tasks were conducted if results by task yielded findings dependent on level of clinical improvement.

Neuroimaging Acquisition

Functional and anatomical brain images were acquired using a 3T General Electric MRI scanner with a 32-channel head coil, with multiband procedures to increase spatial and temporal resolution and thus better infer correlates of clinical improvement. Task stimuli were projected onto a screen at the foot of the fMRI bed and seen by the participant via a mirror attached to the head coil. Participants responded to displayed stimuli using their dominant hand to manipulate a 2-button response box. T2 blood oxygen level dependent (BOLD) images were acquired across 3 runs as 104 interleaved sagittal slices approximately parallel to the AC-PC line, with whole-brain coverage using a 3D multiband EPI pulse sequence [matrix size = 104 × 104 × 60 accelerated by a factor of 6, TR = 800 ms, TE = 29 ms, flip angle = 52°, FOV = 20.8 mm, voxel size = 2 mm × 2 mm × 2 mm, 556 (Face Task) or 370 (Piñata Task) image volumes per run]. High-resolution anatomical images with prospective motion correction (T2-weighted MPRAGE PROMO) were acquired for anatomical localization and spatial normalization (256 1.0 mm sagittal slices, flip angle = 8°, matrix size = 256 × 256, FOV = 25.6 mm, voxel size = 1 mm × 1 mm × 1 mm). The acquisition protocol was not optimized to capture cerebellar signal, so clusters identified within the cerebellum will not be discussed in detail.

fMRI Data Preprocessing

Preprocessing protocols were implemented using Analysis of Functional NeuroImages (AFNI[2]). Preprocessing steps included functional image realignment, slice-time correction, spatial smoothing of 4 mm, and non-linear registration for spatial standardization to the Talairach template (Talairach and Tournoux, 1988). Image volume pairs with frame-wise displacement >1 mm were censored from individual level analysis. Task runs with censoring of ≥35% of image volumes were excluded from analyses (Face Task: 1 run of 1 participant). All participants evidenced mean frame-wise displacement (head motion) ≤0.30 mm.

Data Analysis

Activation

For the Face Task, probing social reward, regressors of interest in the individual-level general linear model included face emotion (happy, sad, angry, neutral) and probe location (congruent, incongruent), convolved with the BLOCK function. Beta images represented estimated activation during each of the conditions.

For the Piñata Task, probing non-social reward, two individual-level general linear models were run to generate estimates of brain activation during anticipation and feedback periods, separately. The regressor of interest during the anticipation period included Reward Condition (no reward, reward). Reward Condition was convolved with AFNI's "dmBLOCK" basis function over the variable duration. Regressors of interest during the feedback period included Reward Condition and Performance (hit, miss). Both were convolved with the "BLOCK" function over 1500 ms. Analyses generated beta coefficients at each voxel for reward and no reward trials during the anticipation period, as well as for reward/hit, reward/miss, no reward/hit, and no reward/miss trials during the feedback period.

For both the social reward and non-social reward tasks, models included head motion in x, y, z, roll, pitch, yaw directions and third-degree polynomials to model low-frequency drift as nuisance regressors.

Connectivity

Generalized psychophysiological interaction analysis (gPPI; McLaren et al., 2012) was utilized to calculate functional connectivity during the Face Task and the feedback period of the Piñata Task, given prior work that found connectivity results in the feedback period (Dougherty et al., 2018). gPPI calculates change in correlations between a seed region of interest and all other brain regions in each condition compared to implicit baseline. gPPI is advantageous as it allows for the evaluation of more than two task conditions in a single model. Given past work on reward tasks (Helfinstein et al., 2013; Dougherty et al., 2014; Wiggins et al., 2017) and prior fMRI work on anxiety (e.g., Blackford and Pine, 2012) and depression (e.g., Kerestes et al., 2014), bilateral amygdalae and ventral striatum (nucleus accumbens) were utilized as seeds for gPPI analyses. Seed regions were identified using the Talairach atlas in AFNI (Talairach and Tournoux, 1988; left amygdala = 1288 mm^3; right amygdala = 1280 mm^3; left ventral striatum = 136 mm^3; right ventral striatum = 168 mm^3). This analysis generated a set of voxel-wise images that represent connectivity between the seed region and the rest of the brain per condition for each task. Variance associated with head motion in x, y, z, roll, pitch, yaw directions was removed and third-degree polynomials were included to remove low-frequency drift.

Second Level Analyses

We conducted whole-brain, group-level ANCOVAs, by task, via AFNI's 3dMVM program to evaluate the association between clinical improvement (CGI-I) and reward-related brain function (activation, connectivity). Clinical improvement was included as a dimensional, between-subjects variable; task conditions were included as within-subjects categorical variables. Interactions between clinical improvement and task condition (Face Task: Clinical Improvement × Face Emotion, Clinical Improvement × Face Emotion × Probe Location; Piñata Task: Clinical Improvement × Reward Condition, Clinical Improvement × Performance, Clinical Improvement × Reward Condition × Performance) indicate the impact of task condition(s) on the relationship between clinical improvement and brain function.

[2]https://afni.nimh.nih.gov/afni/

Due to the small sample size, 3-way interactions were considered exploratory and interpreted with caution. All results were corrected for multiple comparisons, with a whole-brain corrected threshold of $p < 0.05$. The cluster threshold was calculated by 3dClustsim using the mixed-model spatial autocorrelation function (-acf) and the NN1 2-sided option, per the most recent recommendations on cluster correction (Cox et al., 2017). 3dClustsim used a group mask representing brain regions where 90% of participants had valid data. Spatial autocorrelation parameters were calculated by 3dFWHMx for each run separately, averaged over runs for each participant, and then averaged across participants. The cluster extent threshold across all models was $k \geq 56$ voxels with a conservative height threshold of $p < 0.005$, which is appropriate for event-related designs (Cox et al., 2017). To decompose significant interactions, *post hoc* analyses were performed on values that were extracted and averaged from each cluster using SPSS; *z*-scores represented the test of the difference between two dependent correlations with one variable in common (Steiger, 1980; Lee and Preacher, 2013). *Post hoc* correlations were conducted for illustrative purposes to clearly depict the direction of effects.

Additional Analyses

Activation/connectivity values were extracted from clusters representing the main results and averaged for Additional Analyses. Regression analyses evaluated the effects of residual head motion, age, gender, concurrent anxiety, concurrent depression, length of time since post-treatment assessment, and task order on identified findings.

RESULTS

Behavioral Results

On the Face Task, overall mean accuracy ($M = 93.58\%$, $SD = 6.35$) was well above chance (50%). Attention bias was calculated by subtracting reaction time between congruent and incongruent trials within face emotion condition. One-sample *t*-tests revealed no significant attention bias toward happy [$t(14) = 0.84$, $p = 0.415$], sad [$t(14) = 0.51$, $p = 0.621$], or threatening [$t(14) = -1.35$, $p = 0.199$] faces. No significant associations were found between clinical improvement and task accuracy ($r = 0.29$, $p = 0.299$) or bias scores ($r_{happy} = -0.21$, $p = 0.453$; $r_{sad} = 0.26$, $p = 0.354$; $r_{threatening} = -0.31$, $p = 0.257$).

fMRI Social Reward/Face Task

Activation

Within the context of the Face Task, there was a significant main effect of clinical improvement in the right middle frontal gyrus, such that across emotional faces (including social reward faces), decreased activation in this region related to a greater degree of clinical improvement (see **Figure 1A**). Additional significant activation clusters were evidenced in the cerebellum, as a function of degree of clinical improvement (see **Table 2**).

TABLE 2 | Significant clusters resulting from whole-brain analyses evaluating the association between clinical improvement and neural reactivity within the context of social reward ($N = 15$).

k	*F*	*x*	*y*	*z*	BA	Region
Whole-brain activation						
**CGI-I main effect (df = 1, 13)*						
80^{+}	22.4	37	21	30	9	Right middle frontal gyrus
Whole-brain left ventral striatum connectivity						
CGI-I × probe location (df = 1, 13)						
70	29.6	61	−37	−2	21	Right middle temporal gyrus
**CGI-I main effect (df = 1, 13)*						
90^{+}	30.4	−7	−53	4	19	Left lingual gyrus
77^{+}	30.4	−1	−61	44	7	Left precuneus
76^{+}	25.0	17	−71	6	18	Right lingual gyrus/ right cuneus
75^{+}	27.4	−7	−91	−4	17	Left lingual gyrus
58^{+}	47.3	−23	−7	−4	N/A	Left dorsal striatum
Whole-brain right ventral striatum connectivity						
**CGI-I main effect (df = 1, 13)*						
163	36.0	−17	−29	60	2, 3, 4	Left postcentral gyrus/ left precentral gyrus
81^{+}	24.2	−29	−5	56	6	Left middle frontal gyrus/ left precentral gyrus
75^{+}	45.4	−17	−61	52	7	Left precuneus
74	30.4	43	−31	56	40	Right postcentral gyrus
59	33.2	−29	−65	26	39	Left angular gyrus
59	37.8	33	−33	38	40	Right inferior parietal lobule
Whole-brain left amygdala connectivity						
**CGI-I × face emotion (df = 3, 39)*						
73	10.4	65	−17	26	2	Right postcentral gyrus
Whole-brain right amygdala connectivity						
**CGI-I × face emotion (df = 3, 39)*						
98	12.8	11	−73	−20	N/A	Right declive/ right cerebellum
71	9.0	−13	−75	−40	N/A	Left inferior semi-lunar lobule/ left cerebellum
CGI-I × probe location (df = 1, 13)						
148	42.2	47	33	26	9	Right middle frontal gyrus
Probe location main effect (df = 1, 13)						
149	36.3	−23	45	24	10	Left superior frontal gyrus/ left middle frontal gyrus

*Contrasts that did not yield significant clusters are not listed in this table. * indicates a contrast of interest; $^{+}$ indicates clusters from which values were extracted and presented in **Figures 1**, **2**. BA, brodmann area; CGI-I, Clinical Global Impressions, Improvement Scale (Guy, 1976).*

Connectivity

There was a main effect of clinical improvement on right and left ventral striatum connectivity with multiple posterior regions in the Face Task, including lingual gyrus, precuneus, angular gyrus, as well as middle frontal gyrus, inferior parietal lobule, and dorsal striatum (see **Figure 2**). Across all clusters, clinical improvement was associated with less connectivity between the ventral striatum and posterior regions, with the exception of the left ventral striatum to left dorsal striatum connectivity. Within that cluster, clinical improvement was associated with increased connectivity (see **Figure 2A**). Additionally, clusters representing right amygdala connectivity

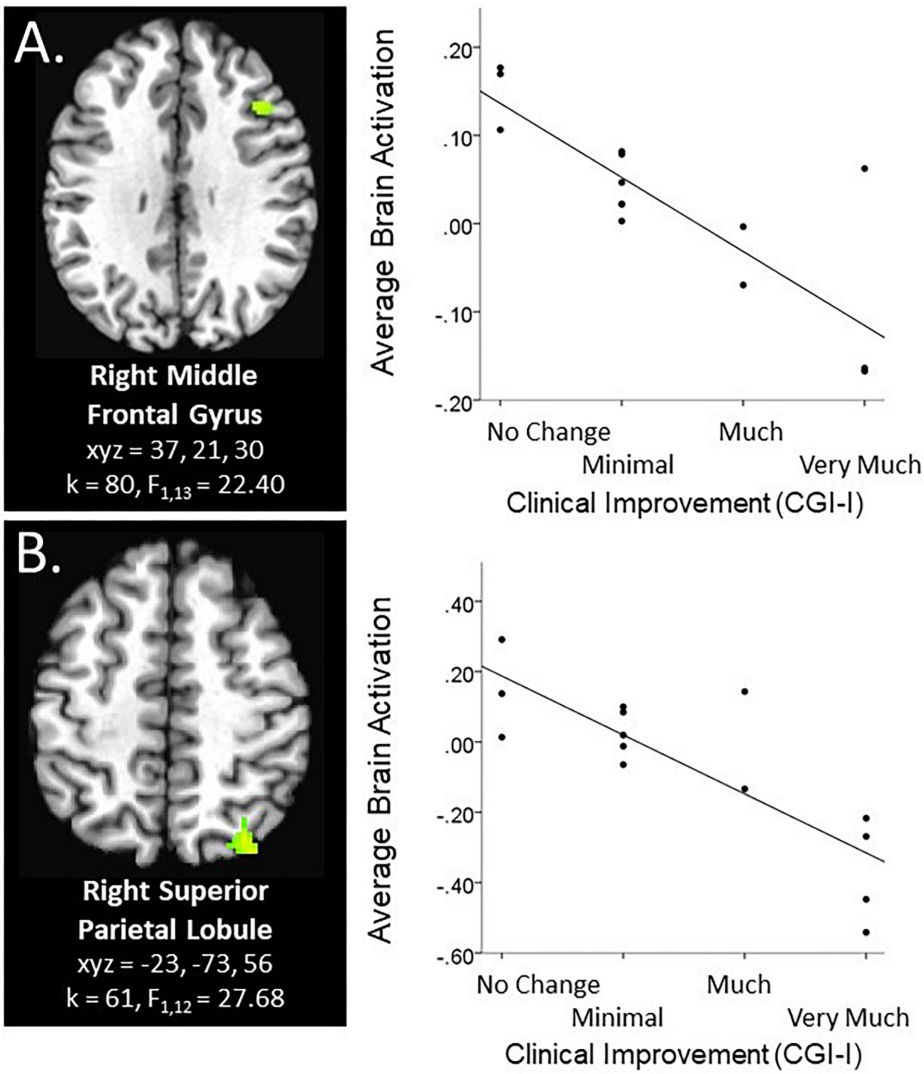


FIGURE 1 | Main effect of clinical improvement during Social and Non-social reward tasks. Scatterplots of significant brain activation averaged across all task conditions in the specified paradigm represent the main effect of CGI-I in **(A)** the right middle frontal gyrus during the social reward paradigm (Face Task; *N* = 15), and **(B)** the right superior parietal lobule during the anticipation phase of the non-social reward paradigm (Piñata Task; *N* = 14). Brain images represent axial sections (left = left) with threshold set at whole-brain FDR-corrected $p < 0.05$. Scatterplots are displayed for illustrative purposes to depict the direction of association. Additionally, CGI-I (i.e., clinical improvement; Guy, 1976) anchors are displayed inversely to improve readability and restricted to reflect the range observed within this dataset.

with cerebellum were significant for Clinical Improvement × Face Emotion (see **Table 2**). Furthermore, the Clinical Improvement × Face Emotion interaction yielded significant left amygdala and post-central gyrus connectivity (see **Table 2**); however, *post hoc* analyses revealed that this cluster does not survive *post hoc* evaluation for potential confounding variables and may be outlier-driven.

Exploratory connectivity analysis

An exploratory Clinical Improvement × Face Emotion × Probe Location interaction in the social reward task revealed significant connectivity between the left ventral striatum and medial frontal gyrus. *Post hoc* analyses indicated that the ventral striatum-medial frontal connectivity cluster was driven by differences in response to happy faces (i.e., the social reward stimulus). Heightened clinical improvement was associated with greater connectivity during happy/congruent trials; however, less connectivity was observed during happy/incongruent trials (see **Table 3** and **Figure 3A**). Similarly, using the right amygdala as the seed-region of interest, the 3-way interaction evidenced significant connectivity between the right amygdala and multiple temporal and frontal clusters, including bilateral temporo-parietal junction, insula, and prefrontal cortex. Specifically, the magnitude of right amygdala connectivity with these temporal and frontal regions differed as a function of degree of clinical improvement and depended on face

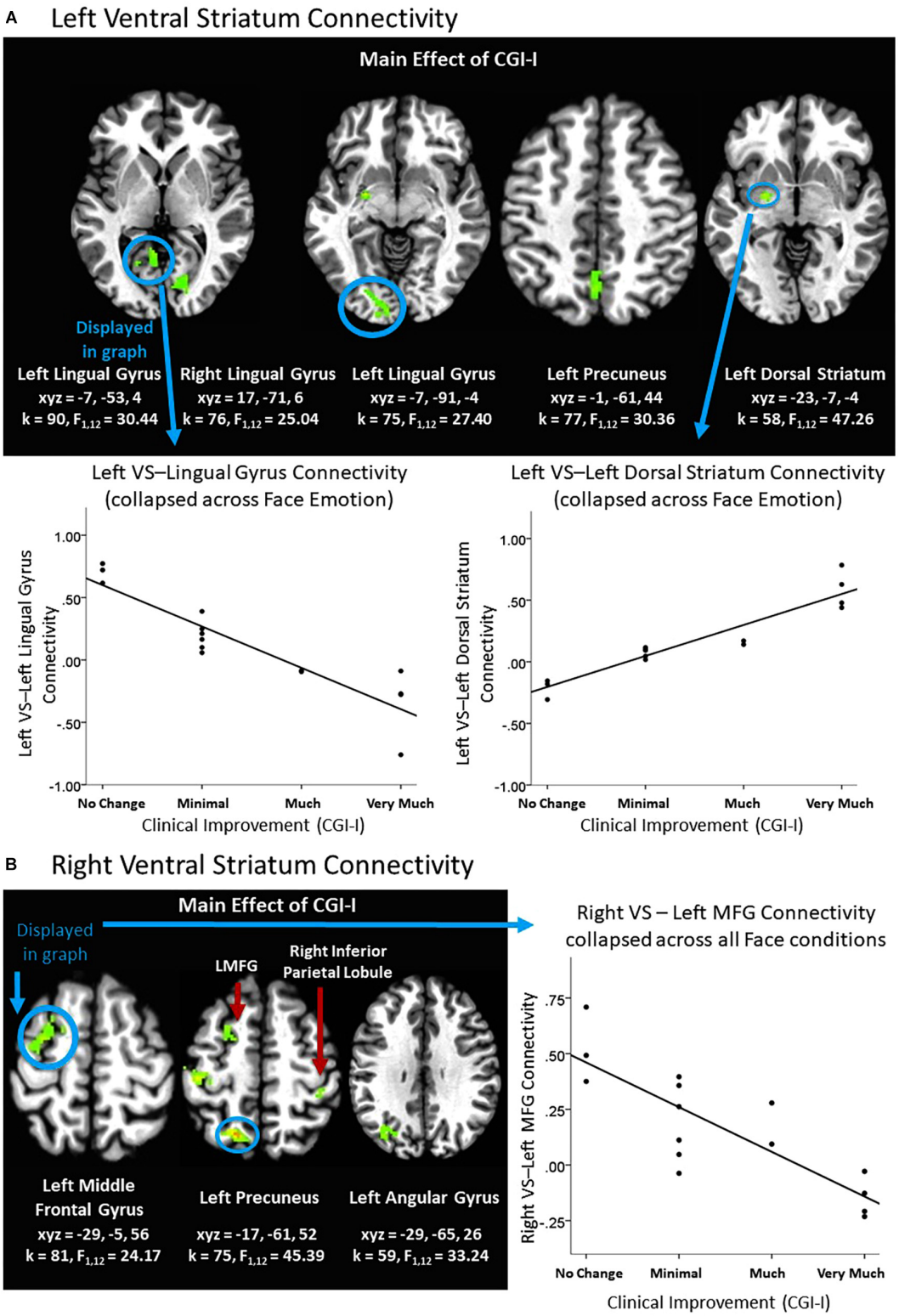


FIGURE 2 | Effects of clinical improvement on ventral striatum connectivity within the context of social reward. **(A)** Left ventral striatum (VS) connectivity; **(B)** Right ventral striatum connectivity. $N = 15$. Brain images represent axial sections (left = left) with threshold set at whole-brain FDR-corrected $p < 0.05$. Scatterplots of the significant connectivity effects for the indicated clusters are displayed for illustrative purposes to depict the direction of association; patterns are similar for other clusters within each contrast. CGI-I (i.e., clinical improvement; Guy, 1976) anchors are displayed inversely to improve readability and restricted to reflect the range observed within this dataset. L, left; MFG, middle frontal gyrus; R, right; TPJ, temporo-parietal junction.

TABLE 3 | Significant clusters resulting from exploratory 3-way interactions evaluating the association between clinical improvement and neural reactivity within the context of social reward (N = 15).

k	*F*	*x*	*y*	*z*	BA	Region
Whole-brain activation						
CGI-I × face emotion × probe location (df = 3, 39)						
154	12.4	1	−67	−22	N/A	Right pyramis/ right cerebellum
77	7.9	−37	−69	−40	N/A	Inferior semi-lunar lobule
Whole-brain left ventral striatum connectivity						
CGI-I × face emotion × probe location (df = 3, 39)						
85+	9.1	−7	9	62	6	Bilateral medial frontal gyrus/ left superior frontal gyrus
71**	10.2	−13	45	42	8	Left medial frontal gyrus/ left superior frontal gyrus
Whole-brain right ventral striatum connectivity						
CGI-I × face emotion × probe location (df = 3, 39)						
81	14.1	−1	−61	−18	N/A	Bilateral declive/ bilateral culmen/ cerebellar vermis/ left cerebellum
73	9.0	3	−39	−38	N/A	Left cerebellar tonsil/ left cerebellum/ lobule IX
Whole-brain right amygdala connectivity						
CGI-I × face emotion × probe location (df = 3, 39)						
162+	13.8	−55	−51	16	39, 22, 13	Left temporo-parietal junction
155+	10.0	−59	1	12	22, 13, 6	Left insula/ left superior temporal gyrus/ left precentral gyrus
85+	9.6	45	−33	14	41	Right temporo-parietal junction
77+	10.9	−29	51	26	9	Left superior frontal gyrus
61+	9.6	−49	31	20	46	Left middle frontal gyrus
58	10.1	37	−71	−32	N/A	Right pyramis/ right cerebellum

*Contrasts that did not yield significant clusters are not listed in this table. ** indicates findings not primarily driven by brain responses to happy faces; + indicates clusters from which values were extracted and presented in **Figure 3**. BA, brodmann area; CGI-I, Clinical Global Impressions, Improvement Scale (Guy, 1976).*

emotion type, as well as congruency. Like findings in the ventral striatum, these interactions were driven by social reward. Participants evidencing less clinical improvement in response to BBT exhibited greater connectivity during happy/congruent trials compared to happy/incongruent trials. In contrast, participants with the most clinical improvement evidenced the opposite pattern: greater connectivity during happy/incongruent trials compared to happy/congruent trials. *Post hoc* analyses supported that correlations between clinical improvement and amygdala connectivity for happy/congruent vs. happy/incongruent trials differed significantly in all clusters (see **Figure 3B**).

Of note, there were additional significant clusters for the Clinical Improvement × Probe Location (see **Table 2**) and the Clinical Improvement × Face Emotion × Probe Location (see **Table 3**) contrasts, but these interactions were not driven by social reward faces.

fMRI Non-social Reward/Piñata Task

Activation

Within the context of the Piñata Task, during the anticipation period, increased clinical improvement related to decreased activation in the superior parietal lobule across reward and no reward conditions (see **Figure 1B**). During the feedback period of the Piñata Task, activation significantly varied as a function of task conditions; however, contrasts that included clinical improvement were not statistically significant. Additional significant activation clusters are reported in **Table 4**.

Connectivity

Differences in connectivity as a function of degree of clinical improvement were evident during the Feedback period of the Piñata task. When the ventral striatum was used as the seed region of interest, left and right ventral striatum connectivity analyses yielded significant clusters in multiple medial prefrontal and parietal regions for the Clinical Improvement × Reward Condition interaction during the Feedback period (see **Table 4** and **Figures 4A,B**). Across all of these clusters, greater clinical improvement was associated with less connectivity during reward conditions yet greater connectivity during the no reward conditions. In addition, greater connectivity between the right ventral striatum and right middle frontal gyrus was observed across reward conditions (see **Figure 4B**). The Clinical Improvement x Reward Condition interaction also yielded significant clusters reflecting connectivity between the left amygdala and right middle occipital gyrus and between the right amygdala and the left precentral gyrus (see **Figures 4C,D**). *Post hoc* analyses within these clusters supported that greater clinical improvement was associated with less connectivity between the left amygdala and right middle occipital gyrus during reward conditions yet greater connectivity between these regions during the no reward conditions across clusters. However, the connectivity patterns between the right amygdala and left precentral gyrus evidenced the opposite pattern of findings.

Exploratory connectivity analysis

An exploratory Clinical Improvement x Reward Condition x Performance interaction during the feedback period of the Piñata Task revealed significant left and right amygdala connectivity with multiple temporal and parietal regions, including temporal-parietal junction (see **Table 5**). In these regions, increased clinical improvement was associated with greater amygdala connectivity when participants either received a reward for hitting the target (i.e., reward/hit condition) or missed the target when no reward was expected (i.e., no reward/miss condition). In contrast, increased clinical improvement was associated with lower levels of amygdala connectivity when participants either hit the target but did not receive a reward (i.e., no reward/hit condition) or missed the target when a reward was expected (i.e., reward/miss condition). *Post hoc* analyses indicated that the relationship between clinical improvement and brain activation in reward vs. no reward conditions differed significantly for both hit and miss trials, across all clusters (see **Figure 5**).

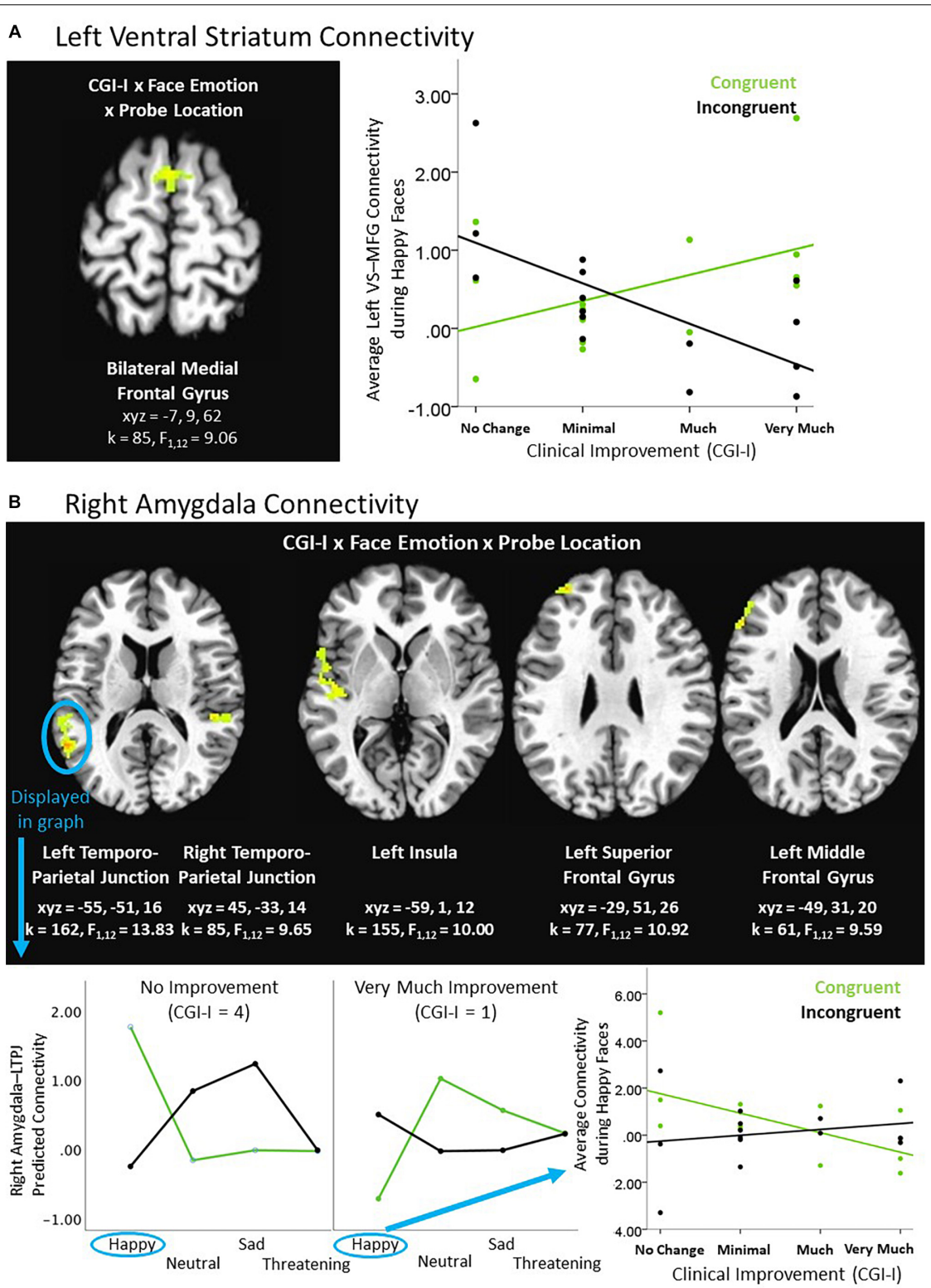


FIGURE 3 | Exploratory higher level interactive effects of clinical improvement on ventral striatum and amygdala connectivity within the context of social reward. **(A)** Left ventral striatum (VS) connectivity; **(B)** Right amygdala connectivity. $N = 15$. Brain images represent axial sections (left = left) with threshold set at whole-brain FDR-corrected $p < 0.05$. Scatterplots of the significant connectivity effects for the indicated clusters are displayed for illustrative purposes to depict the direction of association; patterns are similar for other clusters within each contrast. CGI-I (i.e., clinical improvement; Guy, 1976) anchors are displayed inversely to improve readability and restricted to reflect the range observed within this dataset. L, left; MFG, middle frontal gyrus; R, right; TPJ, temporo-parietal junction.

TABLE 4 | Significant clusters resulting from whole-brain analyses evaluating the association between clinical improvement and neural reactivity within the context of non-social reward (*N* = 14).

k	*F*	*x*	*y*	*z*	BA	Region
Whole-brain activation: cue period						
**CGI-I main effect (df = 1, 12)*						
62	24.3	23	−67	−42	N/A	Right inferior semilunar lobule
61^{+}	27.7	23	−73	56	7	Right superior parietal lobule
Reward condition main effect (df = 1, 12)						
301	100	31	−77	18	19	Right middle occipital gyrus
240	40.6	−29	−83	18	19	Middle occipital gyrus
153	36.9	−27	−65	−4	19	Left declive
146	34.7	23	−67	32	7	Right precuneus
88	37.4	−17	−71	38	7	Left precuneus
82	38.5	55	−27	6	22	Right superior temporal gyrus
Whole-brain activation: feedback period						
Reward condition main effect (df = 1, 12)						
79	40.9	1	33	34	6	Right medial frontal gyrus
Performance main effect (df = 1, 12)						
2047	100.0	9	−81	6	18	Lingual gyrus
1657	100.0	−1	31	24	32	Right medial frontal gyrus
841	96.0	53	−45	12	22	Right superior temporal gyrus
733	100.0	37	17	8	13	Right insula
370	67.2	35	5	34	6	Right precentral gyrus
275	99.0	−31	11	14	13	Left insula
262	40.5	−5	−27	30	23	Left cingulate gyrus
253	64.3	33	39	30	10	Right middle frontal gyrus
173	32.1	−25	51	22	10	Left superior frontal gyrus
160	56.5	37	−37	−6	19	Right parahippocampal gyrus
136	53.4	3	−47	44	7	Right precuneus
122	24.9	39	59	12	10	Right middle frontal gyrus
101	44.5	9	−11	8	N/A	Right thalamus
89	34.2	−33	−51	−30	N/A	Left culmen
62	29.0	−19	−33	32	N/A	Left cingulate gyrus
Whole-brain left ventral striatum connectivity: feedback period						
**CGI-I × reward condition (df = 1, 12)*						
69^{+}	41.5	23	47	2	10	Right superior frontal gyrus
68^{+}	32.4	9	33	−2	32	Right anterior cingulate
Whole-brain right ventral striatum connectivity: feedback period						
**CGI-I × reward condition (df = 1, 12)*						
99^{+}	31.1	41	−63	32	7, 39	Right superior parietal lobule/ right inferior parietal lobule
62^{+}	34.6	−33	−71	42	19, 7	Left precuneus/ left superior parietal lobule
Reward condition x performance (df = 1, 12)						
406	42.1	37	47	22	10	Right middle frontal gyrus/ right superior frontal gyrus
129	32.1	31	11	52	6, 8	Right superior frontal gyrus/ right middle frontal gyrus
**CGI-I main effect (df = 1, 12)*						
65^{+}	23.6	47	51	10	10	Right middle frontal gyrus
Whole-brain left amygdala connectivity: feedback period						
**CGI-I × reward condition (df = 1, 12)*						
87	52.3	33	−93	4	18	Right middle occipital gyrus
Whole-brain right amygdala connectivity: feedback period						
**CGI-I × reward condition (df = 1, 12)*						
80	45.3	−39	−1	26	6	Left precentral gyrus
Reward condition main effect (df = 1, 12)						
57	50.2	7	−53	32	31	Right precuneus

*Contrasts that did not yield significant clusters are not listed in this table. * indicates a contrast of interest; $^{+}$ indicates clusters from which values were extracted and presented in **Figures 1**, **4**. BA, brodmann area; CGI-I, Clinical Global Impressions, Improvement Scale (Guy, 1976).*

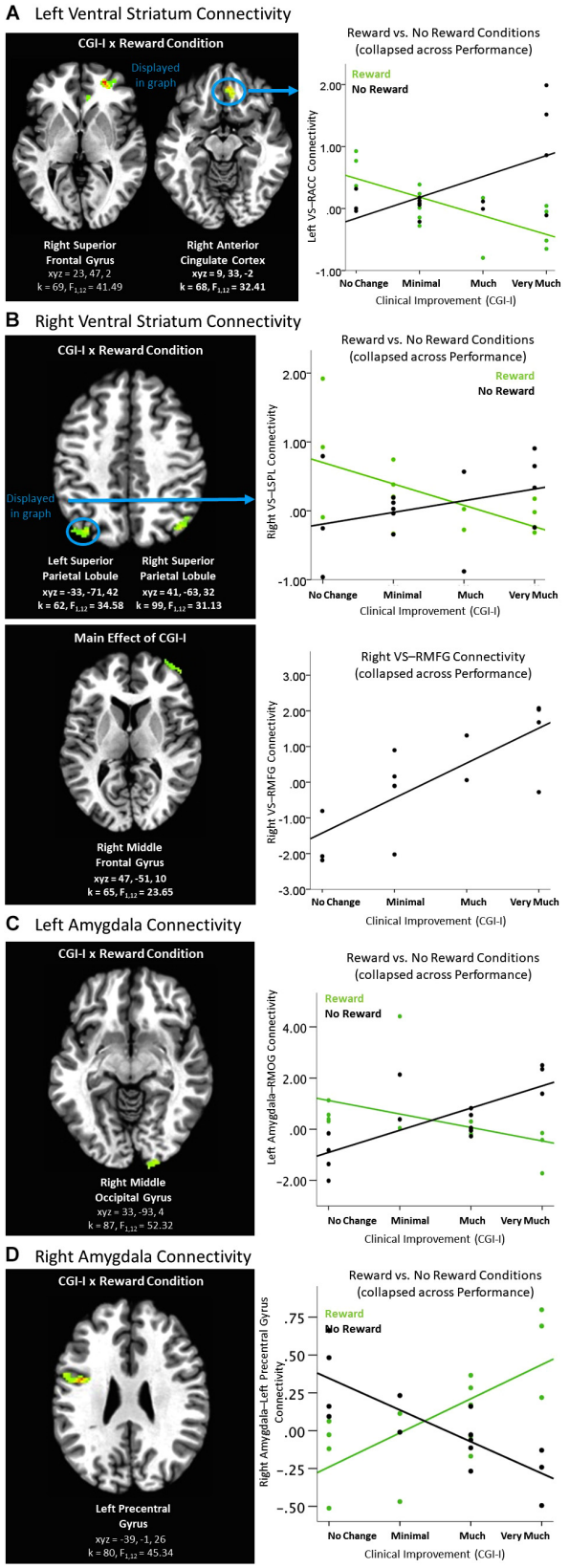


FIGURE 4 | Continued

FIGURE 4 | Effects of clinical improvement on ventral striatum and amygdala connectivity when receiving feedback within the context of non-social reward. **(A)** Left ventral striatum (VS) connectivity; **(B)** Right ventral striatum connectivity; **(C)** Left amygdala connectivity; **(D)** Right amygdala connectivity. $N = 14$. Brain images represent axial sections (left = left) with threshold set at whole-brain FDR-corrected $p < 0.05$. Scatterplots of the significant connectivity effects for the indicated clusters are displayed for illustrative purposes to depict the direction of association; patterns are similar for other clusters within each contrast. CGI-I (i.e., clinical improvement; Guy, 1976) anchors are displayed inversely to improve readability and restricted to reflect the range observed within this dataset. ACC, anterior cingulate cortex; L, left; MFG, middle frontal gyrus; MOG, middle occipital gyrus, R, right; SPL, superior parietal lobule; TPJ, temporo-parietal junction.

TABLE 5 | Significant clusters resulting from exploratory 3-way interactions evaluating the association between clinical improvement and neural reactivity within the context of non-social reward ($N = 14$).

k	*F*	*x*	*y*	*z*	BA	Region
Whole-brain left amygdala connectivity: feedback period						
CGI-I × reward condition × performance (df = 1, 12)						
152	63.0	−29	−57	46	7	Superior parietal lobule[a]
Whole-brain right amygdala connectivity: feedback period						
CGI-I × reward condition × performance (df = 1, 12)						
154[+]	51.5	47	−51	10	22	Right temporo-parietal junction
75[+]	32.6	−49	−1	−2	22	Left superior temporal gyrus
65[+]	57.3	45	−57	14	39, 22	Right middle temporal gyrus
59	47.5	5	−23	−2	N/A	Right brainstem/ right thalamus

Contrasts that did not yield significant clusters are not listed in this table. [a] *indicates a cluster that failed to maintain significance when controlling for parent-rated youth anxiety, irritability, or depression.* [+] *indicates clusters from which values were extracted and presented in* ***Figure 5****. BA, brodmann area; CGI-I, Clinical Global Impressions, Improvement Scale (Guy, 1976).*

Comparison of Findings by Task Type

Our findings implicated connectivity differences during happy-neutral/congruent vs. happy-neutral/incongruent conditions in the Face Task and during reward/hit vs. reward/miss conditions in the Piñata Task. As such, we conducted an exploratory whole-brain ANCOVA to directly compare connectivity within the context of social vs. non-social reward, in relation to clinical improvement as a function of treatment. Contrast images, representing happy/congruent vs. happy/incongruent and reward/hit vs. reward/miss connectivity for left and right amygdalae as well as left and right ventral striata, were calculated and entered into separate 3dMVM models. Task type (social reward, non-social reward) was included as a categorical, within-subjects variable and clinical improvement was maintained as a dimensional, between-subjects variable.

Activation

We were unable to statistically evaluate differences in whole-brain activation across tasks due to a lack of findings dependent on clinical improvement scores during the feedback period of the Piñata Task.

Connectivity

Clinical Improvement × Task Type (i.e., social reward, non-social reward) did not yield significant clusters indicative of

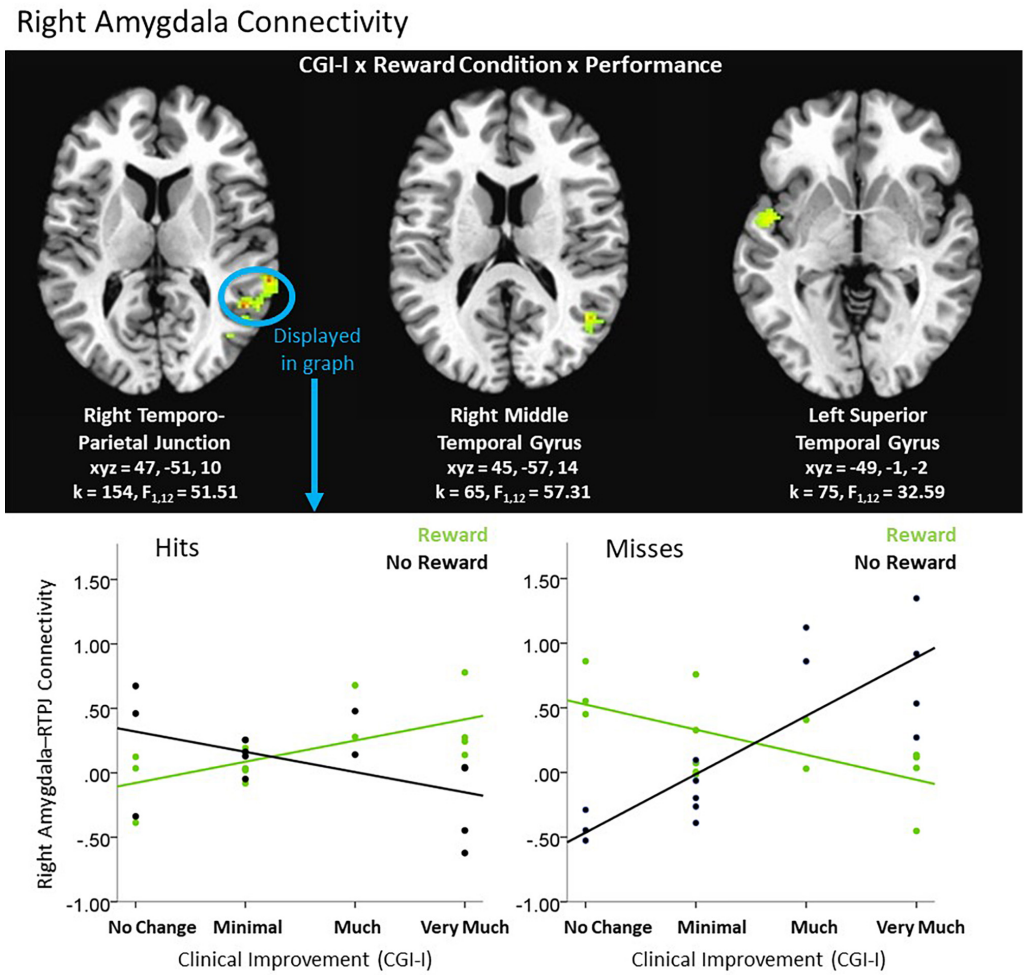


FIGURE 5 | Exploratory higher level interactive effects of clinical improvement on right amygdala connectivity when receiving feedback within the context of non-social reward. *N* = 14. Brain images represent axial sections (left = left) with threshold set at whole-brain FDR-corrected $p < 0.05$. Scatterplots of the significant connectivity effects for the indicated clusters are displayed for illustrative purposes to depict the direction of association; patterns are similar for other clusters within each contrast. CGI-I (i.e., clinical improvement; Guy, 1976) anchors are displayed inversely to improve readability and restricted to reflect the range observed within this dataset. R, right; TPJ, temporo-parietal junction.

connectivity between bilateral amygdalae or ventral striata and other regions in the brain.

Additional Analyses

Additional analyses were run to evaluate the impact of potential confounding factors on the reported results. Hypothesized confounds utilized in these analyses included residual head motion, age, gender, concurrent anxiety, concurrent depression, length of time since post-treatment assessment, and task order. All main results maintained significance after the inclusion of these factors in statistical models.

DISCUSSION

The current study aimed to add to the sparse literature on reward processing in pediatric anxiety and depression. Of note, the focus of this work was to evaluate neural correlates of a successful unified protocol, rather than to determine exclusive and common correlates of depression and anxiety in youth. Future research can build on the results of our work to distinguish neural correlates in these highly comorbid conditions. This investigation is unique in its focus on social as well as non-social reward tasks, use of a clinically impaired service-seeking sample, and effort to probe associations between reward and clinical improvement in a treated sample. Indeed, this study is the only study to investigate reward processing in a treatment context within a sample of anxious youth and one of only four to do so in pediatric depression. Moreover, this was the only study to investigate multiple tasks (i.e., social and non-social) within the same individuals, enabling the evaluation of task context effects. The study design was exploratory and hypothesis-generating in nature; indeed, findings should be interpreted cautiously due to the small sample size. Perhaps the most important message

from this work is that evaluating the relationship between clinical improvement and reward processing neural circuitry, particularly within the context of transdiagnostic samples and treatment paradigms, appears promising for further investigation. Our findings indicate that integrating behavioral neuroscience tools into clinical science can provide a complementary way to "look under the hood" of treatments, and thus inform the generation of more targeted, mechanistically based treatments. Broadly, we found that social and non-social reward paradigms triggered patterns of connectivity in frontal and striatal regions associated with social cognition and reward, and these patterns reliably differed by level of clinical improvement obtained over the course of treatment. Patterns were consistent with the literature at large and suggest value in further efforts to probe shifts in reward processing as a mechanism of treatment-related changes in internalizing pathology in youth.

Findings further illustrate how data from multiple within-subject tasks can be incorporated in a single study and underscore the importance of task context for interpreting differences in brain function. Although both reward and emotion regulation networks were implicated in both the social and non-social reward tasks, the specific regions as well as the direction of differences (e.g., greater vs. less activation/connectivity) depended on task context and conditions. Thus, when summarizing the literature, it may not be enough to state that observed differences in activation or connectivity of a particular region is associated with a disease state, or that reducing or increasing brain function in those regions is the mechanism by which clinical improvement occurs. Rather, our study which compares and contrasts results from two tasks within the same participants suggests that differences in activation or connectivity appear to be highly dependent on task context. More direct comparisons of neural responses to social and non-social feedback, particularly in larger samples, are needed in future work, as findings have implications for the future of clinical care and evaluation of treatment mechanisms.

Although the specific patterns of results differed by task, clinical improvement was associated with alterations in regions involved in emotion regulation, in addition to reward, across both tasks. Observed differences as a function of degree of clinical improvement could reflect "normalization" of circuitry or compensatory mechanisms. This finding has intriguing implications for understanding the integration of emotion regulation and reward processing in treatment. As stated above, both anxious and depressed samples of youth have evidenced aberrant patterns of reward processing and emotion regulation, compared to healthy peers. The guided behavioral activation in concert with targeted skill building included in BBT may have interacted more effectively with reward circuitry compared to the more varied care received by those in ARC. Thus, successful treatment of internalizing pathology may require integration of emotion regulation and reward processing regions, such that youth are able to learn to modulate their emotions – which may in itself be rewarding. Improved emotion regulation skills and exposure in this treatment may have been sufficient to alter both reward and emotion regulation circuitry without an overt cognitive component.

Of note, significant contrasts in the Face Task were driven by the social reward stimulus (i.e., happy faces) in relation to clinical improvement. This is particularly remarkable given that prior work documented that across the lifespan, faces as social reward have been shown to be less impactful in motivating behavior change than monetary incentives (Kohls et al., 2009). Furthermore, the employed tasks were not perfectly parallel in terms of their assessment of social vs. non-social reward. The Face Task paradigm involved the passive viewing of rewarding faces, in contrast to the Piñata Task's dependence on participant action to trigger the reward. Nevertheless, stronger connectivity between the amygdala and multiple frontal and temporal areas implicated in reward-based learning, social prediction error, and reappraisal of emotions triggered by social situations (e.g., Grecucci et al., 2013); but, weaker coupling between the ventral striatum and medial frontal gyrus, another area implicated in social cognition (Amodio and Frith, 2006) was observed when the Face Task probe was located under the neutral rather than happy face (i.e., incongruent trial). BBT's focus on exposure may improve anxiety/depression symptoms by "incentivizing" engagement in adaptive activities, including social interactions; that is, repeated exposure and associated habituation may help participants re-define activities deemed dangerous as inherently rewarding, through the practice of approach behaviors and emotion regulation skills (i.e., a behavioral activation model). In addition, increased clinical improvement was associated with decreased activation in areas associated with re-orienting attention (Japee et al., 2015) and emotion reappraisal (Grecucci et al., 2013). This may moreover suggest that those who improved as a function of BBT may be less prone to distraction by internal processes (e.g., rumination, worry) and more able to maintain focus on their environment, perhaps supporting increased approach behaviors. Whereas we have taken this initial step of comparing tasks, future research can add to the literature base describing these relations using more parallel social vs. non-social task paradigms.

Within pediatric anxiety (e.g., Guyer et al., 2008) and depression (e.g., Silk et al., 2012), social reward processing has been a research target due to the characteristic fears of social evaluation by peers in internalizing youth. Evidence has suggested that youth exhibit a negative bias during social interactions, interpreting peer behavior as overly critical and expecting interactions to be negative in support of their misappraisal. Our findings with social reward stimuli (i.e., happy faces) are consistent with the idea that clinical improvement may occur through amelioration of this negative bias and greater valuation of social reward. Nevertheless, faces are relatively passive stimuli to assess reward processing, and the faces utilized by this task reflect adults, rather than same-aged peers. Moving forward, studies that build on our findings to further investigate social reward processing as a mechanism of treatment response may wish to consider more interactive tasks (e.g., Chatroom Task, Guyer et al., 2008; Virtual School, Jarcho et al., 2013) that include age-appropriate faces and peer evaluation as feedback, as these may be more ecologically valid for adolescents.

Within the context of non-social reward, differential coupling of the affective and cognitive control networks by condition was apparent. Increased clinical improvement was associated with increased connectivity between the amygdala and areas associated with cognitive control and decision making after positive or neutral experiences (e.g., obtaining a reward, missing when no reward was promised). In contrast, the same regions evidenced decreased connectivity in response to frustrating experiences (e.g., hitting the target when no reward was promised, missing the target when a reward was available). This may suggest more effective recruitment of emotion regulation strategies (e.g., decreased influence of emotional responses in decision making after aversive events) so as to maintain adaptive behavior. Interestingly, the areas implicated in non-social reward connectivity analyses also have been shown to be part of social cognition circuitry. As similar regions emerged across tasks, this serves as support that both tasks probe reward-related processes, which may in turn underlie clinical improvement.

Several limitations warrant consideration. First, although our sample size (N = 15) is comparable to that of the few other pediatric studies probing associations between neural mechanisms of reward processing and treatment response (e.g., n = 10, Straub et al., 2015; n = 13, Forbes et al., 2010; n = 15, Mori et al., 2016), our sample size was modest and represents a fraction of the participants who originally participated in the clinical trial (similar to comparable studies as well). Thus, our power was limited and our findings may not generalize to the broader population of youth. Replicating findings within a larger sample could strengthen interpretations and power more complex statistical models. Furthermore, the lack of interest in re-engaging in research suggests potential for sampling bias, as there may be differences between those who completed their scans and those who refused on dimensions not measured by the current battery. Nevertheless, given the paucity of studies characterizing neural treatment mechanisms, and as the only study to include multiple tasks within youth, this study serves as a proof-of-concept for future work.

Second, scanning occurred post-treatment, which limits our ability to determine whether the neural profiles identified are present prior to or as a consequence of clinical improvement. It is possible that our findings reflect that clinical improvement promoted the observed patterns of brain reactivity, suggesting that brain patterns were in fact outcomes of response. However, it is also possible that the observed brain patterns were pre-existing and therefore predictors of treatment outcome. A third option is that clinical improvement and observed brain patterns were both related to a third, unmeasured variable. Additionally, substantial time passed between treatment completion and the scan. Although the additional analyses suggested that our findings primarily reflected neither the amount of time passed nor concurrent symptoms, brain patterns may have nonetheless been influenced by individual, unmeasured characteristics. Moreover, the lack of a comparison group complicates the interpretation of observed patterns of findings, particularly as they relate to what we might expect from healthy youth. Thus, our findings are correlational and speak to neural reactivity in response to intervention. Replication in a study designed to include pre-treatment, post-treatment and follow-up fMRI scans could allow for causal inferences to be made. Such a design would also allow for the maintenance of randomization, to better understand the impact of specific treatment paradigms on changes in reward-related circuitry, and vice versa. Future trials that incorporate imaging at multiple time points across multiple treatment arms, including a control condition can use these findings to generate hypotheses to establish directionality of change.

Change in clinical presentation after the receipt of an intervention has implications for participants' abilities to learn skills within a therapeutic context, and suggests support for treatment match. Findings may also suggest that BBT (and potentially behavioral interventions more broadly) may capitalize on the integration of emotion regulation and social/non-social reward processing networks to promote behavioral activation. Taken together, conclusions should be viewed as preliminary data aimed at hypothesis generation for future work. Ultimately, incorporating behavioral neuroscience tools into clinical science will improve treatment outcomes, as identifying predictors and mechanisms of treatment response is crucial groundwork to move toward a precision medicine approach, including mechanism-based treatment to the individuals whose neural profiles indicate they would benefit the most. This work offers evidence of value in comparing complex data from multiple task contexts and contributes to the establishment of a literature base of neural mechanisms of treatment response in internalizing youth.

DATA AVAILABILITY

The datasets for this study will not be made publicly available because the data are undergoing secondary analyses in preparation for additional publications.

AUTHOR CONTRIBUTIONS

KS, VW, and JW were jointly involved in the study conceptualization and protocol development. KS spearheaded the recruitment for the neuroimaging follow-up, data collection, data preparation, and writing of the manuscript. MK-L led the analytical efforts with ML's assistance. VW contributed the data from the original RCT and approved the use of the sample for the neuroimaging follow-up. JW provided training to facilitate the study completion, supervised the data collection and analytical efforts, and contributed to the writing of the manuscript. All authors critically reviewed the manuscript and approved it prior to submission.

FUNDING

The original randomized controlled trial described was supported by the National Institute of Mental Health

(Grant Numbers 5R01MH084935 to VW and 5R01MH084916 to Dr. David A. Brent). The neuroimaging follow-up component was supported by the National Institutes of Health UL1TR001442 Clinical and Translational Research Institute Pilot Grant and NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation, both awarded to JW.

ACKNOWLEDGMENTS

We would like to thank the families who participated in this study, without whom this project would not have been possible. We would also like to thank Jill Weisberg, Ph.D., for her guidance on analytical techniques and general support of data management and processing. Many thanks to the personnel at UC San Diego's Center for Magnetic Resonance Imaging, particularly Aaron Jacobson, M.A., for their assistance in fMRI training and efforts to ensure high-quality data collection. We are grateful to Rick Reynolds, M.S., and Gang Chen, Ph.D., of the Scientific and Statistical Computing Core of the National Institute of Mental Health for their assistance with the data analyses in AFNI. Finally, we would like to thank the research assistants in the Translational Emotion Neuroscience and Development Laboratory (TEND Lab), particularly Carly Farrington, Ysabella Panggat, and Geneva Toledo, for their assistance in the data collection and management, and David A. Brent, M.D., for his role as the BBT principal investigator for the Pittsburgh site.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2019.00177/full#supplementary-material

REFERENCES

Abend, R., Pine, D. S., and Bar-Haim, Y. (2014). *The TAU-NIMH Attention Bias Measurement Toolbox*. Available at: http://people.socsci.tau.ac.il/mu/anxietytrauma/research/ (accessed April 26, 2016).

Amodio, D. M., and Frith, C. D. (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nat. Rev. Neurosci.* 7, 268–277. doi: 10.1038/nrn1994

Angold, A., Costello, E. J., Pickles, A., Winder, F., and Silver, D. (1987). The development of a questionnaire for use in epidemiological studies of depression in children and adolescents. *Int. J. Methods Psychiatr. Res.* 5, 237–249.

Benson, B. E., Guyer, A. E., Nelson, E. E., Pine, D. S., and Ernst, M. (2015). Role of contingency in striatal response to incentive in adolescents with anxiety. *Cogn. Affect. Behav. Neurosci.* 15, 155–168. doi: 10.3758/s13415-014-0307-6

Birmaher, B., Khetarpal, S., Brent, D., Cully, M., Balach, L., Kaufman, J., et al. (1997). The screen for child anxiety related emotional disorders (SCARED): scale construction and psychometric characteristics. *J. Am. Acad. Child Adolesc. Psychiatry* 36, 545–553. doi: 10.1097/00004583-199704000-00018

Blackford, J. U., and Pine, D. S. (2012). Neural substrates of childhood anxiety disorders: a review of neuroimaging findings. *Child Adolesc. Psychiatr. Clin. N. Am.* 21, 501–525. doi: 10.1016/j.chc.2012.05.002

Burkhouse, K. L., Kujawa, A., Klumpp, H., Fitzgerald, K. D., Monk, C. S., and Phan, K. L. (2017). Neural correlates of explicit and implicit emotion processing in relation to treatment response in pediatric anxiety. *J. Child Psychol. Psychiatry* 58, 546–554. doi: 10.1111/jcpp.12658

Chantiluke, K., Halari, R., Simic, M., Pariante, C. M., Papadopoulos, A., Giampietro, V., et al. (2012). Fronto-striato-cerebellar dysregulation in adolescents with depression during motivated attention. *Biol. Psychiatry.* 71, 59–67. doi: 10.1016/j.biopsych.2011.09.005

Choudhury, S., Blackemore, S., and Charman, T. (2006). Social cognitive development during adolescence. *Soc. Cogn. Affect. Neurosci.* 1, 165–174. doi: 10.1093/scan/nsl024

Chu, B. C., Crocco, S. T., Esseling, P., Areizaga, M. J., Lindner, A. M., and Skriner, L. C. (2016). Transdiagnostic group behavioral activation and exposure therapy for youth anxiety and depression: initial randomized controlled trial. *Behav. Res. Ther.* 76, 65–75. doi: 10.1016/j.brat.2015.11.005

Chuang, J., Whitaker, K. J., Murray, G. K., Elliott, R., Hagan, C. C., Graham, J. M. E., et al. (2016). Aberrant brain responses to emotionally valent words is normalized after cognitive behavioral therapy in female depressed adolescents. *J. Affect. Disord.* 189, 54–61. doi: 10.1016/j.jad.2015.09.008

Compton, S. N., March, J. S., Brent, D., Albano, A. M., Weersing, V. R., and Curry, J. (2004). Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. *J. Am. Acad. Child Adolesc. Psychiatry* 43, 930–959. doi: 10.1097/01.chi.0000127589.57468.bf

Cox, R. W., Chen, G., Glen, D. R., Reynolds, R. C., and Taylor, P. A. (2017). FMRI clustering in AFNI: false-positive rates redux. *Brain Connect.* 7, 152–171. doi: 10.1089/brain.2016.0475

Dougherty, L. R., Schwartz, K. T. G., Kryza-Lacombe, M., Weisberg, J., Spechler, P. A., and Wiggins, J. L. (2018). Preschool- and school-age irritability predict reward-related brain function. *J. Am. Acad. Child Adolesc. Psychiatry* 57, 407–417. doi: 10.1016/j.jaac.2018.03.012

Dougherty, L. R., Smith, V. C., Bufferd, S. J., Carlson, G. A., Stringaris, A., Leibenluft, E., et al. (2014). DSM-5 disruptive mood dysregulation disorder: correlates and predictors in young children. *Psychol. Med.* 44, 2339–2350. doi: 10.1017/S0033291713003115

Ehrenreich-May, J., Rosenfield, D., Queen, A. H., Kennedy, S. M., Remmes, C. S., and Barlow, D. H. (2017). An initial waitlist-controlled trial of the unified protocol for the treatment of emotional disorders in adolescents. *J. Anxiety Disord.* 46, 46–55. doi: 10.1016/j.janxdis.2016.10.0060887-6185/

Ernst, M., Pine, D. S., and Hardin, M. (2006). Triadic model of the neurobiology of motivated behavior in adolescence. *Psychol. Med.* 36, 299–312. doi: 10.1017/S0033291705005891

Forbes, E. E. (2011). fMRI studies of reward processing in adolescent depression. *Neuropsychopharmacology* 36, 372–373. doi: 10.1038/npp.2010.164

Forbes, E. E., Hariri, A. R., Martin, S. L., Silk, J. S., Moyles, D. L., Fisher, P. M., et al. (2009). Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *Am. J. Psychiatry* 166, 64–73. doi: 10.1176/appi.ajp.2008.07081336

Forbes, E. E., May, J. C., Siegle, G. J., Ladouceur, C. D., Ryan, N. D., Carter, C. S., et al. (2006). Reward-related decision-making in pediatric major depressive disorder: an fMRI study. *J. Child Psychol. Psychiatry* 47, 1031–1040. doi: 10.1111/j.1469-7610.2006.01673.x

Forbes, E. E., Olino, T. M., Ryan, N. D., Birmaher, B., Axelson, D., Moyles, D. L., et al. (2010). Reward-related brain function as a predictor of treatment response in adolescents with major depressive disorder. *Cogn. Affect. Behav. Neurosci.* 10, 107–118. doi: 10.3758/CABN.10.1.107

Galvan, A. (2010). Adolescent development of the reward system. *Front. Hum. Neurosci.* 4:6. doi: 10.3389/neuro.09.006.2010

Garber, J., Brunwasser, S., Zerr, A., Schwartz, K. T. G., Sova, K., and Weersing, V. R. (2016). Treatment and prevention of depression and anxiety in youth: test of cross-over effects. *Depress. Anxiety* 33, 939–959. doi: 10.1002/da.22519

Garber, J., and Weersing, V. R. (2010). Comorbidity of anxiety and depression in youth: implications for treatment and prevention. *Clin. Psychol.* 17, 293–306. doi: 10.1111/j.1468-2850.2010.01221.x

Grecucci, A., Giorgetta, C., Bonini, N., and Sanfey, A. G. (2013). Reappraising social emotions: the role of inferior frontal gyrus, temporo-parietal junction and insula in interpersonal emotion regulation. *Front. Hum. Neurosci.* 7:523. doi: 10.3389/fnhum.2013.00523

Guy, W. (1976). "Clinical global impression scale," in *ECDEU Assessment Manual for Psychopharmacology*, ed. W. Guy (Rockville, MD: National Institute of Mental Health), 218–222.

Guyer, A. E., Choate, V. R., Detloff, A., Benson, B., Nelson, E. E., Pérez-Edgar, K., et al. (2012). Striatal functional alteration during incentive anticipation in

pediatric anxiety disorders. *Am. J. Psychiatry* 169, 205–212. doi: 10.1176/appi.ajp.2011.11010006

Guyer, A. E., Lau, J. Y. F., McClure-Tone, E. B., Parrish, J., Shiffrin, N. D., Reynolds, R. C., et al. (2008). Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. *Arch. Gen. Psychiatry* 65, 1303–1312. doi: 10.1001/archpsyc.65.11.1303

Helfinstein, S. M., Kirwan, M. L., Benson, B. E., Hardin, M. G., Pine, D. S., Ernst, M., et al. (2013). Validation of a child-friendly version of the monetary incentive delay task. *Soc. Cogn. Affect. Neurosci.* 8, 720–726. doi: 10.1093/scan/nss057

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., et al. (2010). Research domain criteria (RDoC) toward a new classification framework for research on mental disorders. *Am. J. Psychiatry* 167, 748–751. doi: 10.1176/appi.ajp.2010.09091379

Japee, S., Holiday, K., Satyshur, M. D., Mukai, I., and Ungerleider, L. G. (2015). A role of right middle frontal gyrus in reorienting of attention: a case study. *Front. Syst. Neurosci.* 9:23. doi: 10.3389/fnsys.2015.00023

Jarcho, J. M., Leibenluft, E., Walker, O. L., Fox, N. A., Pine, D. S., and Nelson, E. E. (2013). Neuroimaging studies of pediatric social anxiety: paradigms, pitfalls and a new direction for investigating the neural mechanisms. *Biol. Mood Anxiety Disord.* 3:14. doi: 10.1186/2045-5380-3-14

Jarcho, J. M., Romer, A. L., Shechner, T., Galvan, A., Guyer, A. E., Leibenluft, E., et al. (2015). Forgetting the best when predicting the worst: preliminary observations on neural circuit function in adolescent social anxiety. *Dev. Cogn. Neurosci.* 13, 21–31. doi: 10.1016/j.dcn.2015.03.002

Kaufman, J., Birmaher, B., Brent, D. A., Rao, U., Flynn, C., Moreci, P., et al. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. *J. Am. Acad. Child Adolesc. Psychiatry* 36, 980–988. doi: 10.1097/00004583-199707000-00021

Kerestes, R., Davey, C. G., Stephanou, K., Whittle, S., and Harrison, B. J. (2014). Functional brain imaging studies of youth depression: a systematic review. *Neuroimage Clin.* 4, 209–231. doi: 10.1016/j.nicl.2013.11.009

Kohls, G., Peltzer, J., Herpertz-Dahlmann, B., and Konrad, K. (2009). Differential effects of social and non-social reward on response inhibition in children and adolescents. *Dev. Sci.* 12, 614–625. doi: 10.1111/j.1467-7687.2009.00816.x

Kujawa, A., Swain, J. E., Hanna, G. L., Koschmann, E., Simpson, D., Connolly, S., et al. (2016). Prefrontal reactivity to social signals of threat as a predictor of treatment response in anxious youth. *Neuropsychopharmacology* 41, 1983–1990. doi: 10.1038/npp.2015.368

Lee, I. A., and Preacher, K. J. (2013). *Calculation for the Test of the Difference Between Two Dependent Correlations With One Variable in Common [Computer software]*. Available at: http://quantpsy.org (accessed December 15, 2018).

Martin, F., and Oliver, T. (2018). Behavioral activation for children and adolescents: a systematic review of progress and promise. *Eur. Child Adolesc Psychiatry*. 28, 427–441. doi: 10.1007/s00787-018-1126-z

Maslowsky, J., Mogg, K., Bradley, B. P., McClure-Tone, E., Ernst, M., Pine, D. S., et al. (2010). A preliminary investigation of neural correlates of treatment in adolescents with generalized anxiety disorder. *J. Child Adolesc. Psychopharmacol.* 20, 105–111. doi: 10.1089/cap.2009.0049

McClure, E. B., Adler, A., Monk, C. S., Cameron, J., Smith, S., Nelson, E. E., et al. (2007). fMRI predictors of treatment outcome in pediatric anxiety disorders. *Psychopharmacology*. 191, 97–105. doi: 10.1007/s00213-006-0542-9

McEvoy, P. M., Nathan, P., and Norton, P. J. (2009). Efficacy of transdiagnostic treatments: a review of published outcome studies and future research directions. *J. Cogn. Psychother.* 23, 20–33. doi: 10.1891/0889-8391.23.1.20

McLaren, D. G., Ries, M. L., Xu, G., and Johnson, S. C. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *Neuroimage* 61, 1277–1286. doi: 10.1016/j.neuroimage.2012.03.068

Merikangas, K. R., He, J. P., Burstein, M., Swanson, S. A., Avenevoli, S., Cui, L., et al. (2010). Lifetime prevalence of mental disorders in U.S. adolescents: results from the national comorbidity survey replication–adolescent supplement (NCS-A). *J. Am. Acad. Child Adolesc Psychiatry*. 49, 980–989. doi: 10.1016/j.jaac.2010.05.017

Mori, A., Okamoto, Y., Okada, G., Takagaki, K., Jinnin, R., Takamura, M., et al. (2016). Behavioral activation can normalize neural hypoactivation in subthreshold depression during a monetary incentive delay task. *J. Affect. Disord.* 189, 254–262. doi: 10.1016/j.jad.2015.09.036

Pornpattananangkul, N., Leibenluft, E., Pine, D., and Stringaris, A. (2019). Association between childhood anhedonia and alterations in large-scale resting-state networks and task-evoked activation. *JAMA Psychiatry* 76, 624–633. doi: 10.1001/jamapsychiatry.2019.0020

Queen, A. H., Barlow, D. H., and Ehrenreich-May, J. (2014). The trajectories of adolescent anxiety and depression symptoms over the course of a transdiagnostic treatment. *J. Anxiety Disord.* 28, 511–521. doi: 10.1016/j.janxdis.2014.05.007

Scherf, K. S., Behrmann, M., and Dahl, R. E. (2012). Facing changes and changing faces in adolescence: a new model for investigating adolescent-specific interactions between pubertal, brain and behavioral development. *Dev. Cogn. Neurosci.* 2, 199–219. doi: 10.1016/j.dcn.2011.07.016

Shechner, T., Britton, J. C., Perez-Edgar, K., Bar-Haim, Y., Ernst, M., Fox, N. A., et al. (2012). Attention biases, anxiety, and development: towards or away from threats or rewards? *Depress Anxiety*. 29, 282–294. doi: 10.1002/da.20914

Silk, J., Davis, S., McMakin, D. L., Dahl, R. E., and Forbes, E. E. (2012). Why do anxious children become depressed teenagers? the role of social evaluative threat and reward processing. *Psychol. Med.* 42, 2095–2107. doi: 10.1017/S0033291712000207

Steiger, J. H. (1980). Tests for comparing elements of a correlation matrix. *Psychol. Bull.* 87, 245–251. doi: 10.1037/0033-2909.87.2.245

Steinberg, L., and Morris, A. S. (2001). Adolescent development. *Annu. Rev. Psychol.* 52, 83–110. doi: 10.1146/annurev.psych.52.1.83

Straub, J., Plener, P. L., Sproeber, N., Sprenger, L., Koelch, M. G., Groen, G., et al. (2015). Neural correlates of successful psychotherapy of depression in adolescents. *J. Affect. Disord.* 183, 239–246. doi: 10.1016/j.jad.2015.05.020

Talairach, J., and Tournoux, P. (1988). *Co-Planar Stereotaxic Atlas of the Human Brain*. Stuttgart: Thieme.

Thapar, A., and McGuffin, P. (1997). Anxiety and depressive symptoms in childhood – a genetic study of comorbidity. *J. Child Psychol. Psychiatry* 38, 651–656. doi: 10.1111/j.1469-7610.1997.tb01692.x

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., et al. (2009). The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Res.* 168, 242–249. doi: 10.1016/j.psychres.2008.05.006

Weersing, V. R., Brent, D. A., Rozenman, M. S., Gonzalez, A., Jeffreys, M., Dickerson, J. F., et al. (2017). Brief behavioral therapy for pediatric anxiety and depression in primary care: a randomized clinical trial. *JAMA Psychiatry*. 74, 571–578. doi: 10.1001/jamapsychiatry.2017.0429

Weersing, V. R., Gonzalez, A., Campo, J. V., and Lucas, A. N. (2008). Brief behavioral therapy for pediatric anxiety and depression: piloting an integrated treatment approach. *Cogn. Behav. Pract.* 15, 126–139. doi: 10.1016/j.cbpra.2007.10.001

Weisz, J. R., Kuppens, S., Ng, M. Y., Eckshtain, D., Ugueto, A. M., Vaughn-Coaxum, R., et al. (2017). What five decades of research tells us about the effects of youth psychological therapy: a multilevel meta-analysis and implications for science and practice. *Am. Psychol.* 72, 79–117. doi: 10.1037/a0040360

White, L. K., Sequeira, S., Britton, J. C., Brotman, M. A., Gold, A. L., Berman, E., et al. (2017). Complementary features of attention bias modification therapy and cognitive-behavioral therapy in pediatric anxiety disorders. *Am. J. Psychiatry* 174, 775–784. doi: 10.1176/appi.ajp.2017.16070847

Wiggins, J. L., Schwartz, K. T. G., Kryza-Lacombe, M., Spechler, P. A., Blankenship, S. L., and Dougherty, L. R. (2017). Neural reactivity to reward in school-age offspring of depressed mothers. *J. Affect. Disord.* 214, 81–88. doi: 10.1016/j.jad.2017.03.020

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 27 August 2019
doi: 10.3389/fnbeh.2019.00189

Time-Frequency Delta Activity to Social Feedback Demonstrates Differential Associations With Depression and Social Anxiety Symptoms

Jingwen Jin[1], Amri Sabharwal[1], Zachary P. Infantolino[1], Johanna M. Jarcho[2] and Brady D. Nelson[1]*

[1]Department of Psychology, Stony Brook University, Stony Brook, NY, United States, [2]Department of Psychology, Temple University, Philadelphia, PA, United States

OPEN ACCESS

Edited by:
Bahar Güntekin,
Istanbul Medipol University, Turkey

Reviewed by:
Birgit Mathes,
University of Bremen, Germany
Dan Foti,
Purdue University, United States

***Correspondence:**
Jingwen Jin
jinjingwen111@gmail.com

Specialty section:
This article was submitted to Motivation and Reward, a section of the journal Frontiers in Behavioral Neuroscience

Received: 11 April 2019
Accepted: 06 August 2019
Published: 27 August 2019

Citation:
Jin J, Sabharwal A, Infantolino ZP, Jarcho JM and Nelson BD (2019) Time-Frequency Delta Activity to Social Feedback Demonstrates Differential Associations With Depression and Social Anxiety Symptoms. Front. Behav. Neurosci. 13:189. doi: 10.3389/fnbeh.2019.00189

Social feedback is highly salient and particularly relevant when investigating the pathophysiology of depression and social anxiety. A bourgeoning body of research has demonstrated an association between reward-related delta activity and psychopathology. However, a critical limitation is that these findings are derived from neural responses to *monetary* feedback, and time-frequency representation of social feedback remains unexplored. In addition, no study has isolated the differential/unique associations of positive valence and the intrinsic rewarding experience of being correct with reward-related neural activity. In the present study, 204 participants underwent electroencephalography (EEG) while they completed a novel paradigm comprised of monetary and social feedback tasks that were matched in trial structure, timing, and feedback stimuli. For each task, participants were instructed to correctly identify one of two doors that would provide positive feedback (monetary win behind the door) or one of two peers who would provide positive feedback (social like); or to correctly identify the door or peer that would provide negative feedback (money loss behind the door/social dislike). A principal component analysis (PCA) was conducted on the time-frequency data and revealed two factors in the delta and one factor in the theta frequency ranges. Results indicated that the lower-frequency delta factor (delta-low) was greater to correct vs. incorrect feedback, more so for social vs. monetary tasks, while the higher-frequency delta factor (delta-high) was greater to correct vs. incorrect feedback for social like, social dislike, and monetary win tasks, but not the monetary loss task. In contrast, the theta factor was greater to incorrect relative to correct feedback in negative valence (lose money/social dislike) but not positive valence (win money/social like) tasks. Furthermore, greater delta-high activity for social feedback was associated with greater social anxiety symptoms, whereas lesser delta-high activity for social feedback was associated with greater depressive symptoms. Finally, greater theta activity to monetary feedback was associated with greater depressive symptoms. The present

study provides novel evidence demonstrating unique social vs. monetary feedback-related delta and theta activity, and differential associations between delta activity with depression and social anxiety symptoms. These findings highlight the importance of investigating feedback-related neural responses in the social domain.

Keywords: time-frequency, delta, theta, social feedback processing, social anxiety, depression

INTRODUCTION

Understanding how humans process salient feedback is central not only to economic theories of monetary decision-making (Bernoulli, 1954; Tversky and Kahneman, 1992; Von Neumann and Morgenstern, 2007) but also to theories of social decision-making (Homans, 1958; Sanfey, 2007). Adaptive behavioral changes often rely on successful processing of outcome feedback (Everitt and Robbins, 2005; Wrase et al., 2007). Failure to use feedback to flexibly update decision-making strategies has been linked to various mental disorders, such as depression (Cella et al., 2010) and anxiety disorders (Hartley and Phelps, 2012; Phelps et al., 2014). While responses to positive and negative feedback in monetary (win and loss) and social (being accepted/liked and rejected/disliked) domains are both important in daily life, it remains unclear whether the two domains share the same or have unique neural mechanisms. It is also unknown whether neural responses to monetary and social feedback demonstrate common or differential relationships with depression and anxiety symptoms.

Neuroimaging studies comparing monetary and social feedback have demonstrated that the two domains share overlapping neural circuitry, including the striatum and prefrontal regions (Izuma et al., 2008; Lin et al., 2012; Hausler et al., 2015). On the other hand, accumulating evidence also suggests that monetary and social feedback elicit unique neural responses (Rademacher et al., 2010; Chan et al., 2016). For example, using the monetary incentive delay task, one study found that while monetary reward was associated with thalamic activity, social reward was associated with amygdala activity (Rademacher et al., 2010).

Parallel to these neuroimaging studies, event-related potential (ERP) research has identified the reward positivity (RewP), a positive-going component that peaks approximately 250–350 ms following monetary win feedback that is absent or reduced to monetary loss feedback (Holroyd et al., 2008; Foti et al., 2011; Novak and Foti, 2015; Proudfit, 2015). The RewP has been primarily examined in the context of monetary feedback, but more recent studies have shown that it can also be elicited by positive social feedback (e.g., social acceptance; Kujawa et al., 2014; van der Veen et al., 2016). When directly compared within the same participants, one study found a higher RewP to monetary vs. social reward in emerging adults but not in early adolescents, and the monetary and social RewPs were not correlated across the two groups (Ethridge et al., 2017). However, the social paradigm used in this study had important differences compared with the monetary task. For instance, the paradigm required the participants to decide on accepting or rejecting simulated co-players before receiving acceptance/rejection feedback from the same co-players. Additionally, there were timing differences in trial structure (e.g., the social task contained an additional variable delay between making a choice and receiving feedback). A more recent study that matched the designs of the monetary and social tasks found that the RewP to monetary and social feedback was of comparable magnitude and positively correlated, although only the RewP to social feedback was associated with depressive symptoms (Distefano et al., 2018). Taken together, the current literature suggests that when the paradigms are closely matched, monetary and social feedback may elicit overlapping neural responses. On the other hand, feedback from the two domains may exhibit unique and potentially dissociable relationships with particular forms of psychopathology, such as depression and social anxiety.

In addition to monetary and social paradigm differences, the task designs of previous studies often confounded the positive valence of outcome (i.e., monetary win and being socially accepted) with the intrinsic reward of being correct (i.e., the chosen option yielding win/acceptance feedback). One exception was a recent investigation that examined time-frequency indices in response to monetary win vs. loss and correct vs. incorrect feedback (Bernat et al., 2015). In this study, delta activity was higher both for positive valence (i.e., win) compared to negative valence (i.e., loss) and being correct compared to incorrect, and theta activity was higher for negative valence compared to positive valence, but not incorrect vs. correct outcomes (Bernat et al., 2015). However, the correct/incorrect outcome was dependent on valence such that correct (in contrast to incorrect) indicated a larger win or smaller loss, and therefore was secondary to valence. In sum, no study has investigated time-frequency activity to these two dimensions simultaneously as primary feedback attributes.

Previous studies examining electrocortical responses to win and loss feedback have largely focused on time-domain ERPs. While this line of research has yielded largely consistent findings (Bernat et al., 2015; Proudfit, 2015), there are some notable limitations to this analytic approach. Time-domain ERPs consist of multiple temporally-overlapping components that are often characterized by different frequency profiles (Bernat et al., 2005; Dien, 2010b; Foti et al., 2015). Time-frequency based representation of the signal can help elucidate distinct neural processes that occur at different frequency bands (e.g., delta vs. theta activity) that are otherwise embedded in the time-domain data (Spencer et al., 2001). Furthermore, time-frequency analysis of single-trial data allows researchers to identify non-phase locked aspects of the neural response that might be attenuated or absent in the time-domain signal due to the common practice of trial averaging (Bernat et al., 2005; Cohen et al., 2007; Cohen,

2014). Multiple investigations that conducted time-frequency analysis have found that the neural response in the time range of the RewP shows greater delta activity to monetary win feedback and greater theta activity to monetary loss feedback (Bernat et al., 2011, 2015; Foti et al., 2015). However, no study has investigated the time-frequency activity in the context of social feedback and compared that activity to monetary feedback. Given the unique information time-frequency based representation can provide, it is important to examine whether the delta and theta activities are also present for social feedback.

Examining distinct time-frequency indices in response to monetary and social feedback may also help reveal any differential neural correlates of depression and anxiety. Theoretical and empirical research has suggested that depression is associated with a blunted neural response to monetary win and an enhanced neural response to monetary loss (Henriques and Davidson, 2000; Eshel and Roiser, 2010; Kujawa et al., 2014; Luking et al., 2016). In addition, a blunted RewP to monetary win (compared to loss) has been shown to prospectively predict depressive symptoms and syndromes (Bress et al., 2013; Nelson et al., 2016). Two recent studies using social reward tasks also demonstrated a blunted RewP in association with depression (Kujawa et al., 2014; Distefano et al., 2018). To date, only a small number of studies have examined time-frequency neural activity to monetary feedback in relation to depression. One study found that blunted delta activity to monetary reward was associated with greater depression, anxiety, and stress (Foti et al., 2015). Conversely, a separate study of adolescent girls found that depression was associated with higher loss-related theta activity, but there were no group differences in reward-related delta activity (Webb et al., 2017). Finally, a recent investigation of adolescent girls found that blunted delta activity to monetary reward prospectively predicted first-onset depression, independent of the time-domain RewP (Nelson et al., 2018). Together, this nascent literature suggests that depression might be associated with an aberrant neural response in particular frequency bands. However, no study has examined time-frequency activity to social feedback in relation to depressive symptoms.

Even less is known about the relationship between the neural response to monetary and social feedback and social anxiety. One study using a child sample found that a greater RewP was associated with higher social anxiety symptoms even after controlling for depressive symptoms (Kessel et al., 2015). An important limitation of the current literature is that the neural response to feedback is often examined using monetary tasks, and there is a lack of research examining the ERP response to social feedback in relation to social anxiety. As the hallmark of social anxiety is the fear of social evaluation (American Psychiatric Association, 2013), it is possible that the association between the neural response to feedback and social anxiety is more sensitive to social compared to non-social information. However, no study has examined the time-frequency indices of neural response to social compared to monetary feedback in relation to social anxiety symptoms.

To address these issues, the current study utilized a novel paradigm that carefully matched the trial structure, timing, and visual presentation of feedback stimuli. This design permitted the comparison of participants' neural response to feedback indicating monetary win, monetary loss, social acceptance (i.e., being liked), and social rejection (i.e., being dislike). Furthermore, the tasks were designed to tease apart the effects of feedback domain (monetary vs. social), valence (positive vs. negative), and outcome (correct vs. incorrect). In a large sample of young adults, we employed time-frequency analysis to examine delta and theta activity to feedback across both monetary and social domains. In addition, we investigated relations between these time-frequency indices and individual differences in depression and social anxiety symptoms. We hypothesized that: (1) for both the monetary and social domains, there would be higher delta activity to positive and/or correct feedback and higher theta activity to negative and/or incorrect feedback; and (2) blunted delta activity to positive feedback (across both monetary and social domains) would be associated with more severe depressive symptoms. Due to the exploratory nature of the remaining analyses, we did not have other specific hypotheses for time-frequency activity to social feedback or social anxiety symptoms.

MATERIALS AND METHODS

Participants

Two hundred and five participants were recruited, with one excluded due to not completing the experiment. The final sample included 204 participants (M = 19.92 years old, SD = 2.50), who were 63.7% female, racially/ethnically diverse (45.1% Asians, 5.9% Black, 26.5% Caucasian, 10.8% Latino, and 11.8% "Other"), and participated for course credit. All participants gave informed consent and the study was approved by the Stony Brook University Institutional Review Board.

Measures

Participants completed the Inventory of Depression and Anxiety Symptoms—Expanded Version (IDAS-II; Watson et al., 2007, 2012). IDAS-II is a factor analytically-derived self-administered questionnaire that assesses symptomatology of mood and anxiety disorders in the past 2 weeks using a Likert scale ranging from 1 (*not at all*) to 5 (*extremely*). IDAS-II has demonstrated excellent psychometric properties across various populations, including college students, community, and patient samples (Watson et al., 2012). The current study focused on the 10-item dysphoria scale (M = 19.47, SD = 7.52, Cronbach's α = 0.88), which is the most discriminant symptom dimension of major depressive disorder, and the 6-item social anxiety scale (M = 10.95, SD = 5.22, Cronbach's α = 0.86).

Stimuli

The social feedback task stimuli were identical to a previous investigation (Distefano et al., 2018) and consisted of 120 images of age-matched peers (60 females) compiled from multiple sources [e.g., National Institute of Mental Health's Child Emotional Faces picture set (Egger et al., 2011), internet databases of non-copyrighted images, and photographs of college-aged individuals]. Variability in the appearance of the

social stimuli was necessary in order to corroborate task deception, which suggested participants were being evaluated by actual peers. All images were cropped to a standardized size (3.5" width × 4.5" height), and occupied approximately 8° of visual space horizontally and 10° vertically for participants seated approximately 24" from the monitor. Each trial slide contained a pair of either male peers or female peers (60 pairs of male faces and 60 pairs of female faces), pictured from their shoulders up, with a positive facial expression and a solid background.

Procedure

At the beginning of the experimental session, participants were told that they would complete a social evaluation study with peers at different universities across the United States. Participants were asked to provide a digital photo of themselves that was purportedly uploaded to a study database. Participants believed that once this photograph was uploaded, peers would receive a text message on their cell phone asking them to view the photo and indicate whether they thought they would "like" or "dislike" the participant. Participants were told that later in the experimental session, after enough time had elapsed for the purported peers to have rated their photo, they would be asked to guess which peers "liked" and "disliked" them. Participants were also told that they would be completing monetary guessing tasks. Next, participants completed self-report questionnaires while an electroencephalography (EEG) cap was applied to their head. Finally, participants completed the monetary and social feedback tasks in a counterbalanced order.

Monetary and Social Feedback Tasks

The monetary and social feedback tasks were administered using Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA) and were modified variants of previously established tasks (Proudfit, 2015; Distefano et al., 2018). Overall, there were four total tasks (monetary win, monetary loss, social like, and social dislike) that were presented in a counterbalanced order.

Figure 1 displays the overall task schematic. In the monetary win task, each trial began with the presentation of two identical doors. Participants were told there were three possible scenarios for each trial: (1) both doors contained a $0.25 monetary win; (2) one door contained a $0.25 monetary win while the other door resulted in a break-even outcome (i.e., neither win nor lose); or (3) both doors resulted in a break-even outcome. These instructions ensured that the feedback the participant received would only be informative about the door they chose and not the door they *did not* choose. For example, if a participant chose a door and received feedback indicating a break-even result, the other door could have been a win door [consistent with trial scenario (2) above] or it could have been a break-even door [consistent with trial scenario (3) above]. Conversely, if a participant chose a door and received feedback indicating a win result, the other door could have been a win door [consistent with trial scenario (1) above] or it could have been a break-even door [consistent with trial scenario (2) above]. Participants were told that the goal of these trials was to try and guess which door contained the monetary win. The image of the doors was presented until the participant made a selection. After stimulus offset, a fixation cross (+) was presented for 1,000 ms, and then feedback was presented on the screen for 2,000 ms. Correct selection of the monetary win door resulted in a $0.25 monetary win, indicated by a green arrow pointing upward (↑). Incorrect selection of the break-even door resulted in no monetary win, indicated by a white horizontal dash (–). In actuality, feedback was pre-programmed to generate an equal number of win and break-even trials. The feedback stimulus was followed by a fixation cross presented for 1,500 ms, immediately followed by the message "Click for next round." This prompt remained on the screen until the participant responded with a button press to initiate the next trial. The task consisted of 30 total trials (15 of each outcome).

In the monetary loss trials, trial structure and timing was identical to the monetary win trials, but participants were told there were three possible situations for each trial: (1) both doors contained a $0.25 monetary loss; (2) one door contained a $0.25 monetary loss while the other door resulted in a break-even outcome (i.e., neither win nor lose); or (3) both doors resulted in a break-even outcome. Participants were told that the goal of these trials was to try and guess which door contained the monetary loss. Correct selection of the monetary loss door resulted in a $0.25 monetary loss, indicated by a red arrow pointing downward (↓). Incorrect selection of the break-even door resulted in no monetary loss, indicated by a white horizontal dash (–). All participants were told that they would start with a pot of $5. Given that there were equal number of wins and losses, they were paid $5 at the end of the experiment.

The social like and dislike tasks were identical to the monetary win and loss tasks, respectively, except pictures of gender-matched peers (i.e., two male faces or two female faces) were presented instead of doors. There was an equal number of trials with male and female peers across the social like and social dislike tasks (30 each, 60 total). In the social like trials, participants were told that there were three possible situations for each trial: (1) both people said they would like the participant; (2) one person said they would like the participant while the other person never rated the participant; or (3) neither person rated the participant. Participants were told that the goal of these trials was to try and guess which person said they would like the participant. Correct selection of the person who said they would like the participant was indicated by a green arrow pointing upward (↑). Incorrect selection of the person who never rated the participant was indicated by a white horizontal dash (–).

In the social dislike trials, participants were told there were three possible situations for each trial: (1) both people said they would dislike the participant; (2) one person said they would dislike the participant while the other person never rated the participant; or (3) neither person rated the participant. Participants were told that the goal of these trials was to try and guess which person said they would dislike the participant. Correct selection of the person who said they would dislike the participant was indicated by a red arrow pointing downward (↓). Incorrect selection of the person who never rated the participant was indicated by a white horizontal dash (–). Participants took about 5–7 min for each task.

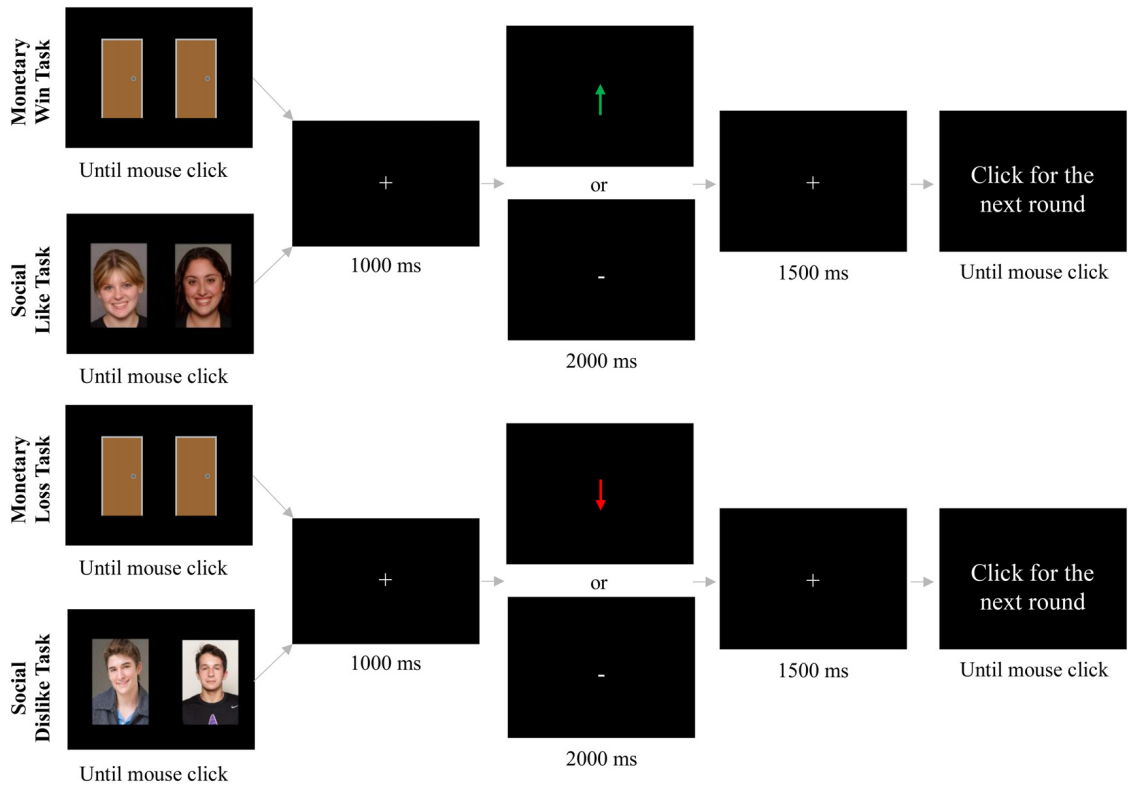


FIGURE 1 | Schematic for monetary win, monetary loss, social like, and social dislike tasks.

EEG Recording and Processing

Continuous EEG was recorded using an elastic cap with 34 electrode sites placed according to the 10/20 system. Electrooculogram (EOG) was recorded using four additional facial electrodes: two placed approximately 1 cm outside of the right and left eyes and two placed approximately 1 cm above and below the right eye. All electrodes were sintered Ag/AgCl electrodes. Data were recorded using the ActiveTwo system (BioSemi, Amsterdam, Netherlands). The EEG was digitized with a sampling rate of 1,024 Hz using a low-pass fifth-order sinc filter with a half-power cut-off of 204.8 Hz. A common mode sense active electrode producing a monopolar (non-differential) channel was used as recording reference.

Offline data processing was conducted using EEGLAB toolbox version 13.6.5b (Delorme and Makeig, 2004) and customized MATLAB scripts (The MathWorks, Inc., Natick, MA, USA). EEG data were first re-referenced to the average of the left and right mastoids, high-pass filtered (0.01 Hz) to remove baseline drift, and segmented into single-trial epochs (−3,000, +3,000 ms) around the feedback onset. Epochs containing artifacts were identified and rejected using Fully Automated Statistical Thresholding for EEG Artifact Rejection (Nolan et al., 2010). Consistent with published guidelines (Nolan et al., 2010), the decision to reject epochs was based on three parameters: the amplitude range of the epoch, the deviation between the epoch and the channel average, and the variance within the epoch. The parameters were converted to *z*-scores and epochs with an absolute *z*-score greater than three were identified and rejected. Eye blinks artifacts were then removed using independent component analyses. The number of trials went into the time-frequency analyses for each condition were: M = 14.77 (SD = 0.77) for monetary loss correct, M = 14.78 (SD = 0.92) for monetary loss incorrect, M = 14.82 (SD = 0.77) for monetary win correct, M = 14.86 (SD = 0.52) for monetary win incorrect, M = 14.80 (SD = 0.88) for social dislike correct, M = 14.72 (SD = 1.05) for social dislike incorrect, M = 14.73 (SD = 1.09) for social like correct, M = 14.79 (SD = 0.97) for social like incorrect.

In order to retain phase and non-phase locked neural responses (Cohen, 2014; Luck, 2014), single-trial epochs for each electrode were then decomposed into their time-frequency representation using Morlet wavelets. Specifically, the power spectrum of the epochs was multiplied by the power spectrum of a set of complex Morlet wavelets that increased by 33 logarithmic steps from 1 to 13 Hz. The frequency band-specific power at each time point was calculated by squaring the absolute value of the complex signal. A decibel transformation was used to normalize the power. Specifically, we took the logarithm of the ratio of post-feedback power divided by the average baseline (−200 to 0 ms) power for each frequency.

Figure 2 displays the time-frequency plots for all four tasks. Following established guidelines (Bernat et al., 2005), a two-step principal component analysis (PCA) was conducted to

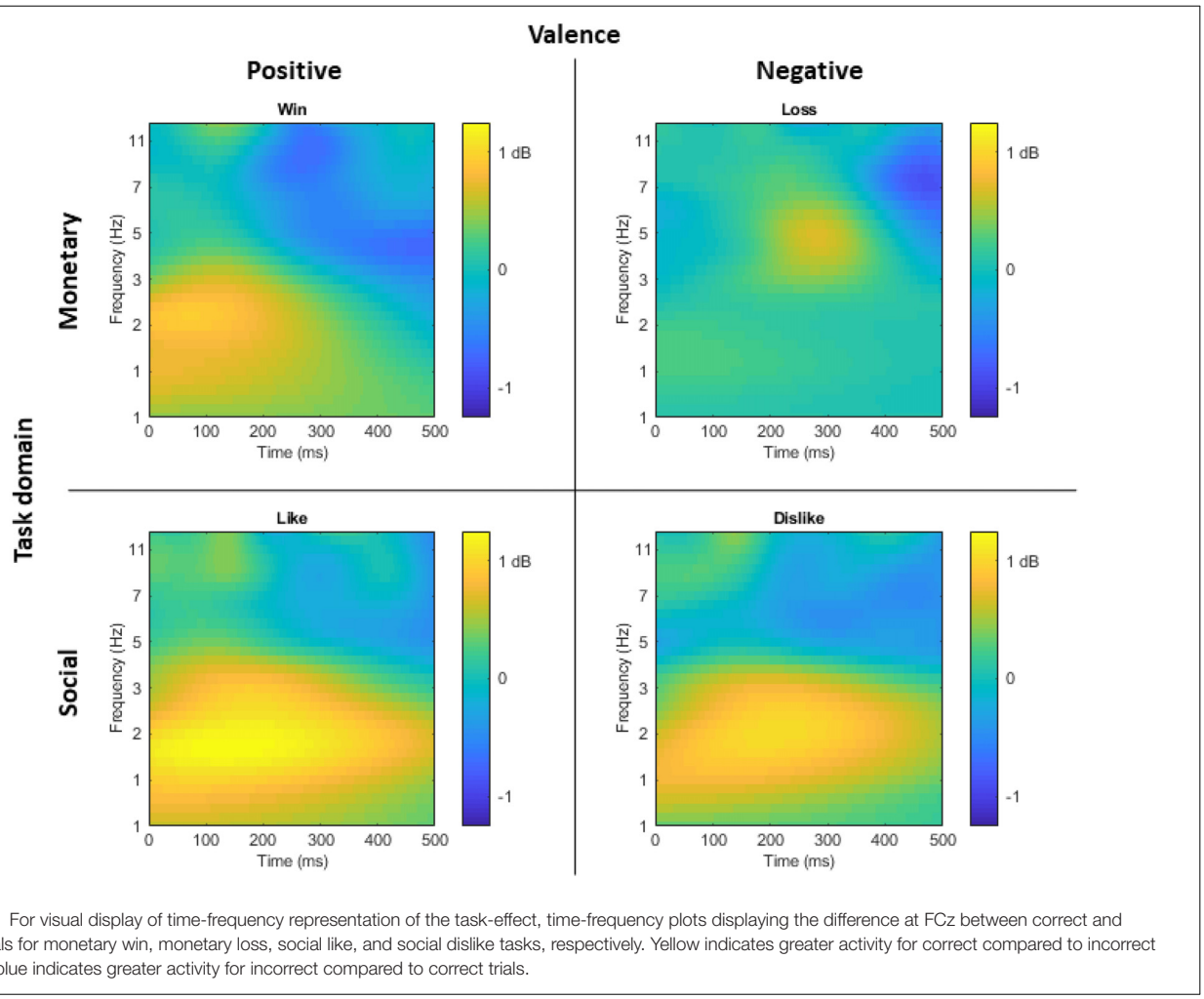


FIGURE 2 | For visual display of time-frequency representation of the task-effect, time-frequency plots displaying the difference at FCz between correct and incorrect trials for monetary win, monetary loss, social like, and social dislike tasks, respectively. Yellow indicates greater activity for correct compared to incorrect trials, while blue indicates greater activity for incorrect compared to correct trials.

better isolate distinct neural responses. Time-frequency surfaces for the 0–500 ms post-feedback segment were vectorized and entered into PCA Toolkit version 2.52 (Dien, 2010a) to conduct a PCA using the time-frequency vectors as variables and the participants, outcomes (correct and incorrect), and tasks (monetary win, monetary loss, social like, social dislike) as observations. Varimax rotation was applied and 55 factors were extracted based on the resulting Scree plot (Cattell, 1966). A spatial PCA was then conducted using an Infomax rotation and four factors were extracted based on the resulting Scree plot (Cattell, 1966). The two-step PCA resulted in 220 temporal-frequency spatial factors in total. With a cut-off of at least 0.5% of the variance explained, 33 factors emerged, accounting for 65.4% variance altogether. Next, we identified PCA factors for data analysis based on a two-step visual inspection approach. First, we organized the factors in order from the most to the least variance accounted for, and we ignored all factors that accounted for <1% of the variance. Second, we only examined factors that overlapped with the delta or theta frequency ranges and contained spatial distributions that centered around frontal and parietal regions. As shown in **Figure 3**, this visual inspection procedure revealed three factors that accounted for the most variance and resembled the expected delta (two delta factors TF1SF1 and TF2SF1) and theta (one theta factor TF4SF1) activity. The delta factor TF1SF1 centered on the lower frequency range (delta-low) and accounted for 10.38% variance, while delta factor TF2SF1 centered on higher frequency range (delta-high) and accounted for 7.51% variance. The theta factor accounted for 4.97% variance.

Data Analyses

We conducted a 2 (Domain: monetary vs. social) × 2 (Valence: positive vs. negative) × 2 (Outcome: correct vs. incorrect) repeated-measures analysis of variance (rmANOVA). Separate analyses were conducted for each PCA factor. We also conducted a 2 (Domain: monetary vs. social) × 2 (Valence: positive vs. negative) × 2 (Outcome: correct vs. incorrect) mixed-measures analysis of covariance (ANCOVA), with dysphoria and social anxiety symptoms entered as simultaneous covariates. When dysphoria and/or social anxiety symptoms were associated with PCA factors, linear regression was conducted to compute the residual scores for one symptom dimension independent of the

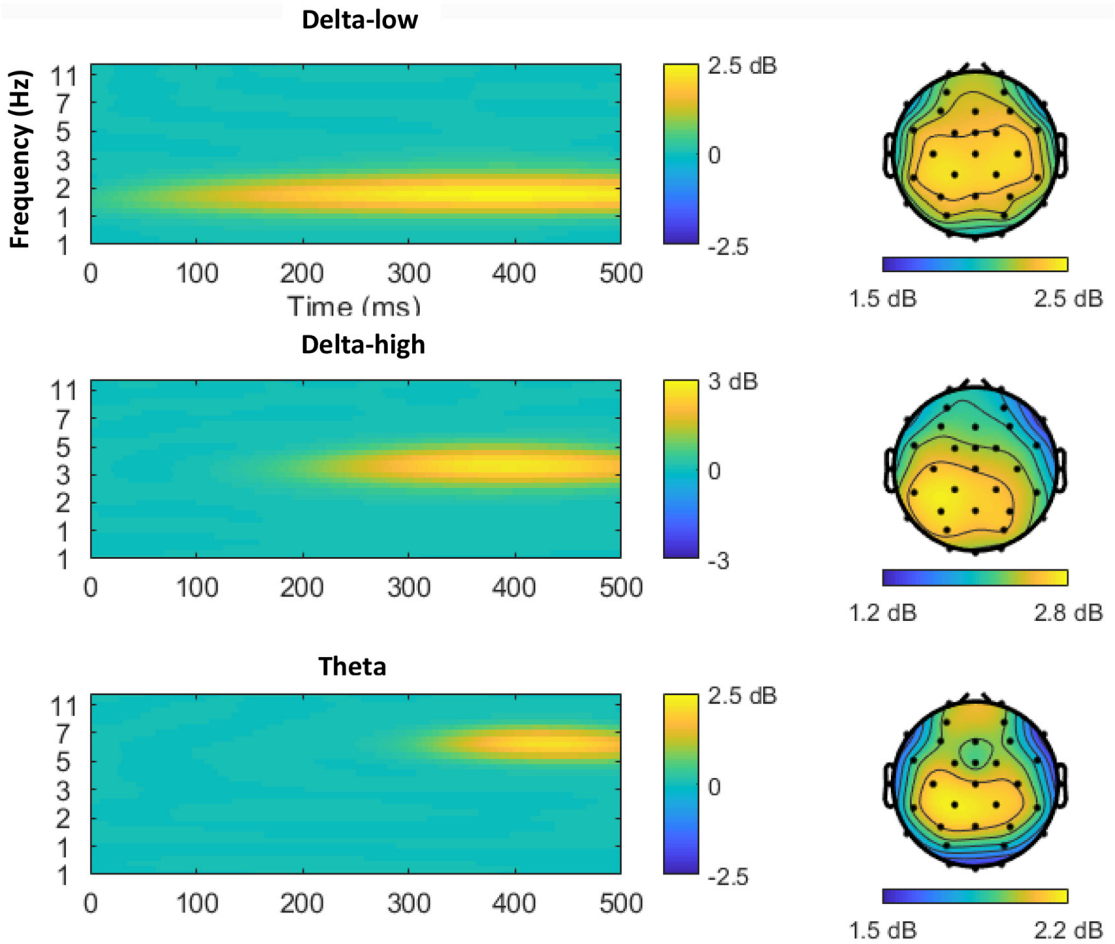


FIGURE 3 | Time-frequency-spatial principal component analysis (PCA) revealed three factors in the delta to theta frequency bands within the time range of the reward positivity (RewP). From top to bottom, the three factors are ordered by the percentage of variance explained from largest to smallest. The left column depicts the time-frequency power spectrum of each factor, with yellow indicating higher power. The right column depicts the scalp distribution of the corresponding factor.

other symptom dimension. These residual scores were then used to further investigate the relationships.

We also conducted a series of analyses examining the potential effects of domain order. For each of the Domain × Valence × Outcome rmANOVAs, we entered Domain Order (monetary first vs. social first) as a between-subjects factor. If significant interactions were identified for the Domain Order variable, we would follow up with additional ANCOVA analyses for depression and social anxiety symptoms, including the Domain Order variable as an additional between-subject covariate. All statistical analyses were conducted in IBM SPSS Statistics, Version 25.0 (Armonk, NY, USA).

RESULTS

Monetary and Social Tasks

Descriptive statistics for the PCA factors and symptom measures were reported in **Table 1**. For the delta-low factor (**Figure 4A**), results indicated a main effect of domain with greater delta activity for monetary vs. social feedback, $F_{(1,203)} = 15.73$, $p < 0.001$, $\eta_p^2 = 0.07$, a main effect of valence with greater delta activity for positive vs. negative feedback, $F_{(1,203)} = 17.71$, $p < 0.001$, $\eta_p^2 = 0.08$, and a main effect of outcome with greater delta activity for correct vs. incorrect feedback, $F_{(1,203)} = 51.48$, $p < 0.001$, $\eta_p^2 = 0.20$. There was also a Domain × Outcome interaction $F_{(1,203)} = 23.95$, $p < 0.001$, $\eta_p^2 = 0.11$. Simple-effect analyses indicated that delta activity was greater for correct compared to incorrect feedback for both monetary (mean difference = 0.29, $p < 0.01$) and social (mean difference = 0.95, $p < 0.001$) tasks, but this increase was greater for the social compared to monetary task.

For the delta-high factor (**Figure 4B**), results indicated a main effect of domain with greater delta activity for monetary vs. social feedback, $F_{(1,203)} = 18.67$, $p < 0.001$, $\eta_p^2 = 0.08$, a main effect of valence with greater delta activity for positive vs. negative feedback, $F_{(1,203)} = 23.30$, $p < 0.001$, $\eta_p^2 = 0.10$, and a main effect of outcome with greater delta activity for correct vs. incorrect feedback, $F_{(1,203)} = 28.90$, $p < 0.001$,

TABLE 1 | Descriptive statistics.

PCA factors (N = 204)			
Factor TF1SF1		**Mean**	**SD**
Monetary loss	Correct	2.51	2.01
	Incorrect	2.39	2.09
Monetary win	Correct	3.06	1.91
	Incorrect	2.60	1.86
Social dislike	Correct	2.54	2.07
	Incorrect	1.60	1.90
Social like	Correct	2.88	1.88
	Incorrect	1.90	2.14
Factor TF2SF1			
Monetary loss	Correct	2.45	2.18
	Incorrect	2.72	2.44
Monetary win	Correct	3.50	2.12
	Incorrect	3.05	2.29
Social dislike	Correct	2.73	2.11
	Incorrect	2.02	1.95
Social like	Correct	2.96	2.18
	Incorrect	2.20	2.20
Factor TF4SF1			
Monetary loss	Correct	1.30	2.47
	Incorrect	2.23	2.65
Monetary win	Correct	2.34	2.53
	Incorrect	2.45	2.31
Social dislike	Correct	1.70	2.09
	Incorrect	2.31	2.10
Social like	Correct	2.45	2.41
	Incorrect	2.61	2.61
Depression and Social Anxiety Measures (N = 204)			
Dysphoria	19.47	7.52	
Social anxiety	10.95	5.22	
Pearson's correlation coefficient	0.664	$p < 0.001$	

$\eta_p^2 = 0.13$. There were also Domain × Valence, $F_{(1,203)} = 7.22$, $p < 0.01$, $\eta_p^2 = 0.03$, Domain × Outcome, $F_{(1,203)} = 29.27$, $p < 0.001$, $\eta_p^2 = 0.13$, and Valence × Outcome interactions, $F_{(1,203)} = 6.84$, $p = 0.05$, $\eta_p^2 = 0.03$, which were qualified by a Domain × Valence × Outcome interaction, $F_{(1,203)} = 6.36$, $p < 0.05$, $\eta_p^2 = 0.03$. To follow-up the three-way interaction, we conducted separate Valence × Outcome rmANOVAs for monetary and social tasks. Simple-effect analyses indicated that for the monetary tasks, delta activity was greater for correct feedback compared to incorrect feedback for positive valence (i.e., win) trials (mean difference = 0.45, $p < 0.01$), but not for negative valence (i.e., loss) trials (mean difference = −0.27, *ns*). For the social tasks, delta activity was greater for correct compared to incorrect feedback for both positive valence (i.e., like) trials (mean difference = 0.76, $p < 0.001$) and negative valence (i.e., dislike) trials (mean difference = 0.72, $p < 0.001$).

For the theta factor (**Figure 4C**), results indicated a main effect of outcome with greater theta activity for incorrect vs. correct feedback, $F_{(1,203)} = 26.72$, $p < 0.001$, $\eta_p^2 = 0.12$, and a main effect of valence with greater theta activity for positive vs. negative valence trials, $F_{(1,203)} = 30.76$, $p < 0.001$, $\eta_p^2 = 0.13$. There was also a Valence × Outcome interaction, $F_{(1,203)} = 16.37$, $p < 0.001$, $\eta_p^2 = 0.08$). Simple-effect analyses indicated that theta activity was greater for incorrect vs. correct feedback for negative valence trials (mean difference = 0.77, $p < 0.001$), but not positive valence trials (mean difference = 0.13, *ns*).

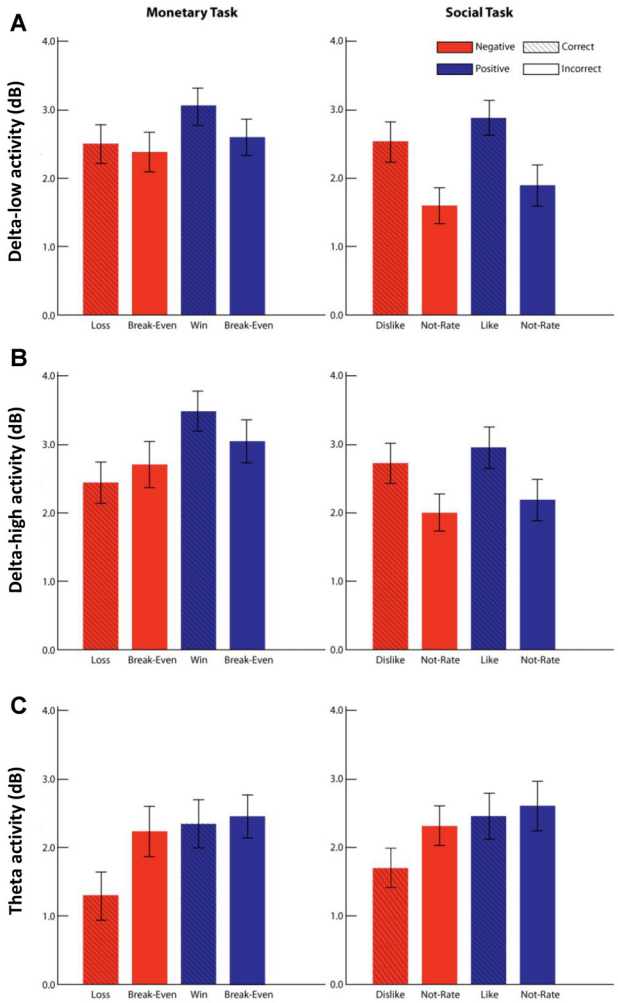


FIGURE 4 | Delta and theta activity during the monetary and social tasks. Panels (**A**–**C**) represent the results for each factor: delta-low (TF1SF1; **A**), delta-high (TF2SF2; **B**), and theta (TF4SF1; **C**). Mean activity for each factor in each condition is shown for monetary (left column) and social (right column) tasks. Error bars represents ± 95% confidence interval. Negative valence is represented in red, and positive valence is represented blue. Correct and incorrect outcomes are differentiated by presence and absence of the line pattern.

Dysphoria and Social Anxiety Symptoms

For the delta-low factor, results indicated a Domain × Social Anxiety interaction, $F_{(1,201)} = 4.02$, $p < 0.05$, $\eta_p^2 = 0.02$. For the follow-up analyses, delta-low activity was averaged across valence and outcome for the monetary and social tasks. As shown in **Figure 5**, follow-up Pearson's correlations indicated that more severe social anxiety symptoms were associated with greater delta activity for social feedback ($r = 0.15$, $p < 0.05$), but not for monetary feedback ($r = 0.05$, *ns*).

For the delta-high factor, results indicated Domain × Outcome × Dysphoria, $F_{(1,201)} = 4.24$, $p < 0.05$, $\eta_p^2 = 0.02$, and Domain × Outcome × Social Anxiety interactions, $F_{(1,201)} = 6.59$, $p < 0.05$, $\eta_p^2 = 0.03$. In order to examine these associations, we first averaged delta-high activity values across

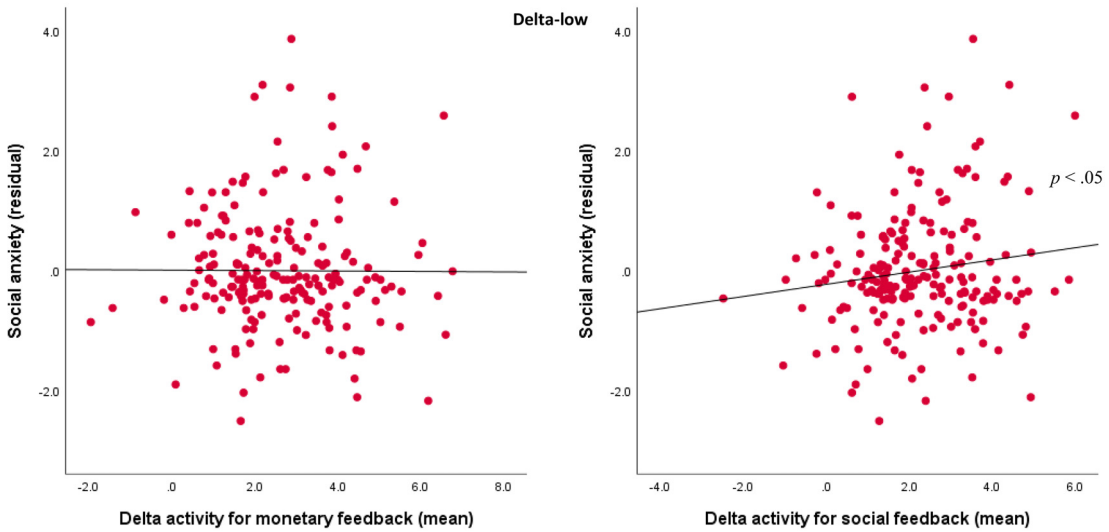


FIGURE 5 | Associations between TF1SF1 (delta-low activity) for social and monetary feedback and symptoms. Scatterplots displaying the associations between social anxiety residuals with delta-low activity for mean monetary feedback averaged across both valence and outcome (left) and mean social feedback averaged across both valence and outcome (right).

the positive and negative valence for each domain and outcome combination. Next, we created separate difference scores for correct and incorrect outcomes (i.e., correct-incorrect) for the monetary and social tasks. Finally, in order to examine the variance explained by domain-specific responses, we computed two residual scores to quantify delta-high activity for the monetary (independent of the social difference score) and social (independent of the monetary difference score) tasks. We also calculated residuals for dysphoria (independent of social anxiety) and social anxiety (independent of dysphoria), and we conducted Pearson's correlations between the two delta-high activity residuals and the two symptom residuals. As shown in **Figure 6**, results indicated that more severe dysphoria symptoms were associated with a lower delta activity to social feedback ($r = -0.16$, $p < 0.05$), but more severe social anxiety symptoms were associated with greater delta activity to social feedback ($r = 0.16$, $p < 0.05$). In contrast, neither dysphoria ($r = 0.07$, *ns*) nor social anxiety symptoms ($r = -0.12$, *ns*) were associated with delta activity for the monetary tasks.

Finally, for the theta factor, results indicated a Domain × Dysphoria interaction, $F_{(1,201)} = 5.29$, $p < 0.05$, $\eta_p^2 = 0.03$. For follow-up analyses, theta activity was averaged across valence and outcome for monetary and social tasks. As shown in **Figure 7**, dysphoria was not significantly correlated with theta activity for monetary feedback ($r = 0.01$, *ns*) or social feedback ($r = -0.10$, *ns*) individually, but was correlated with monetary feedback minus social feedback ($r = 0.16$, $p < 0.05$).

Domain Order

There was no effect of domain order on any of the three PCA factors (*p*s > 0.077). Therefore, no further ANCOVA analyses were conducted for the relationships with dysphoria and social anxiety.

DISCUSSION

The current study is the first to examine the time-frequency representation of electrocortical responses to monetary relative to social feedback. PCA of the time-frequency data in response to feedback revealed two delta factors and one theta factor. The delta factors were both modulated by combinations of task domain (monetary vs. social), valence (positive vs. negative), and outcome (correct vs. incorrect), and showed a general tendency of greater activity to rewarding feedback vs. non-rewarding feedback. In contrast, the theta factor was sensitive to outcome and valence, but not task domain. In addition, for the social domain, delta activity was greater to correct relative to incorrect feedback among those with more severe symptoms of anxiety, but smaller in those with more severe symptoms of depression. Overall, the current study demonstrates the importance of examining neural response to feedback processing *via* time-frequency analysis, especially in the context of the social domain.

PCA of the time-frequency data yielded two distinct delta factors, with one factor capturing lower frequency delta activity and the other factor capturing higher frequency delta activity. These two delta factors were similarly modulated by task effects such that both the intrinsic reward of being correct and positive valence feedback elicited higher delta activity overall across monetary and social domains. These results are consistent with previous findings of reward-related delta activity using monetary tasks (Bernat et al., 2011, 2015; Foti et al., 2011; Webb et al., 2017) and extend that research to the social domain, while

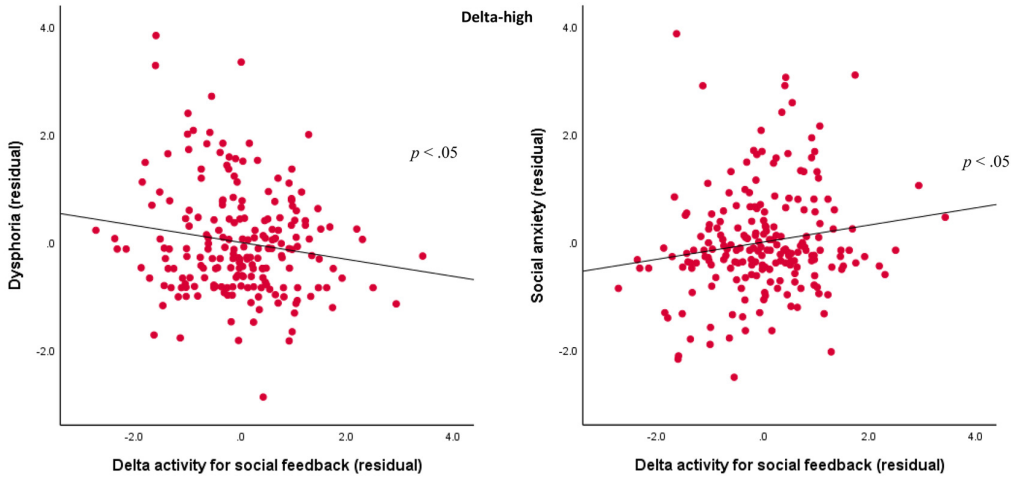


FIGURE 6 | Associations between TF2SF1 (delta-high activity) for social feedback and symptoms. Scatterplots displaying the associations between delta-high activity for social feedback (difference between correct and incorrect trials) residual with dysphoria (left) and social anxiety (right) residuals.

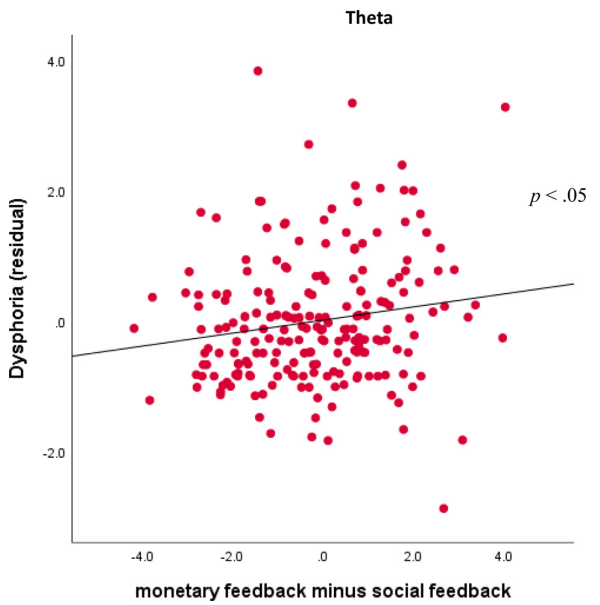


FIGURE 7 | Associations between TF4SF1 (theta activity) for monetary feedback and symptoms. Scatterplots displaying the associations between theta activity for monetary feedback (averaged across valence and outcome) subtracting social feedback (averaged across valence and outcome) and dysphoria symptoms.

also isolating effects associated with the intrinsic reward of being correct. It is important to note that the two delta factors also exhibited differences. Specifically, delta-low was sensitive to positive vs. negative valence and correct vs. incorrect feedback across domains. Delta-high showed greater activity to correct compared to incorrect feedback in both positive and negative social tasks, and in positive but not negative monetary task. In the negative monetary task (i.e., pick the door with the monetary loss), both outcomes were associated with potential conflict (e.g., losing money but being correct or breaking even but being incorrect), and this might explain why delta activity did not differ between the two outcomes. This was not the case for social feedback, suggesting that getting the correct social feedback was most salient. Overall, delta-high exhibited more nuanced task-manipulation effects compared to delta-low.

Unlike delta activity, theta activity was insensitive to task domain and was more sensitive to incorrect vs. correct outcome when the context was negative, and not to the monetary or social nature of the feedback. In experiments designed to elicit response errors, greater theta activity has been associated with error processing and conflict monitoring (Trujillo and Allen, 2007; Cavanagh et al., 2009; Cohen and Donner, 2013), and has been posited to be involved in increased cognitive control after committing errors (Cavanagh and Shackman, 2015). Our finding of greater theta activity to incorrect than correct feedback is hence consistent with these prior findings. On the other hand, previous studies using monetary gambling tasks have found theta activity sensitive to negative valenced outcome (i.e., loss; Bernat et al., 2015; Foti et al., 2015; Webb et al., 2017). However, under the current design, feedback of incorrect outcome and negative valence (i.e., no loss) compared to correct outcome negative valence (i.e., loss) was associated with greater theta activity, suggesting that theta activity may be more sensitive to outcome correctness than valence. In addition, this effect also applies to social feedback such that receiving incorrect feedback when guessing rejection elicited a higher theta than correctly guessing rejection.

The current findings are largely in line with previous studies showing more severe depression is associated with blunted reward-related delta in adults (Foti et al., 2015) and adolescents

(Nelson et al., 2018), as well as greater loss-related theta (Webb et al., 2017). However, there are several unique aspects in the present study. First, none of these previous studies directly compared monetary vs. social tasks or correct vs. incorrect outcomes. The current study demonstrated that when these two variables were examined, the depression-related blunted delta was specific to social tasks and correct feedback, regardless of valence. This discrepancy indicates that being correct may be more salient than obtaining positive feedback and is more sensitive to individual differences in depressive symptoms. Additionally, in the sample of emerging young adults, delta activity to social feedback may be more sensitive to depression compared to monetary feedback. In terms of theta activity, there was no association between just monetary loss-related theta with depressive symptoms. Instead, it was the difference between monetary-related and social-related theta that was related to depression, regardless of valence or outcome. This difference from previous findings is possibly driven by critical task design differences mentioned above. Overall, these findings suggest that depression is related to blunted neural response to correct vs. incorrect social feedback and increased sensitivity to monetary compared to social feedback.

The current study is also the first to examine feedback-related delta and theta activity in association with social anxiety symptoms. Activity of both delta factors to social-feedback was associated with social anxiety symptoms. While lower depressive symptoms were associated with greater delta activity to social feedback, more severe social anxiety symptoms were associated with greater delta activity to social feedback. The positive association between social anxiety and social feedback-related delta activity suggests that individuals with more severe social anxiety show a greater difference in their delta activity in response to correct vs. incorrect social outcomes, regardless of the valence. This may indicate an increased sensitivity to being correct in making social judgments. Our findings suggest that, at least in non-clinical young adult samples, social feedback may be a more sensitive domain to elicit neural responses related to social anxiety symptoms compared to monetary feedback. These findings may underlie the neural processes contributing to the selective biases to negative social signals observed in individuals with social anxiety (Amin et al., 1998; Mogg et al., 2004).

Some limitations of the current study must be acknowledged. First, in order to control potential confounds, social feedback was purportedly provided by strangers. However, decision-making behaviors are sensitive to social feedback provided by a close friend but not strangers (Sip et al., 2015). Therefore, future research is needed to test whether the current results remain when relationship closeness is manipulated. Also, the monetary task involved equal wins and losses which may have negatively impacted participants' motivation due to a lack of substantial incentives. Future studies are needed to examine the neural responses using unbalanced trials or manipulating the probability of winning vs. losing. Second, the study largely included young adults without clinically significant levels of anxiety and depression. Based on recommended cut-off scores from a recent study examining the clinical utility of IDAS-II scales (Stasik-O'Brien et al., 2019), 14 (∼6.9%) and 20 (∼9.8%) participants scored above the clinical cut-offs for depression and social anxiety, respectively. This limits the generalizability of the findings to other demographic populations and clinical samples. Furthermore, future research examining a broader range of socioeconomic status and age range (e.g., adolescence) are needed. Analytically, in order to keep it consistent with our previous investigation (Nelson et al., 2018) the current analyses utilized a baseline window that ended at the time of feedback onset, which can be suboptimal due to the potential temporal leakage of trial-related activity (Cohen, 2014). Future studies should consider the use of an earlier baseline period [e.g., −500 to −300 ms as previously suggested (Cohen, 2014)]. Also, the number of trials in the current study was based on prior psychometric research of time-domain RewP rather than time-frequency measurement. Future studies using a larger number of trials are encouraged to examine the replicability of the current findings. Finally, future research may examine whether the neural results probed by this laboratory experiment predict real-life decision-making both financially and socially. For instance, it remains to be tested whether blunted delta to social feedback and/or increased theta to monetary feedback predicts suboptimal decision-making in social networking and monetary investment.

In conclusion, the current findings suggest that previously demonstrated reward-related delta and non-reward-related theta activity are subject to the specific characteristics of feedback and outcome (e.g., domain, valence, and correctness). In addition, these results demonstrate the usage of time-frequency analyses to investigate dissociable neural processes in response to various aspects of feedback. This study also sheds light on the importance of examining neural responses to social feedback in understanding the neural processes in decision-making and elucidate their associations with psychopathology.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript.

ETHICS STATEMENT

All participants gave written informed consent and the study was approved by the Stony Brook University Institutional Review Board.

AUTHOR CONTRIBUTIONS

JMJ and BN contributed to task design and data collection. JJ, AS, and ZI conducted data analyses. JJ, AS, ZI, JMJ, and BN contributed to manuscript writing.

FUNDING

This study was funded by National Institute of Mental Health (NIMH) grant K01MH107808 awarded to Dr. BN.

REFERENCES

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®).* Arlington, VA: American Psychiatric Pub.

Amin, N., Foa, E. B., and Coles, M. E. (1998). Negative interpretation bias in social phobia. *Behav. Res. Ther.* 36, 945–957. doi: 10.1016/s0005-7967(98)00060-6

Bernat, E. M., Nelson, L. D., and Baskin-Sommers, A. R. (2015). Time-frequency theta and delta measures index separable components of feedback processing in a gambling task. *Psychophysiology* 52, 626–637. doi: 10.1111/psyp.12390

Bernat, E. M., Nelson, L. D., Steele, V. R., Gehring, W. J., and Patrick, C. J. (2011). Externalizing psychopathology and gain-loss feedback in a simulated gambling task: dissociable components of brain response revealed by time-frequency analysis. *J. Abnorm. Psychol.* 120, 352–364. doi: 10.1037/a0022124

Bernat, E. M., Williams, W. J., and Gehring, W. J. (2005). Decomposing ERP time-frequency energy using PCA. *Clin. Neurophysiol.* 116, 1314–1334. doi: 10.1016/j.clinph.2005.01.019

Bernoulli, D. (1954). Exposition of a new theory on the measurement of risk. *Econometrica* 22, 23–36.

Bress, J. N., Foti, D., Kotov, R., Klein, D. N., and Hajcak, G. (2013). Blunted neural response to rewards prospectively predicts depression in adolescent girls. *Psychophysiology* 50, 74–81. doi: 10.1111/j.1469-8986.2012.01485.x

Cattell, R. B. (1966). The scree test for the number of factors. *Multivariate Behav. Res.* 1, 245–276. doi: 10.1207/s15327906mbr0102_10

Cavanagh, J. F., Cohen, M. X., and Allen, J. J. (2009). Prelude to and resolution of an error: EEG phase synchrony reveals cognitive control dynamics during action monitoring. *J. Neurosci.* 29, 98–105. doi: 10.1523/JNEUROSCI.4137-08.2009

Cavanagh, J. F., and Shackman, A. J. (2015). Frontal midline theta reflects anxiety and cognitive control: meta-analytic evidence. *J. Physiol. Paris* 109, 3–15. doi: 10.1016/j.jphysparis.2014.04.003

Cella, M., Dymond, S., and Cooper, A. (2010). Impaired flexible decision-making in major depressive disorder. *J. Affect. Disord.* 124, 207–210. doi: 10.1016/j.jad.2009.11.013

Chan, R. C., Li, Z., Li, K., Zeng, Y. W., Xie, W. Z., Yan, C., et al. (2016). Distinct processing of social and monetary rewards in late adolescents with trait anhedonia. *Neuropsychology* 30, 274–280. doi: 10.1037/neu0000233

Cohen, M. X. (2014). *Analyzing Neural Time Series Data: Theory and Practice.* Cambridge, MA: MIT Press.

Cohen, M. X., and Donner, T. H. (2013). Midfrontal conflict-related theta-band power reflects neural oscillations that predict behavior. *J. Neurophysiol.* 110, 2752–2763. doi: 10.1152/jn.00479.2013

Cohen, M. X., Elger, C. E., and Ranganath, C. (2007). Reward expectation modulates feedback-related negativity and EEG spectra. *Neuroimage* 35, 968–978. doi: 10.1016/j.neuroimage.2006.11.056

Delorme, A., and Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* 134, 9–21. doi: 10.1016/j.jneumeth.2003.10.009

Dien, J. (2010a). The ERP PCA toolkit: an open source program for advanced statistical analysis of event-related potential data. *J. Neurosci. Methods* 187, 138–145. doi: 10.1016/j.jneumeth.2009.12.009

Dien, J. (2010b). Evaluating two-step PCA of ERP data with geomin, infomax, oblimin, promax, and varimax rotations. *Psychophysiology* 47, 170–183. doi: 10.1111/j.1469-8986.2009.00885.x

Distefano, A., Jackson, F., Levinson, A. R., Infantolino, Z. P., Jarcho, J. M., and Nelson, B. D. (2018). A comparison of the electrocortical response to monetary and social reward. *Soc. Cogn. Affect. Neurosci.* 13, 247–255. doi: 10.1093/scan/nsy006

Egger, H. L., Pine, D. S., Nelson, E., Leibenluft, E., Ernst, M., Towbin, K. E., et al. (2011). The NIMH Child Emotional Faces Picture Set (NIMH-ChEFS): a new set of children's facial emotion stimuli. *Int. J. Methods Psychiatr. Res.* 20, 145–156. doi: 10.1002/mpr.343

Eshel, N., and Roiser, J. P. (2010). Reward and punishment processing in depression. *Biol. Psychiatry* 68, 118–124. doi: 10.1016/j.biopsych.2010.01.027

Ethridge, P., Kujawa, A., Dirks, M. A., Arfer, K. B., Kessel, E. M., Klein, D. N., et al. (2017). Neural responses to social and monetary reward in early adolescence and emerging adulthood. *Psychophysiology* 54, 1786–1799. doi: 10.1111/psyp.12957

Everitt, B. J., and Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat. Neurosci.* 8, 1481–1489. doi: 10.1038/nn1579

Foti, D., Weinberg, A., Bernat, E. M., and Proudfit, G. H. (2015). Anterior cingulate activity to monetary loss and basal ganglia activity to monetary gain uniquely contribute to the feedback negativity. *Clin. Neurophysiol.* 126, 1338–1347. doi: 10.1016/j.clinph.2014.08.025

Foti, D., Weinberg, A., Dien, J., and Hajcak, G. (2011). Event-related potential activity in the basal ganglia differentiates rewards from nonrewards: response to commentary. *Hum. Brain Mapp.* 32, 2267–2269. doi: 10.1002/hbm.21357

Hartley, C. A., and Phelps, E. A. (2012). Anxiety and decision-making. *Biol. Psychiatry* 72, 113–118. doi: 10.1016/j.biopsych.2011.12.027

Hausler, A. N., Becker, B., Bartling, M., and Weber, B. (2015). Goal or gold: overlapping reward processes in soccer players upon scoring and winning money. *PLoS One* 10:e0122798. doi: 10.1371/journal.pone.0122798

Henriques, J. B., and Davidson, R. J. (2000). Decreased responsiveness to reward in depression. *Cogn. Emot.* 14, 711–724. doi: 10.1080/026999300501176 84

Holroyd, C. B., Pakzad-Vaezi, K. L., and Krigolson, O. E. (2008). The feedback correct-related positivity: sensitivity of the event-related brain potential to unexpected positive feedback. *Psychophysiology* 45, 688–697. doi: 10.1111/j.1469-8986.2008.00668.x

Homans, G. C. (1958). Social behavior as exchange. *Am. J. Sociol.* 63, 597–606. doi: 10.1086/222355

Izuma, K., Saito, D. N., and Sadato, N. (2008). Processing of social and monetary rewards in the human striatum. *Neuron* 58, 284–294. doi: 10.1016/j.neuron.2008.03.020

Kessel, E. M., Kujawa, A., Hajcak Proudfit, G., and Klein, D. N. (2015). Neural reactivity to monetary rewards and losses differentiates social from generalized anxiety in children. *J. Child Psychol. Psychiatry* 56, 792–800. doi: 10.1111/jcpp.12355

Kujawa, A., Arfer, K. B., Klein, D. N., and Proudfit, G. H. (2014). Electrocortical reactivity to social feedback in youth: a pilot study of the Island Getaway task. *Dev. Cogn. Neurosci.* 10, 140–147. doi: 10.1016/j.dcn.2014.08.008

Lin, A., Adolphs, R., and Rangel, A. (2012). Social and monetary reward learning engage overlapping neural substrates. *Soc. Cogn. Affect. Neurosci.* 7, 274–281. doi: 10.1093/scan/nsr006

Luck, S. J. (2014). *An Introduction to the Event-Related Potential Technique.* Cambridge, MA: MIT Press.

Luking, K. R., Pagliaccio, D., Luby, J. L., and Barch, D. M. (2016). Reward processing and risk for depression across development. *Trends Cogn. Sci.* 20, 456–468. doi: 10.1016/j.tics.2016.04.002

Mogg, K., Philippot, P., and Bradley, B. P. (2004). Selective attention to angry faces in clinical social phobia. *J. Abnorm. Psychol.* 113, 160–165. doi: 10.1037/0021-843x.113.1.160

Nelson, B. D., Infantolino, Z. P., Klein, D. N., Perlman, G., Kotov, R., and Hajcak, G. (2018). Time-frequency reward-related delta prospectively predicts the development of adolescent-onset depression. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 3, 41–49. doi: 10.1016/j.bpsc.2017.07.005

Nelson, B. D., Perlman, G., Klein, D. N., Kotov, R., and Hajcak, G. (2016). Blunted neural response to rewards as a prospective predictor of the development of depression in adolescent girls. *Am. J. Psychiatry* 173, 1223–1230. doi: 10.1176/appi.ajp.2016.15121524

Nolan, H., Whelan, R., and Reilly, R. B. (2010). FASTER: fully automated statistical thresholding for EEG artifact rejection. *J. Neurosci. Methods* 192, 152–162. doi: 10.1016/j.jneumeth.2010.07.015

Novak, K. D., and Foti, D. (2015). Teasing apart the anticipatory and consummatory processing of monetary incentives: an event-related potential study of reward dynamics. *Psychophysiology* 52, 1470–1482. doi: 10.1111/psyp.12504

Phelps, E. A., Lempert, K. M., and Sokol-Hessner, P. (2014). Emotion and decision making: multiple modulatory neural circuits. *Annu. Rev. Neurosci.* 37, 263–287. doi: 10.1146/annurev-neuro-071013-014119

Proudfit, G. H. (2015). The reward positivity: from basic research on reward to a biomarker for depression. *Psychophysiology* 52, 449–459. doi: 10.1111/psyp.12370

Rademacher, L., Krach, S., Kohls, G., Irmak, A., Grunder, G., and Spreckelmeyer, K. N. (2010). Dissociation of neural networks for anticipation

and consumption of monetary and social rewards. *Neuroimage* 49, 3276–3285. doi: 10.1016/j.neuroimage.2009.10.089

Sanfey, A. G. (2007). Social decision-making: insights from game theory and neuroscience. *Science* 318, 598–602. doi: 10.1126/science.1142996

Sip, K. E., Smith, D. V., Porcelli, A. J., Kar, K., and Delgado, M. R. (2015). Social closeness and feedback modulate susceptibility to the framing effect. *Soc. Neurosci.* 10, 35–45. doi: 10.1080/17470919.2014.944316

Spencer, K. M., Dien, J., and Donchin, E. (2001). Spatiotemporal analysis of the late ERP responses to deviant stimuli. *Psychophysiology* 38, 343–358. doi: 10.1017/s0048577201000324

Stasik-O'Brien, S. M., Brock, R. L., Chmielewski, M., Naragon-Gainey, K., Koffel, E., McDade-Montez, E., et al. (2019). Clinical utility of the inventory of depression and anxiety symptoms (IDAS). *Assessment* 26, 944–960. doi: 10.1177/1073191118790036

Trujillo, L. T., and Allen, J. J. (2007). Theta EEG dynamics of the error-related negativity. *Clin. Neurophysiol.* 118, 645–668. doi: 10.1016/j.clinph.2006.11.009

Tversky, A., and Kahneman, D. (1992). Advances in prospect theory: cumulative representation of uncertainty. *J. Risk Uncertain.* 5, 297–323. doi: 10.1007/bf00122574

van der Veen, F. M., van der Molen, M. J., van der Molen, M. W., and Franken, I. H. (2016). Thumbs up or thumbs down? Effects of neuroticism and depressive symptoms on psychophysiological responses to social evaluation in healthy students. *Cogn. Affect. Behav. Neurosci.* 16, 836–847. doi: 10.3758/s13415-016-0435-2

Von Neumann, J., and Morgenstern, O. (2007). *Theory of Games and Economic Behavior*. Princeton, NJ: Princeton University Press.

Watson, D., O'Hara, M. W., Naragon-Gainey, K., Koffel, E., Chmielewski, M., Kotov, R., et al. (2012). Development and validation of new anxiety and bipolar symptom scales for an expanded version of the IDAS (the IDAS-II). *Assessment* 19, 399–420. doi: 10.1177/1073191112449857

Watson, D., O'Hara, M. W., Simms, L. J., Kotov, R., Chmielewski, M., McDade-Montez, E. A., et al. (2007). Development and validation of the inventory of depression and anxiety symptoms (IDAS). *Psychol. Assess.* 19, 253–268. doi: 10.1037/1040-3590.19.3.253

Webb, C. A., Auerbach, R. P., Bondy, E., Stanton, C. H., Foti, D., and Pizzagalli, D. A. (2017). Abnormal neural responses to feedback in depressed adolescents. *J. Abnorm. Psychol.* 126, 19–31. doi: 10.1037/abn0000228

Wrase, J., Kahnt, T., Schlagenhauf, F., Beck, A., Cohen, M. X., Knutson, B., et al. (2007). Different neural systems adjust motor behavior in response to reward and punishment. *Neuroimage* 36, 1253–1262. doi: 10.1016/j.neuroimage.2007.04.001

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 13 September 2019
doi: 10.3389/fnbeh.2019.00209

Social and Non-social Reward Processing and Depressive Symptoms Among Sexual Minority Adolescents

Kristen L. Eckstrand[1], Luis E. Flores Jr.[2], Marissa Cross[1], Jennifer S. Silk[3], Nicholas B. Allen[4], Kati L. Healey[5], Michael P. Marshal[1] and Erika E. Forbes[1]*

[1]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, United States, [2]Department of Psychology, Queen's University, Kingston, ON, Canada, [3]Department of Psychology, University of Pittsburgh, Pittsburgh, PA, United States, [4]Department of Psychology, University of Oregon, Eugene, OR, United States, [5]Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC, United States

OPEN ACCESS

Edited by:
Jason M. Chein, Temple University, United States

Reviewed by:
Yansong Li, Nanjing University, China
Ciara McCabe, University of Reading, United Kingdom

***Correspondence:**
Kristen L. Eckstrand
eckstrandkl@upmc.edu

Specialty section:
This article was submitted to Emotion Regulation and Processing, a section of the journal Frontiers in Behavioral Neuroscience

Received: *07 March 2019*
Accepted: *29 August 2019*
Published: *13 September 2019*

Citation:
Eckstrand KL, Flores LE Jr, Cross M, Silk JS, Allen NB, Healey KL, Marshal MP and Forbes EE (2019) Social and Non-social Reward Processing and Depressive Symptoms Among Sexual Minority Adolescents. Front. Behav. Neurosci. 13:209. doi: 10.3389/fnbeh.2019.00209

Sexual minority adolescents (SMA) are more likely to suffer from depression, putatively through experiences of social stress and victimization interfering with processing of social reward. Alterations in neural reward networks, which develop during adolescence, confer risk for the development of depression. Employing both social and monetary reward fMRI tasks, this is the first neuroimaging study to examine function in reward circuitry as a potential mechanism of mental health disparities between SMA and heterosexual adolescents. Eight SMA and 38 heterosexual typically developing adolescents completed self-report measures of depression and victimization, and underwent fMRI during monetary and peer social reward tasks in which they received positive monetary or social feedback, respectively. Compared with heterosexual adolescents, SMA had greater interpersonal depressive symptoms and exhibited blunted neural responses to social, but not monetary, reward in socioaffective processing regions that are associated with depressive symptoms. Specifically, compared with heterosexual adolescents, SMA exhibited decreased activation in the right medial prefrontal cortex, left anterior insula (AI), and right temporoparietal junction (TPJ) in response to being liked. Lower response in the right TPJ was associated with greater interpersonal depressive symptoms. These results suggest that interpersonal difficulties and the underlying substrates of response to social reward (perhaps more so than response to monetary reward) may confer risk for development of depressive symptoms in SMA.

Keywords: depression, adolescence, social reward, LGBT, fMRI

INTRODUCTION

Sexual minority adolescents (SMA), including those who identify as lesbian, gay, or bisexual, are four times more likely to meet criteria for Major Depressive Disorder and are at three times greater risk for suicidal thoughts and behaviors compared with their heterosexual peers (Fergusson et al., 1999; Marshal et al., 2011; Burton et al., 2013). Minority stress theory posits that mental health

concerns among SMA arise in part as a response to interpersonal stress and victimization (Meyer, 2003). SMA are more likely to experience interpersonal stress and victimization compared with heterosexual peers, and victimization is correlated with greater depression and suicidal ideation that persist into young adulthood (Burton et al., 2013). Expectations of interpersonal rejection are further associated with depression (Feinstein et al., 2012). These adverse experiences emerge at a younger age in SMA than heterosexual peers, sometimes even prior to adolescence.

Depression among SMA is not simply the result of negative interpersonal interactions, but also is postulated to arise from the paucity of positive interactions and social support. SMA who do not have openly accepting and supportive families experience greater depressive symptoms and suicidal ideation than those who do (Ryan et al., 2010). SMA who live in less socially supportive environments are more likely to attempt suicide than those living in supportive environments (Williams et al., 2005; Hatzenbuehler, 2011). Even after disclosing their sexual orientation to others ("coming out"), SMA who perceive that they are not accepted or are a "burden" to others experience greater depressive symptoms and suicidal ideation (Baams et al., 2015). Altogether, these findings suggest that depression among LGB youth results from both the presence of interpersonal stress and disruption of reward, particularly during social situations (e.g., receiving social approval).

Typically developing adolescents tend to exhibit heightened reward function compared with children and adults (Somerville et al., 2010) due to the asynchronous development of "traditional" neural reward circuits [including e.g., ventral striatum, dorsomedial prefrontal cortex (dmPFC)] and self-regulation circuits [including e.g., dorsolateral and ventrolateral prefrontal cortex (vlPFC); Forbes and Dahl, 2012]. As adolescents gain independence, develop greater social orientation, and desire social status gains, these frontostriatal reward networks are particularly influenced by social reward neurocircuitry [e.g., temporoparietal junction (TPJ), anterior insula (AI); Blakemore, 2008]. While social development plays a critical role in typical adolescent brain development, social experiences including victimization, prosocial behavior, low parental support, peer liking and rejection, and social stress are associated with altered activity in both neural reward and social circuits (Auerbach et al., 2014; Casement et al., 2014; Morelli et al., 2014; Telzer et al., 2014). Further, changes in neural reward and social circuits have been associated with the development of depressive symptoms in adolescence (Forbes et al., 2009; Healey et al., 2014; Miller et al., 2015; Stringaris et al., 2015). Together, these literatures suggest that adolescents' altered neural response to reward in general may confer risk for the development of depressive symptoms, and this risk may be influenced by particularly salient social experiences—such as being liked by peers.

The social context of reward could be especially salient for SMA given their unique experiences of social stress and the importance of acceptance with parents, peers, and even romantic/sexual partners. Despite the fact that SMA have unique social experiences including victimization, are more likely to experience depressive symptoms compared with heterosexual peers, and that sexual orientation is typically self-identified and communicated to others beginning in adolescence, the neural circuitry underlying the interplay between social acceptance and the development of depression has not yet been investigated. In this first neuroimaging study comparing SMA and heterosexual youth, we explored neural response to differing reward contexts (e.g., monetary and social reward), victimization, and depressive symptoms between SMA and heterosexual adolescents. We specifically hypothesized that SMA would exhibit decreased activation in social reward neural circuits in response to being liked by peers but would not exhibit these differing responses to monetary reward. We further hypothesized that these altered patterns would be associated with self-reported depressive symptoms. Lastly, we hypothesized that victimization would moderate the association between altered neural activation and self-reported depressive symptoms, where individuals who have experienced victimization would demonstrate the relationship between altered neural activation and self-reported depressive symptoms.

MATERIALS AND METHODS

Participants

Seventy adolescents aged 14–18 with no history of psychiatric disorder/treatment or serious medical problems were recruited from community settings to participate in a study on social reward processing in typically developing adolescents. Of the recruited 70 participants, 46 completed all behavioral, self-report, and neuroimaging measures and were included in the final sample of the present study [19M, 27F (16.3 $\pm$ 1.4 years), 65% white/Caucasian, 24% black/African American, 11% mixed racial background]. Recruited individuals were excluded from the final sample (n = 24) if they did not complete the fMRI scan due to scanning exclusionary criteria (n = 8; three due to recent concussion, three due to claustrophobia, two due to mental health diagnosis), could not be contacted or withdrew from the study after their initial behavioral assessment (n = 5), did not complete the fMRI task or were removed due to scan quality (n = 8), or had missing behavioral data (n = 3). Male and female participants did not differ in age or race. The University of Pittsburgh IRB approved all research procedures and written informed consent was obtained from each participant and a parent or guardian.

Measures

Sexual Orientation Identity

All participants answered the single question, "What is your sexual identity?" with one of the following: 100% Heterosexual (Straight), Mostly Heterosexual (Straight, but somewhat attracted to people of your own sex), Bisexual (Attracted to men and women equally), Mostly Homosexual (Gay, but somewhat attracted to people of the opposite sex), 100% Homosexual (Gay or Lesbian). This demographic question is equivalent to that used in the National Longitudinal Study of Adolescent Health (Chen and Chantala, 2014), defining sexual orientation identity in terms of same-sex sexual attraction.

This approach was used as prior data has demonstrated that adolescents' endorsement of same-sex attraction and same-sex sexual identity varies across adolescent development (Marshal et al., 2013), and only assessing one measure may incorrectly identify SMA as heterosexual. All individuals who identified with a non-same sex identity or attraction were classified as SMA.

Depressive Symptoms

Participants completed the Center for Epidemiologic Studies Depression Scale (Radloff, 1977; CES-D) to assess depressive symptoms. The CES-D is a 20-item self-report scale, where higher scores indicate the presence of more symptomatology. Four previously determined factors of the CES-D were examined: depressed affect, positive affect, somatic symptoms, and interpersonal difficulty (Radloff, 1977).

Victimization

The Youth Risk Behavior Survey (YRBS) 2009 (Eaton et al., 2010) is a validated epidemiologic self-report instrument assessing health-risk behaviors in high school students, including victimization. All participants completed the YRBS, and victimization was calculated based on a previously identified YRBS measure items of victimization among SMA (Russell et al., 2014). Items assessing victimization were related to fighting, bullying, and safety (see **Supplementary Material**). The composite measure of victimization was calculated as the standardized mean of these individual items.

Social Reward Task

Participants completed an fMRI social reward task to investigate neural response to positive social feedback as previously described in Healey et al. (2014). Prior to scanning, participants rated photos of other adolescents (40 photos; 50% female) based on how much they thought they would like the individuals in the photos (1 = "not at all" to 9 = "very much"); participants were told their photos would be "rated" by the other adolescents. A personalized stimulus set was created for each participant containing blocks of *positive feedback*, where participants received feedback that their peers rated them favorably and *neutral feedback* where they were informed that peers had not yet rated them.

Personalized stimulus sets were presented in a block design composed of *positive feedback* and *neutral feedback* blocks. Each of the 32 stimuli was presented three times over eight blocks, with each block consisting of 12 stimuli and lasting 84 s. Of the eight blocks, four were *positive feedback* and four were *neutral feedback*. Each block also contained two images of the opposite stimulus type in order to minimize habituation and predictability from the block design (e.g., positive feedback blocks contained 10 *positive feedback* stimuli and two *neutral feedback* stimuli). Each image was presented for 3 s, with a jittered inter-trial interval between stimuli and an inter-block interval of 8 s. Participants were instructed to press a button every time they saw a face to confirm they were attending to the task. At the end of the scan, the deception of the task was disclosed, and participants were told that their image had not been rated by other adolescents.

Monetary Reward Task

Neural response to monetary reward was assessed using an adapted task card-guessing task (Delgado et al., 2000; Nusslock et al., 2012). In this event-related paradigm, each trial was comprised of an anticipation period and an outcome period, where potential outcomes could be a win, loss, or no-change trial. Participants were told that they would receive $1 for win trials, lose $0.50 in loss trials, and neither win nor lose money in the no-change trial. However, trials were fixed in a pseudorandomized fashion where all participants received the same number of win, loss, or no-change trials. Participants were unaware of the fixed outcomes.

Each trial began with a "decision" card containing a question mark symbol where participants had 4 s to guess, through button press, whether the value of a presented card was higher or lower than five. The anticipation phase began with a card presenting the trial type (reward or loss). After 6 s, the actual numerical value of the card (1–9) was presented (500 ms). The outcome phase was then shown (a green upward-facing arrow for win, a red downward-facing arrow for loss, or a yellow circle for neutral feedback; 500 ms) and a crosshair presented for 9 s. There were six trials of each outcome (i.e., win, loss, no win, no loss).

fMRI Acquisition and Preprocessing

Participants were scanned using a Siemens 3T Trio scanner at the University of Pittsburgh Magnetic Resonance Research Center (MRRC). MPRAGE structural images were acquired with high-resolution T1-weighted images with 1 mm isometric voxels (TR/TE/flip angle = 2,300 ms/2.98 ms/9; FOV = 256 × 240; 1.2 mm slice; 160 slices; 256 × 240 matrix; 1 Nex). Functional blood oxygen level dependent (BOLD) images were acquired using gradient echo planar imaging (EPI) sequences: 39 oblique axial slices (3.1 mm thick, 0 mm gap) beginning at the cerebral vertex and encompassing the entire cerebrum and the majority of the cerebellum, oriented to the AC-PC line (TR/TE = 2,000 MS/30 ms, FOV = 205 × 205, matrix = 64 × 64). A reference EPI scan acquired prior to fMRI data collection was visually inspected for artifacts and signal quality.

Preprocessing and fMRI image analysis was performed using Statistical Parametric Mapping software, version 8[1]. Images for each subject were realigned, motion-corrected, and high-pass temporally filtered with a cut-off of 128 s Volumes with high motion and artifacts were adjusted using ART (volumes where average image intensity deviated >3SD from the mean intensity or where movement exceeded 0.5 mm in translation or 0.01° in rotation from the previous image[2], Chai et al., 2014). The mean functional image was coregistered with the high-resolution 3D anatomic image, normalized to standard stereotactic space (Montreal Neurological Institute template) using a 12-parameter affine model, and spatially smoothed with a 6 mm full-width at half-maximum Gaussian filter.

[1]http://www.fil.ion.ucl.ac.uk/spm
[2]https://www.nitrc.org/projects/artifact_detect

Data Analysis

Second Level fMRI

Neural response to being liked in the social reward task was determined for each individual by contrasting brain activity during receipt of positive feedback compared with blocks of neutral feedback (*positive > neutral feedback*), as this contrast reflects social reward and corresponds to adolescents' experience of others' evaluation in social settings (e.g., social media). Neural response to monetary reward was determined for each individual by contrasting brain activity during anticipation of a reward in a win condition compared with anticipation in neutral (no-change) conditions (*win anticipation > neutral*). Both of these contrasts have been demonstrated to reflect the neural reward response in social and monetary contexts, respectively, in adolescents (Nusslock et al., 2012; Healey et al., 2014). Whole-brain individual contrast images were entered into two separate two-sample *t*-tests to examine differences in brain activation between SMA and heterosexual adolescents in response to: (1) peer liking; and (2) monetary reward anticipation. Age, gender, and race were included as covariates in the model. Age was included as a continuous variable; gender (male, female) and race (white/Caucasian, black/African American, mixed racial background) were included as nominal variables. Given that socioaffective circuitry encompasses multiple neural regions across networks, whole brain analyses were used for second-level analyses.

Monte Carlo simulations using REST v1.8[3] were used to estimate the minimum number of contiguous voxels per cluster (activated at $p_{unc} < 0.005$) corrected to avoid Type I error ($p_{corr} < 0.05$), resulting in a cluster extent threshold of 154 voxels for whole-brain analyses of social reward and 379 voxels for reward anticipation. As discussed in detail in the **Supplementary Material**, these thresholding criteria were selected because block designs with longer activity durations analyzed in SPM with two groups, as in the social reward task in this study, are less affected by cluster extent thresholding errors and are expected to yield a false positive rate of ≤5% (Eklund et al., 2016). Individual parameter estimates of the BOLD response for clusters reaching significance in second-level analyses were extracted using Marsbar[4]. One participant was removed from the analyses as an outlier, due to their BOLD signal cluster of interest >3 standard deviations from the mean.

Depressive Symptoms and Victimization

To address potential outliers, a 95% winsorization was applied to self-report scales where data points >3 standard deviations from the mean were replaced by values exactly 3 standard deviations from the mean. Across depressive symptom subscales and victimization, only one data point required winsorizing (see **Supplementary Figure S1**). Winsorizing this data point did not affect the significance of group differences (see **Supplementary Table S2**). As expected from a typically-developing sample, behavioral data were not normally distributed using the Kolmogorov–Smirnov test and were instead skewed towards having lower or no symptoms (*CES-D Subscales*: somatic symptoms, $D_{(46)} = 0.154$, $p = 0.008$; depressed affect, $D_{(46)} = 0.252$, $p < 0.001$; positive affect, $D_{(46)} = 0.175$, $p = 0.001$; interpersonal difficulty, $D_{(46)} = 0.402$, $p < 0.001$; *Victimization*: $D_{(46)} = 0.449$, $p < 0.001$). As such, differences in depressive symptoms based on sexual orientation and victimization were determined using non-parametric two-sample tests with bootstrapping (n = 10,000 resamples) implemented in SPSS v23. As behavioral variables were not normally distributed, a multiple linear regression analysis with bootstrapping (n = 10,000 resamples) was performed to test the robustness of the association between neural activation in areas where activation differed by sexual orientation and depressive symptoms (Fox, 2002). The four CES-D depressive symptom subscales were included as dependent variables and neural activation in the aforementioned regions were included as independent variables in the single model. Because neural activation measures had already been corrected for demographic variables, these variables were not re-entered into the multiple linear regression model. Finally, the PROCESS macro (Hayes, 2013) was used to test the moderating effect of victimization.

[3]http://restfmri.net/forum/REST_V1.8
[4]http://marsbar.sourceforge.net/

RESULTS

No Difference in Demographic Factors Between SMA and Heterosexual Adolescents

Of the 46 adolescents included in the final sample, 38 identified with the sexual identity of "100% Heterosexual" whereas the remaining 8 identified with a sexual minority sexual identity. There was no difference between heterosexual adolescents and SMA by age (Heterosexual: 16.3 ± 1.4 years; SMA: 16.3 ± 1.2 years; $t_{(1,42)} = 0.20$, $p = 0.84$), gender (Heterosexual: 18M/20F; SMA: 1M/7F; ($\chi^2 = 3.26$, $p = 0.07$) or race (Heterosexual: 68% White, 24% Black/AA, 8% Multiracial; SMA: 50% White, 25% Black/AA, 25% Multiracial; $\chi^2 = 2.17$, $p = 0.34$).

Greater Interpersonal Depressive Symptoms Among SMA

SMA had significantly greater interpersonal depressive symptoms compared with heterosexual adolescents, although did not differ on other CES-D depressive subscales (see **Table 1**). Depressive symptoms did not differ based by age, gender, or race. Ten participants experienced one or more instances of victimization (see **Supplementary Table S1**), including two SMA and eight heterosexual adolescents. Across participants, experiencing victimization was positively associated with interpersonal depressive symptoms ($R^2 = 0.08$, $p = 0.05$) but not with other depressive symptoms. SMA did not experience greater victimization than heterosexual adolescents ($Z_{(1,45)} = -0.48$, $p = 0.69$). Males, however, did report more experiences of victimization compared with females (M: 0.21 ± 0.34, F: 0.04 ± 0.16; $Z_{(1,45)} = -2.17$, $p = 0.03$). Victimization was unrelated to age or race (see **Table 1**).

TABLE 1 | Depressive symptoms and victimization by sexual orientation.

		Orientation[a]		Race[b]		Gender[a]		Age[c]	
		Z	*p*	χ^2	*p*	*Z*	*p*	*F*	*p*
CES-D[†]	Somatic symptoms	−1.04	0.31	2.65	0.27	−0.11	0.91	0.36	0.55
	Depressive affect	−1.19	0.25	1.34	0.52	−0.49	0.63	0.45	0.50
	Positive affect	−0.28	0.79	0.30	0.99	−0.05	0.97	0.88	0.36
	Interpersonal difficulty	−2.18	**0.02**	0.66	0.73	−0.52	0.59	0.40	0.53
Victimization[†]		−0.48	0.69	1.62	0.49	−2.17	**0.03**	1.50	0.23

CES-D, Center for Epidemiologic Studies Depression Scale; SMA, sexual minority adolescents. [†]Performed with bootstrapping (n = 10,000 resamples). [a]Non-parametric two-sample test. [b]Non-parametric k-sample test. [c]Multiple linear regression. Bold values indicate p < 0.05.

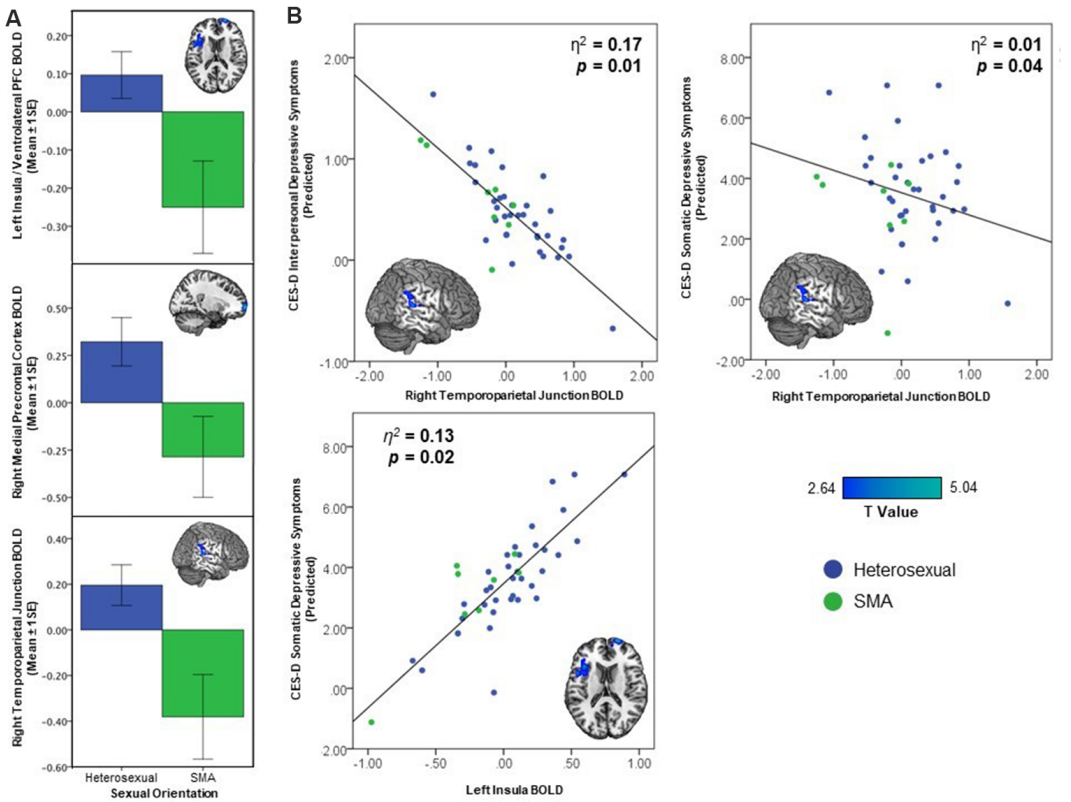


FIGURE 1 | Activation differences between sexual minority adolescents (SMA) and heterosexual adolescents In response to being liked demonstrating **(A)** less activation in the right mPFC, left anterior insula (AI)/ventrolateral prefrontal cortex (vlPFC), and right temporoparietal junction (TPJ), and **(B)** greater depressive symptoms associated with decreasing brain activation in the right TPJ and increased depressive symptoms in left AI/vlPFC.

SMA and Neural Response to Social and Monetary Reward

Whole brain analyses revealed differences based on sexual minority status in response to being liked (see **Figure 1A**). SMA exhibited less activation compared to their heterosexual peers in the right mPFC, left AI, and right TPJ during receipt of social reward (see **Table 2**). In contrast, there were no differences observed in neural activation to monetary reward anticipation between SMA and heterosexual adolescents. To test whether differences in reward response were isolated to social stimuli, we further examined neural response to monetary reward receipt (*win outcome* > *neutral outcome*) and did not observe differences between SMA and heterosexual adolescents.

Depression Association With Regions Distinguishing SMA and Heterosexual Adolescents

The three clusters that distinguished neural response to social reward in SMA and heterosexual adolescents were included in a multiple linear regression predicting depression subscales. The right TPJ—within the cluster whose activity distinguished SMA from heterosexual adolescents—was associated with depressive symptoms. Specifically, lower right TPJ activation was associated

TABLE 2 | Activation differences in response to being liked between heterosexual and sexual minority adolescents (SMA), and relationship of BOLD response to depressive symptoms (CES-D).

Brain region	Hemi.	Vox.	Max T	x	y	z	Reg.	CES-D†				
								Somatic symptoms	Depressed affect	Positive affect	Interpersonal difficulty	f^2
Less activation in SMA												
medial prefrontal cortex	R	360	5.05	18	66	−2	β	0.50	0.88	0.27	<−0.01	0.04
							p	0.47	0.25	0.70	0.99	
Insula	L	456	4.38	−48	12	8	β	4.63	0.88	0.36	0.92	0.21
							p	**0.01**	0.60	0.88	0.07	
Temporoparietal junction	R	160	3.81	62	−32	10	β	−1.95	−1.07	0.36	−0.82	0.27
							p	**0.02**	0.19	0.64	**0.05**	

CES-D, Center for Epidemiologic Studies Depression Scale. †Multiple linear regression performed using bootstrapping (n = 10,000 resamples). Bold values indicate p < 0.05.

with higher interpersonal [β = −0.82, p = 0.05, 95% CI (−1.69, −0.18)] and somatic [β = −1.95, p = 0.02, 95% CI (−3.99, −0.55)] depressive symptoms (see **Figure 1B**, **Table 2**). Higher left insula activation was associated with greater somatic depressive symptoms [β = 4.63, p = 0.01, 95% CI (1.52, 8.35)]. While demographic variables were not re-included as covariates in the multiple linear regression model given neural activation values were already corrected for these variables, their inclusion in the multiple linear regression model did not change the significance of the above findings (see **Supplementary Table S3**). Contrary to our hypothesis, victimization did not moderate these associations ($F_{(1,41)}$ = 1.15, p = 0.29).

DISCUSSION

This is the first study to examine differences in brain function between sexual minority and heterosexual typically developing adolescents. The findings from this study suggest that SMA—who experienced greater interpersonal depressive symptoms compared with heterosexual adolescents—may exhibit altered function in salience and social processing networks in response to social reward compared with heterosexual adolescents. Furthermore, blunted neural response in the right TPJ—a region implicated in perspective-taking and processing social information—was associated with higher interpersonal depressive symptom severity.

SMA are a population at high risk for depression, and they are more likely than heterosexual youth to have experienced social stressors, such as interpersonal victimization and rejection (Burton et al., 2013). Consistent with this, sexual minority status in our sample remained the key predictor of interpersonal depressive symptoms whereas age, gender, and race did not.

The present study provides preliminary support for neural correlates of these disparities, demonstrating decreased activation to social reward in mPFC, AI, vlPFC, and TPJ in a sample of SMA. These regions are consistent with altered function in social reward circuitry in youth with depression (Forbes et al., 2009; Healey et al., 2014). Further, SMA experienced greater interpersonal depressive symptoms, and lower right TPJ response to social reward was associated with greater interpersonal depressive symptoms. In contrast, SMA did not exhibit differential patterns of the neural response to monetary reward anticipation. Decreased activation to monetary reward is also associated with depression in adolescence (Keren et al., 2018). This suggests that social reward processes may be particularly important in understanding the development of depression in SMA. Given that the current fMRI task involved peer feedback, participants were provided an opportunity for spontaneous perspective-taking including considering others' perceptions of them. The right TPJ is critical for perspective-taking (Krall et al., 2015), and lower activation in this region in response to social reward suggests that SMA may be less engaged during socially rewarding feedback compared with heterosexual youth. Such cognitive disengagement in rewarding social situations may explain depression-associated lower TPJ response in SMA and subsequently the heightened interpersonal depressive symptoms experienced by SMA.

It is important to note that while deactivation in the right TPJ—a region in which SMA demonstrated decreased activation compared to heterosexual adolescents—was associated with greater depressive symptom severity, deactivation in the AI was associated with *decreased* somatic symptom severity. This may be due to the differences in function between the TPJ and AI/vlPFC. Whereas the TPJ is a critical region in socioaffective processing, the AI is implicated in somatosensory, interoceptive, and salience processing (Smith et al., 2014). The decreased activation of the AI may be due to the prior experiences or expectation of peer rejection and subsequently decreased salience by SMA in response to being liked (Rudolph et al., 2016). However, greater activation of AI is expected with somatosensory experiences, including those associated with depressive symptoms (e.g., sleep, appetite). Alternatively, this finding raises the possibility that the specific activation patterns seen among SMA may confer both risk and resilience in the development of depression. Altogether, these findings indicate that SMA demonstrate altered activity in a network of regions with putative socioaffective function. Furthermore, this different pattern of neural activity might serve as a mechanism for increased risk for the social and affect regulation difficulties that are considered central to depression (Davey et al., 2008; Burnett et al., 2011; Auerbach et al., 2014). Future work is necessary to examine the role of SMA-related

discrimination in socioaffective circuitry and, subsequently, affective states.

Unexpectedly, heterosexual adolescents and SMA did not differ in victimization experiences, and victimization did not moderate SMA effects on depression. This may be due to the measures of victimization included in the YRBS, which focus primarily on violent victimization. While this is one component of victimization is experienced by SMA, more specific scales have been developed to measure additional aspects of sexual minority-related stress (Newcomb and Mustanski, 2010; Goldbach et al., 2017). These scales, which include questions such as "There are times when I do not want to be LGBTQ" and "I expect people to reject me when they find out that I am LGBTQ," measure a wider variety of victimization and negative interpersonal experiences not present in the YRBS (Goldbach et al., 2017). Further studies examining the impact of orientation-related stress on social reward circuits and depressive symptoms are necessary. Further, the focus on violent victimization may explain the observed effect of gender, as adolescent males typically have more experiences of violent victimization than females (Tillyer and Tillyer, 2016).

It is worth noting that few research studies examine multiple classes of reward in the same study, with the current results suggesting that depressive symptoms in SMA may be more related to social, but not monetary reward. However, there are clear differences between the two reward fMRI tasks utilized in this study that limit their direct comparison (e.g., the social reward task was a block design while the monetary reward task was an event-related design) and future studies may want to examine neural correlates of classes of rewarding stimuli using similarly designed fMRI tasks. Further, while the results do demonstrate differences in neural activation between SMA and heterosexual adolescents, the association between these regions and depressive symptoms does not specifically demonstrate an SMA-related pattern of depressive symptoms as the associations between activation and depressive symptoms were across the entire sample. While mPFC involvement in adolescent depression is well-recognized, the present study demonstrates mPFC deactivation among SMA in a more anteriorly located mPFC region (Etkin et al., 2011); it is currently unclear what role deactivation of this region has on social reward processing and depression. Again, additional work is necessary to understand how the unique social and environmental experiences associated with being a SMA could influence adolescent neurodevelopment and affective states. Finally, while images of all genders were included in the individualized paradigms, we did not control for attraction and it is likely that all participants felt some degree of romantic/sexual attraction to some of the peer images irrespective of sexual orientation. While there is evidence for neural correlates of sexual reward and attraction (Gola et al., 2015; Eckstrand et al., 2017), whether there are detectable neural differences between SMA and heterosexual adolescents remains unclear. The degree to which sexual/romantic attraction is influencing the presented results is unknown and is a potential area for future research.

Even with the apparent relevance of these findings to affective psychopathology in SMA, the present study is clearly preliminary given the small sample size and results should be interpreted with caution. Given the small size of the SMA group, there is the chance for Type II error or the chance that we were underpowered to detect smaller but meaningful group differences. Several methods were applied to support the replicability and power of the data. First, covariates that potentially influence the presented results—including age, gender, and race—were corrected for in the imaging model. Second, a multiple linear regression was performed to minimize multiple comparisons. All models were performed with bootstrapping, supporting the reliability of findings and stability of the data. Lastly, *post hoc* power analyses supported that the presented data were adequately powered to detect medium-to-large effects (see **Supplementary Figure S2**). While these tests better characterize the clear limitations of the sample size and results, larger studies drawn from a population with a wider range of clinical depressive symptoms—with ample power to detect smaller group differences and sample sizes robust to the influence of outliers—will be critical for elucidating the presence and meaning of differences (Poldrack et al., 2017). However, based on the striking disparities in interpersonal stress-related depression and suicide risk among SMA, it is critical to further explore the relationships between interpersonal interactions related to sexual identity development and the neural circuits underlying the development of depression. Such research is important, even in those who are psychiatrically healthy, particularly given that adolescents normatively have higher depressive symptoms and that examining subthreshold clinical variability may be helpful in understanding individual risk.

Despite these limitations, the present study is noteworthy for being the first to examine differences in neural activation between SMA and heterosexual adolescents. It offers novel initial findings suggesting that blunted neural responses to social, but not monetary, reward in socioaffective processing regions distinguish SMA from heterosexual adolescents and may serve as a mechanism for depression. These findings overlap with the observed disparity in—and provide a plausible neural signature for the development of—depression prevalence among SMA. Further, these findings can provide important guidance for future studies using prospective designs and sampling from broader SMA populations to explore the interaction between social experiences, brain development, to potentially lead to depression among SMA.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the University of Pittsburgh Institutional Review Board with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the University of Pittsburgh Institutional Review Board.

AUTHOR CONTRIBUTIONS

KE, JS, NA, MM and EF contributed to the conception of the work. KE, LF, MC and KH contributed to the acquisition, analysis, and interpretation of data for the work. KE, LF, MM and EF drafted and revised the work for important intellectual content. All authors gave final approval for publication of the work and agree to accountable for the accuracy and integrity of the work.

FUNDING

This work was supported by the National Institutes of Health [R21 DA033612 (EF, PI)].

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2019.00209/full#supplementary-material

REFERENCES

Auerbach, R. P., Admon, R., and Pizzagalli, D. A. (2014). Adolescent depression: stress and reward dysfunction. *Harv. Rev. Psychiatry* 22, 139–148. doi: 10.1097/hrp.0000000000000034

Baams, L., Grossman, A. H., and Russell, S. T. (2015). Minority stress and mechanisms of risk for depression and suicidal ideation among lesbian, gay, and bisexual youth. *Dev. Psychol.* 51, 688–696. doi: 10.1037/a0038994

Blakemore, S.-J. (2008). The social brain in adolescence. *Nat. Rev. Neurosci.* 9, 267–277. doi: 10.1038/nrn2353

Burnett, S., Sebastian, C., Kadosh, K. C., and Blakemore, S.-J. (2011). The social brain in adolescence: evidence from functional magnetic resonance imaging and behavioural studies. *Neurosci. Biobehav. Rev.* 35, 1654–1664. doi: 10.1016/j.neubiorev.2010.10.011

Burton, C. M., Marshal, M. P., Chisolm, D. J., Sucato, G. S., and Friedman, M. S. (2013). Sexual minority-related victimization as a mediator of mental health disparities in sexual minority youth: a longitudinal analysis. *J. Youth Adolesc.* 42, 394–402. doi: 10.1007/s10964-012-9901-5

Casement, M. D., Guyer, A. E., Hipwell, A. E., McAloon, R. L., Hoffmann, A. M., Keenan, K. E., et al. (2014). Girls' challenging social experiences in early adolescence predict neural response to rewards and depressive symptoms. *Dev. Cogn. Neurosci.* 8, 18–27. doi: 10.1016/j.dcn.2013.12.003

Chai, X. J., Ofen, N., Gabrieli, J. D. E., and Whitfield-Gabrieli, S. (2014). Development of deactivation of the default-mode network during episodic memory formation. *Neuroimage* 84, 932–938. doi: 10.1016/j.neuroimage.2013.09.032

Chen, P., and Chantala, K. (2014). *Guidelines for Analyzing Add Health Data.* Chapel Hill, NC: Carolina Population Center, University of North Carolina at Chapel Hill.

Davey, C. G., Yücel, M., and Allen, N. B. (2008). The emergence of depression in adolescence: development of the prefrontal cortex and the representation of reward. *Neurosci. Biobehav. Rev.* 32, 1–19. doi: 10.1016/j.neubiorev.2007.04.016

Delgado, M. R., Nystrom, L. E., Fissell, C., Noll, D. C., and Fiez, J. A. (2000). Tracking the hemodynamic responses to reward and punishment in the striatum. *J. Neurophysiol.* 84, 3072–3077. doi: 10.1152/jn.2000.84.6.3072

Eaton, D. K., Kann, L., Kinchen, S., Shanklin, S., Ross, J., Hawkins, J., et al. (2010). Youth risk behavior surveillance—United States, 2009. *MMWR Surveill. Summ.* 59, 1–142.

Eckstrand, K. L., Choukas-Bradley, S., Mohanty, A., Cross, M., Allen, N. B., Silk, J. S., et al. (2017). Heightened activity in social reward networks is associated with adolescents' risky sexual behaviors. *Dev. Cogn. Neurosci.* 17, 1–9. doi: 10.1016/j.dcn.2017.07.004

Eklund, A., Nichols, T. E., and Knutsson, H. (2016). Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. *Proc. Natl. Acad. Sci. U S A* 113, 7900–7905. doi: 10.1073/pnas.1602413113

Etkin, A., Egner, T., and Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn. Sci.* 15, 85–93. doi: 10.1016/j.tics.2010.11.004

Feinstein, B. A., Goldfried, M. R., and Davila, J. (2012). The relationship between experiences of discrimination and mental health among lesbians and gay men: an examination of internalized homonegativity and rejection sensitivity as potential mechanisms. *J. Consult. Clin. Psychol.* 80, 917–927. doi: 10.1037/a0029425

Fergusson, D. M., Horwood, L. J., and Beautrais, A. L. (1999). Is sexual orientation related to mental health problems and suicidality in young people? *Arch. Gen. Psychiatry* 56, 876–880. doi: 10.1001/archpsyc.56.10.876

Forbes, E. E., and Dahl, R. E. (2012). Research review: altered reward function in adolescent depression: what, when and how? *J. Child Psychol. Psychiatry* 53, 3–15. doi: 10.1111/j.1469-7610.2011.02477.x

Forbes, E. E., Hariri, A. R., Martin, S. L., Silk, J. S., Moyles, D. L., Fisher, P. M., et al. (2009). Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *Am. J. Psychiatry* 166, 64–73. doi: 10.1176/appi.ajp.2008.07081336

Fox, J. (2002). *Bootstrapping Regression Models. An R and S-PLUS Companion to Applied Regression: A Web Appendix to the Book.* Thousand Oaks, CA: Sage. Available online at: http://citeseerx.ist.psu.edu/viewdoc/summary?doi=10.1.1.182.9082. Accessed January 4, 2018.

Gola, M., Miyakoshi, M., and Sescousse, G. (2015). Sex, impulsivity, and anxiety: interplay between ventral striatum and amygdala reactivity in sexual behaviors. *J. Neurosci.* 35, 15227–15229. doi: 10.1523/JNEUROSCI.3273-15.2015

Goldbach, J. T., Schrager, S. M., and Mamey, M. R. (2017). Criterion and divergent validity of the sexual minority adolescent stress inventory. *Front. Psychol.* 8:2057. doi: 10.3389/fpsyg.2017.02057

Hatzenbuehler, M. L. (2011). The social environment and suicide attempts in lesbian, gay, and bisexual youth. *Pediatrics* 127, 896–903. doi: 10.1542/peds.2010-3020

Hayes, A. F. (2013). *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach.* New York, NY: Guilford Press.

Healey, K. L., Morgan, J., Musselman, S. C., Olino, T. M., and Forbes, E. E. (2014). Social anhedonia and medial prefrontal response to mutual liking in late adolescents. *Brain Cogn.* 89, 39–50. doi: 10.1016/j.bandc.2013.12.004

Keren, H., O'Callaghan, G., Vidal-Ribas, P., Buzzell, G. A., Brotman, M. A., Leibenluft, E., et al. (2018). Reward processing in depression: a conceptual and meta-analytic review across fMRI and EEG studies. *Am. J. Psychiatry* 11, 1111–1120. doi: 10.1176/appi.ajp.2018.17101124

Krall, S., Rottschy, C., Oberwelland, E., Bzdok, D., Fox, P., Eickhoff, S., et al. (2015). The role of the right temporoparietal junction in attention and social interaction as revealed by ALE meta-analysis. *Brain Struct. Funct.* 220, 587–604. doi: 10.1007/s00429-014-0803-z

Marshal, M. P., Dermody, S. S., Cheong, J., Burton, C. M., Friedman, M. S., Aranda, F., et al. (2013). Trajectories of depressive symptoms and suicidality among heterosexual and sexual minority youth. *J. Youth Adolesc.* 42, 1243–1256. doi: 10.1007/s10964-013-9970-0

Marshal, M. P., Dietz, L. J., Friedman, M. S., Stall, R., Smith, H. A., McGinley, J., et al. (2011). Suicidality and depression disparities between sexual minority and heterosexual youth: a meta-analytic review. *J. Adolesc. Health* 49, 115–123. doi: 10.1016/j.jadohealth.2011.02.005

Meyer, I. H. (2003). Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. *Psychol. Bull.* 129, 674–697. doi: 10.1037/0033-2909.129.5.674

Miller, C. H., Hamilton, J. P., Sacchet, M. D., and Gotlib, I. H. (2015). Meta-analysis of functional neuroimaging of major depressive disorder in youth. *JAMA Psychiatry* 72, 1045–1053. doi: 10.1001/jamapsychiatry.2015.1376

Morelli, S. A., Torre, J. B., and Eisenberger, N. I. (2014). The neural bases of feeling understood and not understood. *Soc. Cogn. Affect. Neurosci.* 9, 1890–1896. doi: 10.1093/scan/nst191

Newcomb, M. E., and Mustanski, B. (2010). Internalized homophobia and internalizing mental health problems: a meta-analytic review. *Clin. Psychol. Rev.* 30, 1019–1029. doi: 10.1016/j.cpr.2010.07.003

Nusslock, R., Almeida, J. R., Forbes, E. E., Versace, A., Frank, E., Labarbara, E. J., et al. (2012). Waiting to win: elevated striatal and orbitofrontal cortical activity during reward anticipation in euthymic bipolar disorder adults. *Bipolar Disord.* 14, 249–260. doi: 10.1111/j.1399-5618.2012.01012.x

Poldrack, R. A., Baker, C. I., Durnez, J., Gorgolewski, K. J., Matthews, P. M., Munafò, M. R., et al. (2017). Scanning the horizon: towards transparent and reproducible neuroimaging research. *Nat. Rev. Neurosci.* 18, 115–126. doi: 10.1038/nrn.2016.167

Radloff, L. S. (1977). The CES-D scale a self-report depression scale for research in the general population. *Appl. Psychol. Meas.* 1, 385–401. doi: 10.1177/014662167700100306

Rudolph, K. D., Miernicki, M. E., Troop-Gordon, W., Davis, M. M., and Telzer, E. H. (2016). Adding insult to injury: neural sensitivity to social exclusion is associated with internalizing symptoms in chronically peer-victimized girls. *Soc. Cogn. Affect. Neurosci.* 11, 829–842. doi: 10.1093/scan/nsw021

Russell, S. T., Everett, B. G., Rosario, M., and Birkett, M. (2014). Indicators of victimization and sexual orientation among adolescents: analyses from Youth Risk Behavior Surveys. *Am. J. Public Health* 104, 255–261. doi: 10.2105/ajph.2013.301493

Ryan, C., Russell, S. T., Huebner, D., Diaz, R., and Sanchez, J. (2010). Family acceptance in adolescence and the health of LGBT young adults. *J. Child Adolesc. Psychiatr. Nurs.* 23, 205–213. doi: 10.1111/j.1744-6171.2010.00246.x

Smith, A. R., Steinberg, L., and Chein, J. (2014). The role of the anterior insula in adolescent decision making. *Dev. Neurosci.* 36, 196–209. doi: 10.1159/000358918

Somerville, L. H., Jones, R. M., and Casey, B. (2010). A time of change: behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. *Brain Cogn.* 72, 124–133. doi: 10.1016/j.bandc.2009.07.003

Stringaris, A., Vidal-Ribas Belil, P., Artiges, E., Lemaitre, H., Gollier-Briant, F., Wolke, S., et al. (2015). The brain's response to reward anticipation and depression in adolescence: dimensionality, specificity, and longitudinal predictions in a community-based sample. *Am. J. Psychiatry* 172, 1215–1223. doi: 10.1176/appi.ajp.2015.14101298

Telzer, E. H., Fuligni, A. J., Lieberman, M. D., and Galván, A. (2014). Neural sensitivity to eudaimonic and hedonic rewards differentially predict adolescent depressive symptoms over time. *Proc. Natl. Acad. Sci. U S A* 111, 6600–6605. doi: 10.1073/pnas.1323014111

Tillyer, M. S., and Tillyer, R. (2016). Race, ethnicity, and adolescent violent victimization. *J. Youth Adolesc.* 45, 1497–1511. doi: 10.1007/s10964-016-0416-3

Williams, T., Connolly, J., Pepler, D., and Craig, W. (2005). Peer victimization, social support, and psychosocial adjustment of sexual minority adolescents. *J. Youth Adolesc.* 34, 471–482. doi: 10.1007/s10964-005-7264-x

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 25 September 2019
doi: 10.3389/fnbeh.2019.00222

Neural Activation to Parental Praise Interacts With Social Context to Predict Adolescent Depressive Symptoms

Stefanie L. Sequeira[1]*, *Rosalind D. Butterfield*[1], *Jennifer S. Silk*[1], *Erika E. Forbes*[2] and *Cecile D. Ladouceur*[2]

[1]Department of Psychology, University of Pittsburgh, Pittsburgh, PA, United States, [2]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, United States

OPEN ACCESS

Edited by:
Jason M. Chein,
Temple University, United States

Reviewed by:
Johanna M. Jarcho,
Temple University, United States
Michael Fritz,
Linköping University, Sweden
Charlis Raineki,
University of British Columbia, Canada

***Correspondence:**
Stefanie L. Sequeira
SLS234@pitt.edu

Specialty section:
This article was submitted to Individual and Social Behaviors, a section of the journal Frontiers in Behavioral Neuroscience

Received: 28 February 2019
Accepted: 09 September 2019
Published: 25 September 2019

Citation:
Sequeira SL, Butterfield RD, Silk JS, Forbes EE and Ladouceur CD (2019) Neural Activation to Parental Praise Interacts With Social Context to Predict Adolescent Depressive Symptoms. Front. Behav. Neurosci. 13:222. doi: 10.3389/fnbeh.2019.00222

Negative relationships with parents and peers are considered risk factors for depression in adolescence, yet not all adolescents perceiving negative social relationships develop depression. In line with neurobiological susceptibility to social context models, we examined how individual differences in neural processing of parental praise, a unique form of social reward, might explain variability in susceptibility to perceived maternal acceptance and peer victimization. During neuroimaging, 38 11- to 17-year-olds with a history of anxiety listened to audio clips of a parent (predominately mothers) providing personalized praise and neutral statements. Average activation during parental praise clips relative to neutral clips was extracted from several anatomically-defined reward-related regions-of-interest (ROIs): the subgenual anterior cingulate cortex, caudate nucleus, amygdala, nucleus accumbens, and insula. Moderation models included direct effects and interactions between neural activation to social reward, peer victimization, and maternal acceptance at the time of scanning on depressive symptoms 1 year later. Results showed a significant three-way interaction for the bilateral caudate such that peer victimization was associated with depressive symptoms only for individuals with higher caudate response to praise who perceived maternal acceptance as low. Consistent with neurobiological susceptibility to social context models, caudate activation to social reward could represent a neural marker that helps explain variability in adolescent sensitivity to social contexts. High caudate activation to praise could reflect a history of negative experiences with parents and/or peers that places youth at greater risk for depressive symptoms. Findings suggest that interactions between neural response to reward and salient social contexts may help us understand changes in depressive symptoms during a period of development marked by significant biopsychosocial change.

Keywords: social reward, adolescence, depression, peer victimization, parenting, neuroimaging (functional)

INTRODUCTION

Rates of depression increase significantly during adolescence. While only about 2%–3% of 9- to 12-year-olds meet diagnostic criteria for any depressive disorder (Costello et al., 2003), this number jumps to 10%–20% between the ages of 13 and 18 (Lewinsohn et al., 1993; Merikangas et al., 2010) and may be even higher in youth with a history of anxiety (Pine et al., 1998; Kessler et al., 2001). Research investigating biopsychosocial risk factors for major depression in early-mid adolescence (ages 9–15) suggests that negative relationships with peers and parents (Reinherz et al., 1993) and altered functioning in reward-related brain regions (Forbes and Dahl, 2012) can increase the risk for developing a depressive disorder by age 18. The joint influence of these factors has rarely been tested but may be key to understanding changes in depressive symptoms during adolescence. Developmental models suggest that social stressors influence depressive symptoms through effects on reward-related brain function (Forbes and Dahl, 2005; Nelson et al., 2005; Davey et al., 2008). A recent framework also suggests that trait-like individual differences in reward-related brain activity may help explain variability in susceptibility to negative peer and familial interactions (Schriber and Guyer, 2016). Examining how neurobiological and interpersonal factors work together to influence depressive symptoms is of heightened importance during adolescence, given significant changes in brain structure and function and reorganization of the social environment that occurs during this developmental period (Nelson et al., 2005).

Social contexts change dramatically during adolescence. The amount of time spent outside the home increases significantly from early childhood to adolescence (Gifford-Smith and Brownell, 2003), and peers begin to fulfill needs for intimacy, companionship, and reinforcement of personal worth that were previously fulfilled by parents (Rubin et al., 2006). Co-occurring with this increase in social salience of peers, however, is an increase in peer victimization. Peer victimization, also commonly labeled harassment or bullying, is common, with about 10%–20% of high school students in the US reporting moderate to high frequency of peer victimization (Nansel et al., 2001; Brunstein Klomek et al., 2007). Peer victimization in childhood and adolescence has damaging effects on psychological adjustment and is strongly associated cross-sectionally and longitudinally with symptoms of depression (Hawker and Boulton, 2000; Desjardins and Leadbeater, 2011; Ttofi et al., 2011; Stapinski et al., 2015) that can endure into adulthood (Olweus, 1993; Gladstone et al., 2006). Although the negative outcomes associated with victimization are salient and can be persistent, not all youth who experience bullying and rejection develop significant symptoms of depression. Identifying potential protective factors that make some youth more resilient to the negative effects of peer victimization is critical to developing appropriate prevention and intervention programs.

One such protective factor may be parental support and acceptance. Although adolescents become more dependent on peers during this developmental period, there is clear evidence that support from parents is still important (Colarossi and Eccles, 2003; Rueger et al., 2010). Further, greater perceived parental support and acceptance has been consistently linked to lower rates of adolescent depression (Zimmerman et al., 2000; Barber et al., 2005). The stress-buffering model proposes that high parental support and acceptance as experienced by the child can work to buffer the negative effects of peer victimization on depression (Cohen and Wills, 1985). Theoretically, peer victimization is thought to lead to a sense of incompetence and other depressive self-schemas (Bilsky et al., 2013). High perceived parental acceptance might serve as a source of positive information that can increase feelings of competence and self-worth to offset the depressive effects of peer victimization (Cole et al., 1997). Research testing the stress-buffering model has yielded mixed results, with some work finding support for this model (e.g., Bonanno and Hymel, 2010) and other work finding more support for a main effects model in which supportive parenting and peer victimization exert main effects on depressive symptoms but do not interact (e.g., Bilsky et al., 2013). Additional studies have found support for both a stress-buffering model and a main effects model (Conners-Burrow et al., 2009; Stadler et al., 2010). Most of this work relied on self-report measures of victimization, parental support, and depressive symptoms, suggesting that methodological differences likely do not entirely explain conflicting results.

An alternative explanation for the inconsistent results regarding how peer victimization and parental support influence depressive symptoms in adolescence may be individual differences in how adolescents perceive or respond to positive parenting behaviors, such as parental support and warmth. A recent framework proposed by Schriber and Guyer (2016) suggests that adolescent development is influenced by brain-based individual differences in sensitivity to social contexts, including relationships with parents and peers. The authors propose that activity in social-affective/reward-related brain regions (e.g., striatum, amygdala, insula, subgenual anterior cingulate cortex) may serve as stable, trait-like markers of sensitivity to social contexts, as these regions appear to be functionally sensitive to social experiences (for a review see Schriber and Guyer, 2016). Although brain structure and function are undoubtedly shaped by environmental influences, brain function is also largely determined by genes and is relatively stable within and across adolescence and adulthood (Manuck et al., 2007; Caceres et al., 2009; Zuo et al., 2010; Koolschijn et al., 2011). Thus, neural response to maternal praise in social reward and social-affective brain regions including the nucleus accumbens, caudate, amygdala, anterior insula, and subgenual anterior cingulate cortex, may be shaped by a combination of genes and a history of parenting influences, and this activation may provide insight into how receptive an individual is to current and future maternal warmth and acceptance.

This question is particularly relevant given that adolescence is characterized by increases in reward-seeking behavior and corresponding changes in reward-related brain circuitry (Galvan, 2010). In addition, aberrant function in regions of reward

circuitry, including the striatum and medial prefrontal cortex (mPFC), has been linked to greater depressive symptoms in adolescence (for a review see Forbes and Dahl, 2012). Although early work focused on relations between depressive symptoms and neural activation to monetary rewards (e.g., Forbes et al., 2009), increasing focus is currently being paid to how alterations in neural activation to social rewards may be linked to adolescent depressive symptoms. This is especially important given that depressed mood is thought to have a strong social function (Allen and Badcock, 2003) and given the heightened salience of social-affective information during adolescence (Blakemore and Mills, 2014). Some research has found that adolescents with or at high risk for depression show attenuated neural response in the striatum and amygdala to passive social rewards, such as happy faces (Monk et al., 2008; Olino et al., 2015), as well as to active social rewards, such as maternal praise (Aupperle et al., 2016; Silk et al., 2017). However, one study found that adolescents with depression showed heightened activation to positive social feedback in subcortical structures including the amygdala (Davey et al., 2011). Depression in adolescence has also been linked to heightened amygdala activation to maternal criticism (Aupperle et al., 2016) and to heightened neural response to peer rejection in the amygdala, subgenual anterior cingulate, anterior insula, and nucleus accumbens (Silk et al., 2014). Together, these latter findings may suggest that adolescents with depression are more sensitive to social feedback, regardless of valence, in daily life.

In support of the hypothesis that social experiences may affect function in reward-related brain regions, several studies have linked normative variations in parenting behaviors to individual differences in youth's neural responses to salient affective information from both parents and peers. For example, in a sample of 11- to 17-year-olds, Tan et al. (2014) examined how normative variations in maternal affect during a parent-child problem-solving task are associated with a child's brain function during peer evaluation. Longer durations of maternal negative affect during the dyadic task were associated with reduced neural response to peer acceptance in the subgenual anterior cingulate, amygdala, nucleus accumbens, and anterior insula (Tan et al., 2014). This may suggest that greater maternal negative affect works to dampen the child's neural processing of rewarding social interactions. A second study using a sample of boys also found that greater maternal warmth in early childhood (18 and 24 months), observed during mother-child interactions, was associated with reduced activation in sons' mPFC when anticipating monetary loss in late adolescence (age 20; Morgan et al., 2014). Further, greater maternal warmth in adolescence (10 and 11 years) was associated with reduced mPFC when winning rewards and greater striatal activation when losing rewards at age 20. These findings suggest that reward-related brain regions are sensitive to maternal behaviors in childhood and adolescence. Although no work has yet been done specifically linking parental warmth and acceptance to neural activation to parental praise, Lee et al. (2014) found that perceived parental warmth was negatively correlated with neural activity in the temporoparietal junction and precuneus, social cognitive processing regions, when healthy adolescents (ages 9–17) listened to maternal criticism. The authors suggest that youth who feel more supported by their parents may be more motivated to reduce social cognitive processing while receiving criticism to protect their relationship with their parents. Together, these studies (Lee et al., 2014; Morgan et al., 2014; Tan et al., 2014) suggest potential associations between parental warmth and acceptance and brain function in adolescence.

Despite what is known about the separate effects of social stress and neural processing of social reward on depression, as well as what is known about the potential influence of social relationships on the brain, surprisingly little is known about how social stressors and brain function might interact to influence the development of depression. Developmental models posit that social stressors, including peer victimization and low parental warmth and acceptance, may influence depression through effects on neural reward circuitry (Forbes and Dahl, 2005; Nelson et al., 2005; Davey et al., 2008), though this has rarely been tested. One recent study, however, did examine specifically how low parental warmth, peer victimization, and depressive symptoms predict neural response during reward anticipation of monetary reward several years later in a large sample of adolescent girls. Casement et al. (2014) found that peer victimization in early adolescence (ages 11–12) was associated with decreased response in the mPFC to rewards in mid-adolescence (age 16). They also found that low parental warmth in early adolescence (ages 11–12) was associated in mid-adolescence (age 16) with increased activation to monetary rewards in the striatum (including the nucleus accumbens and caudate), amygdala, and the mPFC. Importantly, increased activity in the striatum and mPFC to rewards mediated the relationship between low parental warmth (ages 11–12) and depressive symptoms at age 16. Results provided initial support that normative variations in peer victimization and parental warmth may affect functioning of reward circuitry, which in turn may influence depressive symptoms. This may also suggest that high neural activity to rewards reflects past experiences of low parental warmth, which may place youth at risk for future depression. This interpretation aligns with the neurobiological susceptibility to social context framework (Schriber and Guyer, 2016). The goal of the current study was to test a complementary moderation model to further examine this framework in an independent sample, with the aim of exploring the extent to which neural activation to parental praise, a reward both social and personal in nature, may moderate the effects of concurrent perceptions of parental warmth and peer victimization on the development of depressive symptoms.

Investigating how interactions between neural reward processing and perceptions of social relationships influence depressive symptoms may be especially relevant for children with a history of anxiety, who may be at increased risk for developing depressive disorders in adolescence compared to children without a history of anxiety (Brady and Kendall, 1992; Orvaschel et al., 1995; Cummings et al., 2014). Although not all youth with anxiety will go on to develop depression, up to 75% of adolescents with depression have a history of at least one anxiety disorders (Kessler et al., 2001). Anxious

youth also generally report more negative interactions with parents and peers (Ginsburg et al., 1998; Caster et al., 1999; Hale et al., 2006). Further, over 50% of youth diagnosed with anxiety disorders report being victimized by peers (Cohen and Kendall, 2015). Finally, evidence is growing for the importance of reward processing in the pathophysiology of anxiety. Research suggests that youth with anxiety and at temperamental risk for anxiety exhibit heightened neural responses to the anticipation and receipt of monetary and social rewards, especially when rewards are contingent on performance (Guyer et al., 2006, 2012; Bar-Haim et al., 2009; Benson et al., 2015). Socially anxious adolescents also exhibit heightened striatal responses to unexpected positive social feedback compared to healthy adolescents (Jarcho et al., 2015). Based on existing evidence, Silk et al. (2012) theorized that youth with anxiety disorders experience a heightened sensitivity to social evaluative threat and altered reward processing, which interact during adolescence to influence the onset of depression. Thus, interactions between neural reward processing and negative interactions with parents and peers may be particularly important for influencing depressive symptoms in youth with a history of anxiety.

CURRENT STUDY

Building off prior literature (e.g., Lee et al., 2014; Tan et al., 2014; Casement et al., 2014), and guided in part by the neurobiological susceptibility to social context framework (Schriber and Guyer, 2016), the current study aimed to address how neural activation to parental praise, perceived maternal acceptance, and peer victimization predict depressive symptoms 1 year later in adolescents ages 11–18 with a history of an anxiety disorder. Almost all parents who provided praise statements for the fMRI task were biological mothers, with the exception of one biological father. Our primary analysis tested the three-way-interaction between neural activity, maternal acceptance, and peer victimization. Aligning with the neurobiological susceptibility to social context framework (Schriber and Guyer, 2016), which suggests that youth with high neurobiological susceptibility may be more sensitive to their social contexts, we hypothesized that youth with high neural response to parental praise would show the strongest interaction between maternal acceptance and peer victimization on depressive symptoms. Specifically, we hypothesized that youth with high neural activity and low perceived maternal acceptance would show the strongest relationship between peer victimization and increases in depressive symptoms, while youth with high neural activity and high perceived maternal acceptance would show the weakest relationship between peer victimization and increases in depressive symptoms. Given the increase in depressive symptoms that occurs during mid- late-adolescence, around the same time that significant brain maturation is occurring, examining how interactions between brain function, peers, and parenting contribute to this increase may provide critical insight into how to better prevent and treat depression during this developmental period.

MATERIALS AND METHODS

Participants

Participants were 38 youth (20 female) ranging in age from 11 to 17 years (M_{age} = 13.52 years, SD = 1.34). The sample was predominantly (94.7%) white. Total family income over the past year was reported on a scale of 0 (0–10, 000) to 10 (100,000+). In the current sample, mean total income was between $70,000 and 80,000, with a range between $20,000 and $100,000+. See **Table 1** for participant characteristics.

Participants were recruited from a randomized control trial (RCT) to take part in the Child Anxiety Treatment Study-Depression Follow-Up (CATS-D) study. Data used for the current study were collected as part of the CATS-D study. A primary aim of CATS-D was to examine the impact of prior anxiety treatment on the development of subsequent depressive symptoms (see Silk et al., 2018). Thus, all participants had a history of an anxiety disorder. At the time of CATS-D initiation, only 9 of the 38 participants met diagnostic criteria for at least one anxiety disorder; six participants were diagnosed with generalized anxiety disorder, three were diagnosed with social anxiety disorder, and one participant was diagnosed with separation anxiety disorder. No participants had developed co-occurring MDD.

As part of the RCT from which participants were recruited, youth were randomized to 16 sessions of either cognitive behavioral therapy (CBT) or Child-Centered Therapy (CCT) at a 2:1 ratio. Full RCT procedures, including a description of diagnostic exclusionary criteria, are described in Silk et al. (2017). Briefly, exclusionary criteria included an IQ below 70 as assessed by the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1997), a current primary diagnosis of major depressive disorder, attention-deficit/hyperactivity disorder (ADHD)-combined type of predominately hyperactive-impulsive type, ongoing treatment with psychoactive medication, acute suicidality or risk for harm to self or others, and failing to meet MRI safety requirements.

Procedure

In brief, 95 participants were recruited from the RCT into CATS-D and invited to return to the lab for assessments approximately 2 years post-treatment (Time 1). All procedures were approved by a University Institutional Review Board; youth and a parent/legal guardian provided informed consent. During the first visit, clinical diagnoses were determined by a master's level independent evaluator who was blind to treatment assignment using a semi-structured

TABLE 1 | Descriptive statistics of sample (n = 38).

	n (%)	M (SD)	Range
Age (years)	-	13.52 (1.34)	11–17
Sex–Female	20 (53%)	-	-
Total family income	-	$70,000–80,000	$20,000–100,000+
Anxiety diagnosis*			
Generalized anxiety disorder	6	-	-
Social anxiety disorder	3	-	-
Separation anxiety disorder	1	-	-

*Note: *Anxiety diagnoses determined at time of data collection for the current study.*

diagnostic interview. Participants completed self-report measures on depressive symptoms, perceived maternal behaviors, and peer victimization. During this visit, the participating parent, most often the biological mother, also recorded audio clips to be used in the fMRI assessment. The fMRI assessment was completed during their second visit, a few weeks following the first visit. Immediately prior to the fMRI assessment, participants were trained on the task and practiced remaining still in an MRI simulator.

As part of the CATS-D study, the self-report measure of depressive symptoms was also collected at 1-year follow-up (3 years post-treatment; Time 2). Complete data, including neuroimaging data, were available for a final sample of 38 participants. Most participating parents (n = 37) were biological mothers; one participating parent was a biological father. An additional nine participants had completed the neuroimaging scan but were missing data on depressive symptoms at 1-year follow-up (Time 2). These nine participants did not differ from included participants (n = 37) on age, sex, anxiety severity, or depressive symptoms at the time of CATS-D study initiation (all $ps > 0.50$).

Measures

Structured Diagnostic Interview

The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997), a structured diagnostic interview based on the DSM-IV (American Psychological Association, 1994), was administered by a trained clinician to all participants before confirming their inclusion in the larger study. Parents and youth were interviewed separately, with clinicians using data from both informants to arrive at a final diagnosis. Participants were included in the original treatment study if they received a diagnosis of GAD, SocAD, and/or SAD (see Silk et al., 2018). Inter-rater reliability between interviewers was calculated for 16% of interviews and found to be high (kappa = 0.97). The interview was conducted again 2-years following the completion of treatment, at the time that data collection for the current study began (Time 1). Reliability and validity analyses suggest the K-SADS-PL is a reliable and valid instrument for diagnosing anxiety disorders in children. The instrument has good test-retest reliability and high concurrent validity, such that children diagnosed with an anxiety disorder scored significantly higher than other children on self-reported anxiety measures (Kaufman et al., 1997).

Depressive Symptoms

The Mood and Feelings Questionnaire (MFQ; Angold and Costello, 1987) is a 33-item checklist that assesses a broad range of cognitive and vegetative symptoms of depression in children and adolescents. Each item is scored on a scale of 0 (*not true for me in the past 2 weeks*), 1 (*sometimes true for me in the past 2 weeks*), or 2 (*true for me in the past 2 weeks*), for a maximum score of 66. Children completed the child self-report version of the MFQ. In the current sample, scores on the MFQ ranged from 0 to 42 (with a mean of 9.93) at Time 1 (2 years post-treatment) and 0–30 (with a mean of 8.71) at Time 2 (3 years post-treatment). Although on average scores decreased from Time 1 to Time 2, around half the sample (n = 16) did show increases in depressive symptoms from Time 1 to Time 2. Scores above 27 on the MFQ may indicate the presence of depression. In the current sample, two participants had scores above 27 at Time 1 and three participants had scores above 27 at Time 2. However, no participants were diagnosed with MDD based on the K-SADS-PL. Cronbach's alpha for the MFQ at Time 2 was 0.93.

Maternal Acceptance

Adolescents completed a shortened version of the Children's Report of Parent's Behavior Inventory (CRPBI; Schaefer, 1965; Schludermann and Schludermann, 1970). This 30-item self-report questionnaire contains descriptions of maternal child-rearing behaviors rated by children. The CRPBI includes several subscales representing three dimensions of parenting: acceptance/rejection, autonomy/psychological control, and firm/lax behavioral control. For the current study, only the acceptance/rejection dimension was used (10 items). The acceptance/rejection dimension captures the extent to which mothers express care and affection (e.g., "Tells me how much she loves me"). Children rate how much the described parenting behavior applies to their own mother using a 3-point scale from 0 = *like*, 1 = *sometimes like*, or 2 = *not like*. Cronbach's alpha for the acceptance/rejection scale in this study was 0.89.

Peer Victimization

Peer victimization was measured using the Peer Relations Questionnaire (PRQ; Rigby and Slee, 1993). The PRQ is a widely-used self-report measure of bullying with three scales: a Bully scale, Victim scale, and Prosocial scale. The five-item Victim scale was used in the current study as a measure of perceived peer victimization, with scores ranging from 5 (low peer victimization) to 20 (high peer victimization). These items tap into social/relational victimization (e.g., "Other leave me out of things on purpose"), physical victimization (e.g., "I get hit and pushed around by others"), and verbal victimization (e.g., "I get called names by others"). In the current sample, scores ranged from 5 to 12. Cronbach's alpha for the Victim scale in this study was 0.80.

Anxiety Symptoms

Anxiety symptoms were measured from two sources at distinct time points for use in sensitivity analyses. First, youth self-reported on their anxiety symptoms using the Screen for Child Anxiety and Related Emotional Disorders (SCARED) at Time 1 (2 years post-treatment). Cronbach's alpha for the SCARED in this study was 0.92.

Second, as part of the larger RCT, independent evaluators rated child anxiety severity using the Pediatric Anxiety Rating Scale (PARS) at pre-treatment and post-treatment (Silk et al., 2017). A total PARS score was created by summing six items assessing anxiety severity, frequency, distress, avoidance, and

interference inside and outside the home over the prior week. Treatment response was coded dichotomously; youth were considered to have responded to treatment if they demonstrated at least a 35% reduction in diagnostician-rated PARS from pre- to post-treatment (Caporino et al., 2013). Cronbach's alpha for the PARS in this study was 0.62.

fMRI Assessment

Participants underwent an fMRI scan during which they listened to a parent's comments about them, delivered using MRI compatible headphones. The task included two audio clips for critical, praising, and neutral comments, which each lasted for 30 s. Procedures for obtaining the audio clips followed those used in previous studies (Hooley et al., 2005, 2009; Silk et al., 2017). Each parent produced two 30 s clips describing things that bothered her about her child (critical statements) beginning with "[Name], one thing that bothers me about you is…", two 30 s clips describing things she likes about her child (praise statements) beginning with, "[Name], one thing I really like about you is…", and two 30 s neutral clips about something their child would not find interesting (e.g., the weather). Critical, praising, and neutral statements were delivered in separate blocks (one block each). Each block consisted of two 30.06 s presentations (30 s audio clip and 0.06 duration to match 1.67 s TR) and three 30.06 s rest periods. The neutral block was presented first and the praise and criticism blocks were counterbalanced for order.

BOLD Functional MRI Acquisition, Preprocessing, and Analysis

Imaging Acquisition

Images were acquired using a 3T Siemens Trio scanner. Blood-oxygen-level-dependent (BOLD) functional images were acquired using a T2* weighted reverse echo planar imaging (EPI) sequence. Thirty-two 3.2 mm axial slices were acquired parallel to the anterior-posterior commissure line (TR/TE = 1,670/29 ms, FOV = 205 mm, flip angle = 75°). There were three blocks. Each block lasted for 150.3 s, and 90 images were collected in each block. Before the start of the fMRI task, a high-resolution T1-weighted MPRAGE image (1 mm, axial) was collected for each participant.

fMRI Data Preprocessing

Images were preprocessed and analyzed using SPM12. Volumes were manually re-oriented to the anterior-posterior commissure line and corrected for slice timing. Images were then realigned to correct for motion, segmented, and co-registered to the mean functional image. Realigned images were spatially normalized to standard MNI template and smoothed with a 6 mm full-width at half-maximum Gaussian filter. Voxels were resampled during preprocessing to be 2 mm^3. Volumes with motion greater than 5 mm/5° and global intensities more than 3 standard deviations from the mean were detected using SPM ART toolbox. Data were excluded from analyses if >25% of volumes per session were detected as outliers. Despiking was completed with interpolation using the ArtRepair toolbox in SPM. Motion parameters were included as regressors in the general linear model design in first level analyses to correct for slow-drift motion.

fMRI Analyses

First-level analyses included repaired pre-processed volumes, six motion parameters, and all conditions from each run (i.e., criticism, praise, neutral, rest). The contrast included for the current analyses was Praise > Neutral. Final analyses used a region-of-interest (ROI) approach. Based on similar previous literature (Silk et al., 2014, 2017; Tan et al., 2014) and based on what is known about brain regions that activate to social reward, nine *a priori* ROIs were included in current analyses—left and right nucleus accumbens, left and right caudate nucleus, left and right amygdala, left and right anterior insula, and subgenual ACC. Anatomically-defined masks for each region were created using the Talaraich atlas in the WFU PickAtlas tool (Maldjian et al., 2003). For each participant, the main effects of the task at each voxel in the brain were calculated using a *t*-statistic, producing a statistical image for each participant for the contrast of interest: Praise > Neutral. Parameter estimates for this contrast of interest were extracted from each anatomical ROI using MarsBaR (Brett et al., 2002) and loaded into SPSS v24.0.

Data Analysis

Data were analyzed using SPSS version 24.0. All independent variables were mean-centered prior to analyses, with the exception of sex which was dummy coded (0 = male; 1 = female). Main and interactive effects of peer victimization, maternal acceptance, and neural activation to parental praise at Time 1 (2 years post-treatment) on depressive symptoms at Time 2 (1 year later; 3 years post-treatment) were examined using hierarchical linear regression. Peer victimization, maternal acceptance, neural activation to parental praise (parameter estimates), and covariates (age, sex, depressive symptoms at Time 1) were entered in Step 1. All possible two-way interactions were entered in Step 2, and the three-way interaction between peer victimization, maternal acceptance, and neural activation to parental praise was entered in Step 3. Given that peer victimization is most commonly associated with depressive symptoms, we specified the models such that peer victimization was the independent variable, with maternal acceptance and neural activation to praise as the moderators. Probing of the three-way interaction was conducted using the PROCESS macro for SPSS, version 3.1 (Hayes, 2018), which allows all study variables and covariates to be entered simultaneously and provides confidence intervals with bootstrapped standard errors (10,000 resamples).

PROCESS generates a regression model with simple slope effects. Significant interactions were probed in two ways using PROCESS: (1) examining Johnson-Neyman regions of significance (Bauer and Curran, 2005), which identifies the range of values of the moderator (in this case, neural activation) for which the association between the two-way interaction (peer victimization × maternal acceptance) and outcome (depressive symptoms) is significant; and (2) examining simple slopes of peer victimization predicting depressive symptoms at the mean and 1 SD above and below the mean of each moderator. Region of

significance values were expressed in standard deviation units (mean = 0) and raw scores for ease of interpretability. Age, sex, and depressive symptoms at baseline (Time 1) were included as covariates in all analyses.

Separate models were run with parameter estimates for each ROI (nine models in total). Benjamini–Hochberg procedures (Benjamini and Hochberg, 1995) were used to account for multiple tests with a false discovery rate of 0.05.

Sensitivity Analyses

Given that this sample received psychological treatment for an anxiety disorder, we conducted a set of sensitivity analyses to examine how treatment and/or anxiety status might impact the effects of interactions between peer victimization, maternal acceptance, and neural activation to praise on depressive symptoms. The following covariates were entered into the PROCESS macro following identification of significant models from the primary analysis: treatment type (CBT/CCT) when enrolled in the RCT, treatment response (yes/no) when enrolled in the RCT, and presence of an anxiety disorder diagnosis (yes/no) at Time 1 (2 years post-treatment). In separate models, we substituted a continuous measure of anxiety symptoms at Time 1 (SCARED scores) for the presence of an anxiety disorder diagnosis.

RESULTS

Preliminary Results

Intercorrelations between variables included in the model can be found in **Table 2**. No marked skewness or kurtosis was found. Males and females differed significantly in perceived maternal acceptance ($t_{(36,1)} = 3.11$, $p = 0.004$), such that males reported higher acceptance than females. Males and females also differed in perceived peer victimization ($t_{(36,1)} = -2.09$, $p = 0.044$), such that females reported more peer victimization than males. Moderate correlations between age and activation in several brain regions were also found. Analyses remained controlling for sex and age. No differences between youth diagnosed with an anxiety disorder at the time of data collection vs. youth not diagnosed with an anxiety disorder were found for age, sex, depressive symptoms, maternal acceptance, peer victimization, or neural activation to parental praise in any brain region.

Intercorrelations also revealed a modest correlation between activation in the right amygdala to maternal praise and perceived maternal acceptance ($r = -0.34$, $p = 0.036$), such that adolescents with greater right amygdala activation perceived lower maternal acceptance. Moderate to high correlations also emerged between perceived maternal acceptance and depressive symptoms at time 1 ($r = -0.61$, $p < 0.001$) and depressive symptoms at time 2 ($r = -0.69$, $p < 0.001$), such that adolescents reporting higher depressive symptoms also reported lower perceived maternal acceptance.

Regression Results

In all nine ROI models, only perceived maternal acceptance was significantly associated with depressive symptoms at Time

TABLE 2 | Intercorrelations between included variables in primary analysis.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
1. MFQ (T1)	1																
2. MFQ (T2)	0.59***	1															
3. Age	0.28	0.16	1														
4. Sex	0.29	0.27	−0.09	1													
5. L caud	0.19	0.08	0.21	−0.04	1												
6. R caud	0.21	0.07	0.20	0.00	0.92***	1											
7. L amyg	0.08	0.19	0.18	−0.04	0.51**	0.48**	1										
8. R amyg	0.35*	0.26	0.24	−0.06	0.45**	0.44**	0.64***	1									
9. L NAcc	0.27	0.10	0.11	0.02	0.40*	0.43**	0.45**	0.57***	1								
10. R NAcc	0.22	0.08	0.17	0.12	0.46**	0.53**	0.16	0.31	0.41*	1							
11. L insula	−0.22	−0.14	0.21	0.02	0.61***	0.59***	0.55***	0.41*	0.42**	0.27	1						
12. R insula	−0.18	−0.23	0.15	−0.15	0.48**	0.54***	0.47**	0.43**	0.48**	0.20	0.85***	1					
13. sgACC	0.21	0.22	0.06	0.12	0.64***	0.65***	0.53**	0.16	0.24	0.31	0.41*	0.32	1				
14. Accept	−0.61***	−0.69***	−0.20	−0.46**	−0.19	−0.18	−0.19	−0.34*	−0.28	−0.25	0.00	0.07	−0.19	1			
15. Victim	0.23	0.26	0.04	0.33*	−0.14	−0.11	−0.03	−0.02	0.02	0.07	−0.13	0.00	−0.18	−0.24	1		
M	9.93	8.71	13.59	0.56	0.25	0.25	−0.16	−0.06	0.03	0.08	0.01	−0.09	0.42	25.08	6.62		
SD	9.57	10.13	1.51	0.50	1.14	1.04	1.50	1.55	1.56	1.34	1.38	1.13	1.27	4.37	1.99		
Range	0–42	0–30	11–16	-	−4.11–2.39	−2.76–2.42	−3.38–2.55	−3.08–3.20	−2.87–2.35	−2.56–2.98	−3.06–3.18	−2.29–2.40	−3.21–2.74	17–30	5–12		

*Note. MFQ, Mood and Feelings Questionnaire (measure of depressive symptoms); Caud, caudate nucleus; Amyg, amygdala; NAcc, nucleus accumbens; sgACC, subgenual anterior cingulate cortex; Accept, maternal acceptance; Victim, peer victimization; M, Mean; SD, Standard Deviation; Sex is dummy coded (1 = female); ***p < 0.001, **p < 0.01, *p < 0.05.*

2 (βs = −0.54 to −0.60, ps < 0.005) when main effects and covariates were entered in Step 1 (R^2 = 0.54–0.56; ps < 0.001).

When all possible two-way interactions were entered into the models in Step 2, a significant interaction between peer victimization and activation in the left nucleus accumbens on depressive symptoms emerged (ΔR^2 = 0.13, p = 0.021). No other significant two-way interactions emerged in other ROI models. This two-way interaction was not interpreted, as the three-way interaction between peer victimization, maternal acceptance, and left nucleus accumbens activation to praise on depressive symptoms was also significant (ΔR^2 = 0.05, p = 0.037), though this latter finding did not survive corrections for multiple comparisons.

Following corrections for multiple tests, significant three-way interactions between peer victimization, maternal acceptance, and neural activation to praise on depressive symptoms emerged in Step 3 for two regions, the left caudate (ΔR^2 = 0.11, p = 0.004) and right caudate (ΔR^2 = 0.10, p = 0.007). Full results from the regression analysis for the left and right caudate are provided in **Tables 3**, **4** and results from probing of these interactions using PROCESS are described below.

Left Caudate

The final model was significant ($F_{(10,27)}$ = 6.44, R^2 = 0.70, p < 0.001). In addition to a main effect of depressive symptoms at time 1 [β = 0.53, B = 0.51 (SE = 0.15), $t_{(1,27)}$ = −3.19, p = 0.002, 95% CI (0.22–0.84)], a significant three-way interaction between maternal acceptance, peer victimization, and left caudate activation emerged [β = −0.30, B = −0.34 (SE = 0.11), uncorrected p = 0.004, 95% CI (−0.49 to −0.11), Benjamini–Hochberg p = 0.03]. The Johnson-Neyman procedure revealed that the peer victimization × maternal acceptance interaction was significantly negative for values of left caudate activation above −0.09 (0.26 SDs below the mean; 63% of the sample). The effect size of the interaction increased with increasing values of left caudate activation. The Johnson-Neyman procedure also revealed that for adolescents with very low left caudate activation to praise (below −2.94 or 3.11 SDs below the mean), a significant negative interaction between peer victimization and maternal acceptance emerged. However, this only represented 2.6% of the sample, or one participant. Findings held controlling for the presence of an anxiety disorder at the time of scanning and treatment type.

Figure 1 depicts this interaction by showing simple slopes representing the association between peer victimization and depressive symptoms at varying combinations of low, average, and high maternal acceptance and left caudate activation. At average and high (+1 SD) levels of left caudate activation to praise, peer victimization was positively associated with symptoms of depression only when maternal acceptance was low [simple slope at average left caudate activity: β = 0.30, B = 1.47 (SE = 0.71), $t_{(1,27)}$ = 3.57, p = 0.048, 95% CI (0.003–0.60); simple slope at high left caudate activity: β = 0.86, B = 4.18 (SE = 1.17), $t_{(1,27)}$ = 3.57, p = 0.013, 95% CI (0.37–1.36)].

TABLE 3 | Summary of regression model predicting depressive symptoms at 1-year follow-up using activation values from the left caudate.

	F	R^2	Δ*F*	ΔR^2	*β*	*t*	Uncorrected *p*-value	Benjamini–Hochberg *p*-value
Model 1	6.06***	0.54						
Age					−0.03	−0.27	0.792	
Sex					−0.11	−0.76	0.456	
MFQ T1					0.27	1.74	0.091	
L Caud					−0.06	−0.50	0.620	
Peer					0.09	0.66	0.513	
Accept					−0.56	−3.40**	0.002	
Model 2	4.54**	0.59	1.23	0.05				
Age					−0.06	−0.45	0.658	
Sex					−0.06	−0.41	0.683	
MFQ T1					0.31	2.00	0.055	
L Caud					−0.14	−1.06	0.300	
Peer					0.11	0.81	0.424	
Accept					−0.47	−2.66*	0.013	
Peer × Accept					−0.17	−1.30	0.204	
L Caud × Accept					0.07	0.55	0.584	
L Caud × Peer					0.05	0.42	0.679	
Model 3	6.44***	0.71	10.18**	0.11				
Age					−0.05	−0.39	0.701	
Sex					−0.03	−0.22	0.826	
MFQ T1					0.53	3.50**	0.002	
L Caud					−0.05	−0.41	0.685	
Peer					0.01	0.05	0.962	
Accept					−0.29	−1.77	0.088	
Peer × Accept					−0.30	−2.50*	0.019	
L Caud × Accept					0.04	0.41	0.688	
L Caud × Peer					0.26	2.16*	0.040	
L Caud × Peer × Accept					−0.30	−3.19**	0.004	0.030

*Note. Peer, Peer victimization; Accept, Maternal acceptance; L Caud, Left caudate activation to praise > neutral; *p < 0.05, **p < 0.005, ***p < 0.001.*

TABLE 4 | Summary of regression model predicting depressive symptoms at 1-year follow-up using activation values from the right caudate.

	F	R^2	ΔF	ΔR^2	β	*t*	Uncorrected *p*-value	Benjamini–Hochberg *p*-value
Model 1	6.09***	0.54						
Age					−0.03	−0.26	0.797	
Sex					−0.11	−0.74	0.464	
MFQ T1					0.27	1.77	0.087	
R Caud					−0.07	−0.60	0.554	
Peer					0.09	0.66	0.514	
Accept					−0.56	−3.41**	0.002	
Model 2	4.72**	0.60	1.44	0.06				
Age					−0.06	−0.46	0.648	
Sex					−0.03	−0.22	0.826	
MFQ T1					0.32	2.07*	0.047	
R Caud					−0.12	−0.99	0.332	
Peer					0.13	0.95	0.349	
Accept					−0.45	−2.68*	0.012	
Peer × Accept					−0.12	−0.96	0.345	
R Caud × Accept					0.08	0.72	0.477	
R Caud × Peer					0.11	0.93	0.362	
Model 3	6.26***	0.70	8.62**	0.10				
Age					−0.07	−0.61	0.548	
Sex					−0.04	−0.29	0.772	
MFQ T1					0.47	3.20**	0.003	
R Caud					−0.10	−0.89	0.382	
Peer					−0.01	−0.11	0.914	
Accept					−0.40	−2.64*	0.014	
Peer × Accept					−0.24	−2.01	0.054	
R Caud × Accept					0.10	0.99	0.329	
R Caud × Peer					0.18	1.71	0.099	
R Caud × Peer × Accept					−0.25	−2.94*	0.007	0.030

*Note. Peer, Peer victimization; Accept, Maternal acceptance; R Caud, Right caudate activation to praise > neutral; *p < 0.05, **p < 0.005, ***p < 0.001.*

Right Caudate

The final model was significant ($F_{(10,27)}$ = 6.26, R^2 = 0.70, $p < 0.001$). A main effect of depressive symptoms at time 1 [β = 0.47, B = 0.45 (SE = 0.14), $t_{(1,27)}$ = 3.20, p = 0.004, 95% CI (0.17–0.76)] and maternal acceptance [β = −0.40, B = −1.13 (SE = 0.43), $t_{(1,27)}$ = −2.63, p = 0.014, 95% CI (−0.70 to −0.08)] emerged. A significant three-way interaction between maternal acceptance, peer victimization, and left caudate activation also emerged (β = −0.25, B = −0.34 (SE = 0.11), uncorrected p = 0.007, 95% CI [−0.43 to −0.08], Benjamini–Hochberg p = 0.03). The Johnson-Neyman procedure revealed that the peer victimization × maternal acceptance interaction was significantly negative for values of right caudate activation above 0.16 (0.03 SDs above the mean; 45% of the sample). The effect size of the interaction increased with increasing values of right caudate activation. Findings reported held controlling for the presence of an anxiety disorder at the time of scanning and treatment type.

Figure 2 depicts this interaction by showing simple slopes representing the association between peer victimization and depressive symptoms at varying combinations of low, average, and high maternal acceptance and right caudate activation. At high (+1 SD) levels of right caudate activation to praise, peer victimization was positively associated with symptoms of depression only when maternal acceptance was low [simple slope: β = 0.66, B = 3.20, SE = 0.98, $t_{(1,27)}$ = 3.27, p = 0.003, 95% CI (1.19–5.21)].

Sensitivity Analyses

The three-way interaction between peer victimization, maternal acceptance, and left caudate activation to maternal praise on depressive symptoms remained significant when controlling for treatment type (CBT/CCT), treatment response (yes/no), and presence of an anxiety disorder diagnosis at Time 1 (2 years post-treatment; p = 0.022). The interaction also remained significant when controlling for treatment type, treatment response, and child-rated anxiety symptoms at Time 1 (p = 0.017). Similar results were seen with the right caudate. The three-way interaction between peer victimization, maternal acceptance, and right caudate activation to maternal praise on depressive symptoms remained significant when controlling for treatment type (CBT/CCT), treatment response (yes/no), and presence of an anxiety disorder diagnosis at Time 1 (2 years post-treatment; p = 0.045). The interaction also remained significant when controlling for treatment type, treatment response, and child-rated anxiety symptoms at Time 1 (p = 0.049). Treatment type, treatment response, presence of an anxiety disorder diagnosis, or child-rated anxiety symptoms were not significantly associated with depressive symptoms in any models (ps > 0.12).

DISCUSSION

The current study suggests that interactions between adolescents' caudate activation to social reward and perceived peer victimization and maternal acceptance help explain the

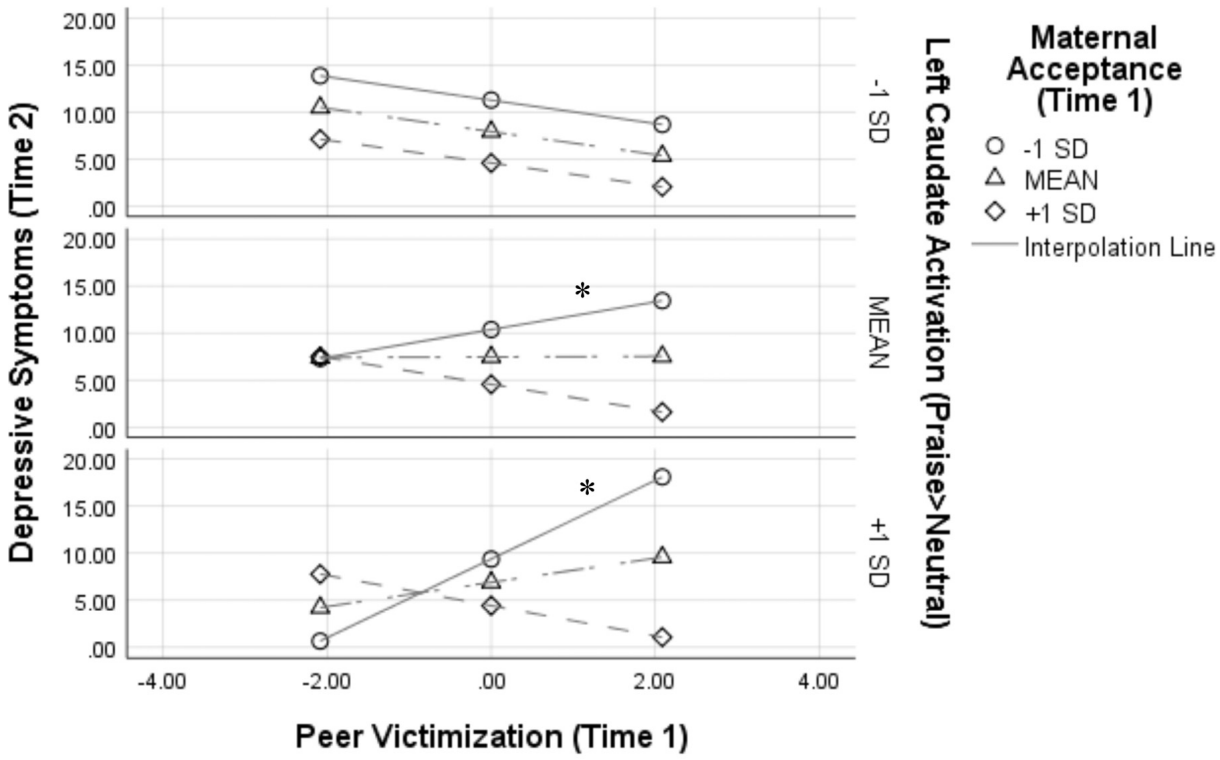


FIGURE 1 | Results from the peer victimization × maternal acceptance × left caudate activation interaction on depressive symptoms 1 year later. Analyses controlled for depressive symptoms at Time 1, age, and sex. Variables were centered prior to analyses, thus a score of 0 for peer victimization represents the mean; $^{*}p < 0.05$.

development of depressive symptoms 1 year later. Findings show that perceived maternal acceptance is most likely to interact with peer victimization to predict depressive symptoms for youth with higher bilateral caudate nucleus activation to parental praise. Consistent with hypotheses, youth with high caudate activation to parental praise who reported the lowest level of maternal acceptance showed the strongest positive association between peer victimization and depressive symptoms. Notably, including the three-way interaction between caudate activation, peer victimization, and maternal acceptance at Time 1 accounted for an additional 10%–11% of the variance in explaining Time 2 depressive symptoms in this sample.

Consistent with neurobiological susceptibility to social context models (Schriber and Guyer, 2016), caudate activation to social reward could represent a neural marker that helps explain variability in adolescent sensitivity to social contexts. The caudate nucleus is implicated in reward-based learning. Activity in the caudate nucleus has been positively correlated with reward prediction errors during instrumental learning tasks in both humans (O'Doherty et al., 2004; Haruno and Kawato, 2006) and monkeys (e.g., Asaad and Eskandar, 2011). Consistent with current results, Jarcho et al. (2015) recently showed that adolescents with social anxiety disorder showed significant caudate activation to unexpected positive feedback from peers of high value, corresponding to a social evaluation prediction error. One interpretation of the current findings could be that youth with positive caudate activation to praise may not have expected to hear parental praise during the task, possibly as a result of learning in the real world that positive social feedback is infrequent or fleeting. Positive caudate activation to praise could thus reflect a history of negative experiences with parents and/or peers that places youth at greater risk for depressive symptoms. This interpretation aligns with Schriber and Guyer's (2016) proposal that neurobiological susceptibility to social context is formed throughout childhood and adolescence through ongoing consolidation of the brain's coding of social experiences in functionally sensitive social-affective neural circuitry. This interpretation is also supported by prior work showing how parental warmth and peer victimization influences activity in reward-related brain areas (e.g., Casement et al., 2014; Morgan et al., 2014). Aligning with our interpretation that high caudate activation to praise could reflect a history of negative social experiences that places youth at risk for depressive symptoms, Casement et al. (2014) found that higher activity in a striatal region that included the caudate to reward anticipation (age 16) mediated the link between low parental warmth (ages 11–12) and higher depressive symptoms (age 16) in a sample of adolescent girls.

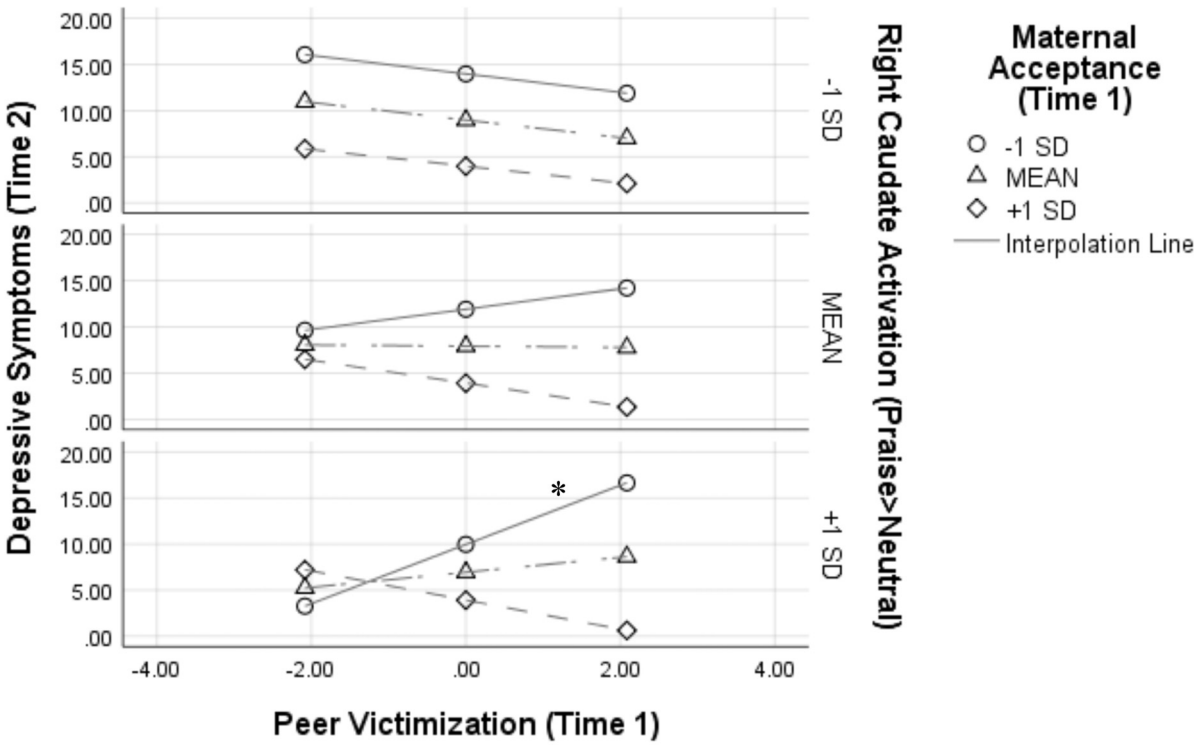


FIGURE 2 | Results from the peer victimization × maternal acceptance × right caudate activation interaction on depressive symptoms 1 year later. Analyses controlled for depressive symptoms at Time 1, age, and sex. Variables were centered prior to analyses, thus a score of 0 for peer victimization represents the mean; $^{*}p < 0.05$.

Current findings could also be related to the nature of this sample; that is, this is a unique sample of youth with a history of anxiety. This could help explain consistencies between current findings and prior work showing that youth with social anxiety display heightened caudate activation to unexpected positive feedback from highly valued peers compared to healthy youth (Jarcho et al., 2015). Jarcho et al. (2015) also showed that high caudate activation to unexpected positive feedback was related to disrupted recall of peer feedback. The authors suggest that social anxiety in adolescence is associated with altered neural processing of social prediction errors that contributes to impaired social learning. Results from the current study may suggest that youth with a history of anxiety demonstrating altered neural processing of social prediction errors are also most at-risk for the development of depression symptoms (Jarcho et al., 2015).

More generally, past research has also shown that youth with anxiety disorders and youth with shy/inhibited temperaments display higher caudate responses to reward than healthy youth (Guyer et al., 2006, 2012). Given the role of the caudate in motivational processes (Delgado et al., 2004), high caudate activation to social reward could reflect high approach motivation in youth with a history of anxiety (Caouette and Guyer, 2014). Although high motivation to seek out positive social experiences is likely developmentally appropriate in adolescence (Davey et al., 2008), this could lead to greater depressive symptoms when social experiences are not viewed as positive. This may be especially relevant for the current sample, as youth reporting anxiety symptoms tend to view their relationships with parents and peers as less positive (Ginsburg et al., 1998; Caster et al., 1999; Hale et al., 2006). Given that caudate activation has also been linked to various forms of arousal (e.g., Miller et al., 2014), findings may also reflect more complex influences, such as heightened fear that is characteristic of youth with anxiety (Jarcho et al., 2015). Relatedly, high caudate activity to praise may reflect greater severity of anxiety symptoms, which when combined with low parental support and high peer victimization, places adolescents at highest risk for depressive symptoms. Although current findings might not generalize to youth without a history of anxiety, this study provides valuable insight into a population of youth who are at increased risk for peer victimization and depression compared to their peers who have never been diagnosed with an anxiety disorder (Cole et al., 1998; Cohen and Kendall, 2015). Research in this population is especially important considering that over one-third of 13–18-year-olds meet criteria for an anxiety disorder (Merikangas et al., 2010). Thus, although the sample may be a limitation in that results may not generalize, it is also a unique strength.

This study benefits from the use of an ecologically-valid fMRI task and longitudinal measurement of depressive symptoms,

though it has several notable limitations. First, this study relied on self-report measures of peer victimization and maternal acceptance at one point in time. Given that parental influences tend to be stronger than peer influences in childhood, with peers becoming more important into adolescence, it may be that parental tuning of reward systems early in life influences how adolescents respond not only to future parenting behaviors but also to peers. Moreover, perceptions of low parental warmth in childhood may modulate the brain's reward system, which may impact relationships with peers. Because peer relationships are so salient in adolescence, poor relationships and increased victimization may then place adolescents at increased risk for depressive symptoms. However, future work using longitudinal measures will be needed to fully examine how the timing of peer and parental influences impacts reward-related brain development to influence depressive symptoms. This longitudinal work will also be able to address not only how perceived peer and parental interactions influence brain function, but also how brain function influences perceived social interactions. Future research could also extend beyond brain function to examine how structural brain differences, such as caudate volume, interact with an adolescent's perceptions of social interactions to predict depressive symptoms, given evidence of altered caudate volume in adults with major depression (Krishnan et al., 1992; Kim et al., 2008).

It should also be noted that no participants in the current study were diagnosed with major depressive disorder at Time 2, and only three participants had scores on the MFQ that may indicate the presence of depression. Thus, for the majority of participants, levels of depressive symptoms at Time 2 were in a normal or subclinical range. However, good variability in depressive symptoms at Time 2 was found. We suspect that rates of depression are lower than would be anticipated in a high-risk sample due to the fact that participants previously received treatment for anxiety, which may have secondary effects on depressive symptoms (Silk et al., 2019). Additionally, results can only speak to the quality of maternal warmth, not other forms of parenting, such as harsh or inconsistent parenting. Results also cannot speak to the quality of paternal warmth, as the questionnaire was only completed about mothers. Future research assessing how other forms of parenting, child-parent attachment quality, and/or personality characteristics or psychopathology of the parent influences the associations between child brain activity, perceptions of social relationships, and depressive symptoms may be of interest. Finally, the sample was small (n = 38) and three-way interaction results with small sample sizes should be interpreted with caution. Interestingly, depressive symptoms did not increase with increasing levels of peer victimization for youth with low levels of caudate activation, regardless of level of maternal acceptance. Though this could suggest that low caudate activation to social reward might represent a protective marker for youth reporting high peer victimization and low maternal acceptance, this finding could be attributable to the small sample size in the current study and the small subsample with low caudate response. Though current results may be seen as preliminary, the moderate effect sizes and significant proportions of variance explained by the interactions inspire confidence that findings are meaningful. Nonetheless, future work replicating the current findings with larger samples is needed.

Findings suggest that reward-related neural circuitry may signify a biological marker of individuals who are highly susceptible to their social environments. Further, the interaction between reward-related brain function and salient social contexts may help us understand increases in depressive symptoms seen during this period of development marked by significant biopsychosocial change. This aligns with developmental psychopathology models suggesting that social stressors during childhood and adolescence can impact neural reward processing and risk for depression later in life. These results may have implications for understanding individual differences in how adolescents are affected by negative relationships with parents and peers. Further, differences in how parental support and acceptance buffer negative interactions with peers may be due, in part, to individual differences in neurobiological sensitivity to parental support and acceptance. Findings suggest that understanding increases in depressive symptoms during adolescence requires acknowledgment of both intra- and interindividual biopsychosocial factors and how these factors interact. This acknowledgment may have clinical implications for treating youth reporting significant depressive symptoms.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the University of Pittsburgh Institutional Review Board with written informed consent from all subjects and their primary caregiver/legal guardian. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the University of Pittsburgh Institutional Review Board.

AUTHOR CONTRIBUTIONS

RB and SS performed the statistical analyses. JS, EF, and CL contributed to study conception and data interpretation. SS wrote the first draft of the manuscript. RB, JS, EF, and CL contributed to significant and critical revisions. All authors have read and approved the document for publication.

FUNDING

This project was supported by Foundation for the National Institutes of Health grant MH091327.

ACKNOWLEDGMENTS

APC charges for this article were fully paid by the University Library System, University of Pittsburgh.

REFERENCES

Allen, N. B., and Badcock, P. B. (2003). The social risk hypothesis of depressed mood: evolutionary, psychosocial, and neurobiological perspectives. *Psychol. Bull.* 129, 887–913. doi: 10.1037/0033-2909.129.6.887

American Psychological Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders.* 4th Edn. Washington, DC: American Psychological Association.

Angold, A., and Costello, E. J. (1987). *Mood and Feelings Questionnaire (MFQ).* Durham: Developmental Epidemiology Program, Duke University.

Asaad, W. F., and Eskandar, E. N. (2011). Encoding of both positive and negative reward prediction errors by neurons of the primate lateral prefrontal cortex and caudate nucleus. *J. Neurosci.* 31, 17772–17787. doi: 10.1523/JNEUROSCI.3793-11.2011

Aupperle, R. L., Morris, A. S., Silk, J. S., Criss, M. M., Judah, M. R., Eagleton, S. G., et al. (2016). Neural responses to maternal praise and criticism: relationship to depression and anxiety symptoms in high-risk adolescent girls. *Neuroimage Clin.* 11, 548–554. doi: 10.1016/j.nicl.2016.03.009

Barber, B. K., Stolz, H. E., Olsen, J. A., Collins, W. A., and Burchinal, M. (2005). Parental support, psychological control, and behavioral control: assessing relevance across time, culture, and method. *Monogr. Soc. Res. Child Dev.* 70, 1–137. doi: 10.1111/j.1540-5834.2005.00365.x

Bar-Haim, Y., Fox, N. A., Benson, B., Guyer, A. E., Williams, A., Nelson, E. E., et al. (2009). Neural correlates of reward processing in adolescents with a history of inhibited temperament. *Psychol. Sci.* 20, 1009–1018. doi: 10.1111/j.1467-9280.2009.02401.x

Bauer, D. J., and Curran, P. J. (2005). Probing interactions in fixed and multilevel regression: inferential and graphical techniques. *Multivariate Behav. Res.* 40, 373–400. doi: 10.1207/s15327906mbr4003_5

Benjamini, Y., and Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. B* 57, 289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x

Benson, B. E., Guyer, A. E., Nelson, E. E., Pine, D. S., and Ernst, M. (2015). Role of contingency in striatal response to incentive in adolescents with anxiety. *Cogn. Affect. Behav. Neurosci.* 15, 155–168. doi: 10.3758/s13415-014-0307-6

Bilsky, S. A., Cole, D. A., Dukewich, T. L., Martin, N. C., Sinclair, K. R., Tran, C. V., et al. (2013). Does supportive parenting mitigate the longitudinal effects of peer victimization on depressive thoughts and symptoms in children? *J. Abnorm. Psychol.* 122, 406–419. doi: 10.1037/a0032501

Blakemore, S. J., and Mills, K. L. (2014). Is adolescence a sensitive period for sociocultural processing? *Annu. Rev. Psychol.* 65, 187–207. doi: 10.1146/annurev-psych-010213-115202

Bonanno, R. A., and Hymel, S. (2010). Beyond hurt feelings: investigating why some victims of bullying are at greater risk for suicidal ideation. *Merrill Palmer Q.* 56, 420–440. doi: 10.1353/mpq.0.0051

Brady, E. U., and Kendall, P. C. (1992). Comorbidity of anxiety and depression in children and adolescents. *Psychol. Bull.* 111, 244–255. doi: 10.1037/0033-2909.111.2.244

Brett, M., Anton, J. L., Valabregue, R., and Poline, J. B. (2002). "Region of interest analysis using an SPM toolbox," in *Proceedings of the 8th International Conference on Functional Mapping of the Human Brain* (vol. 16), Sendai, Japan, 497.

Brunstein Klomek, A., Marrocco, F., Kleinman, M., Schonfeld, I. S., and Gould, M. S. (2007). Bullying, depression, and suicidality in adolescents. *J. Am. Acad. Child Adolesc. Psychiatry* 46, 40–49. doi: 10.1097/01.chi.0000242237.84925.18

Caceres, A., Hall, D. L., Zelaya, F. O., Williams, S. C., and Mehta, M. A. (2009). Measuring fMRI reliability with the intra-class correlation coefficient. *Neuroimage* 45, 758–768. doi: 10.1016/j.neuroimage.2008.12.035

Caouette, J. D., and Guyer, A. E. (2014). Gaining insight into adolescent vulnerability for social anxiety from developmental cognitive neuroscience. *Dev. Cogn. Neurosci.* 8, 65–76. doi: 10.1016/j.dcn.2013.10.003

Caporino, N. E., Brodman, D. M., Kendall, P. C., Albano, A. M., Sherrill, J., Piacentini, J., et al. (2013). Defining treatment response and remission in child anxiety: signal detection analysis using the pediatric anxiety rating scale. *J. Am. Acad. Child Adolesc. Psychiatry* 52, 57–67. doi: 10.1016/j.jaac.2012.10.006

Casement, M. D., Guyer, A. E., Hipwell, A. E., McAloon, R. L., Hoffmann, A. M., Keenan, K. E., et al. (2014). Girls' challenging social experiences in early adolescence predict neural response to rewards and depressive symptoms. *Dev. Cogn. Neurosci.* 8, 18–27. doi: 10.1016/j.dcn.2013.12.003

Caster, J. B., Inderbitzen, H. M., and Hope, D. (1999). Relationship between youth and parent perceptions of family environment and social anxiety. *J. Anxiety Disord.* 13, 237–251. doi: 10.1016/s0887-6185(99)00002-x

Cohen, J. S., and Kendall, P. C. (2015). Peer victimization among children and adolescents with anxiety disorders. *Child Psychiatry Hum. Dev.* 46, 393–405. doi: 10.1007/s10578-014-0479-x

Cohen, S., and Wills, T. A. (1985). Stress, social support, and the buffering hypothesis. *Psychol. Bull.* 98, 310–357. doi: 10.1037//0033-2909.98.2.310

Colarossi, L. G., and Eccles, J. S. (2003). Differential effects of support providers on adolescents' mental health. *Soc. Work Res.* 27, 19–30. doi: 10.1093/swr/27.1.19

Cole, D. A., Martin, J. M., and Powers, B. (1997). A competency-based model of child depression: a longitudinal study of peer, parent, teacher, and self-evaluations. *J. Child Psychol. Psychiatry* 38, 505–514. doi: 10.1111/j.1469-7610.1997.tb01537.x

Cole, D. A., Peeke, L. G., Martin, J. M., Truglio, R., and Seroczynski, A. D. (1998). A longitudinal look at the relation between depression and anxiety in children and adolescents. *J. Consult. Clin. Psychol.* 66, 451–460. doi: 10.1037//0022-006x.66.3.451

Conners-Burrow, N. A., Johnson, D. L., Whiteside-Mansell, L., McKelvey, L., and Gargus, R. A. (2009). Adults matter: protecting children from the negative impacts of bullying. *Psychol. Sch.* 46, 593–604. doi: 10.1002/pits.20400

Costello, E. J., Mustillo, S., Erkanli, A., Keeler, G., and Angold, A. (2003). Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch. Gen. Psychiatry* 60, 837–844. doi: 10.1001/archpsyc.60.8.837

Cummings, C. M., Caporino, N. E., and Kendall, P. C. (2014). Comorbidity of anxiety and depression in children and adolescents: 20 years after. *Psychol. Bull.* 140, 816–845. doi: 10.1037/a0034733

Davey, C. G., Allen, N. B., Harrison, B. J., and Yücel, M. (2011). Increased amygdala response to positive social feedback in young people with major depressive disorder. *Biol. Psychiatry* 69, 734–741. doi: 10.1016/j.biopsych.2010.12.004

Davey, C. G., Yücel, M., and Allen, N. B. (2008). The emergence of depression in adolescence: development of the prefrontal cortex and the representation of reward. *Neurosci. Biobehav. Rev.* 32, 1–19. doi: 10.1016/j.neubiorev.2007.04.016

Delgado, M. R., Stenger, V. A., and Fiez, J. A. (2004). Motivation-dependent responses in the human caudate nucleus. *Cereb. Cortex* 14, 1022–1030. doi: 10.1093/cercor/bhh062

Desjardins, T. L., and Leadbeater, B. J. (2011). Relational victimization and depressive symptoms in adolescence: moderating effects of mother, father, and peer emotional support. *J. Youth Adolesc.* 40, 531–544. doi: 10.1007/s10964-010-9562-1

Forbes, E. E., and Dahl, R. E. (2005). Neural systems of positive affect: relevance to understanding child and adolescent depression? *Dev. Psychopathol.* 17, 827–850. doi: 10.1017/s095457940505039x

Forbes, E. E., and Dahl, R. E. (2012). Research review: altered reward function in adolescent depression: what, when and how? *J. Child Psychol. Psychiatry* 53, 3–15. doi: 10.1111/j.1469-7610.2011.02477.x

Forbes, E. E., Hariri, A. R., Martin, S. L., Silk, J. S., Moyles, D. L., Fisher, P. M., et al. (2009). Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *Am. J. Psychiatry* 166, 64–73. doi: 10.1176/appi.ajp.2008.07081336

Galvan, A. (2010). Adolescent development of the reward system. *Front. Hum. Neurosci.* 4:6. doi: 10.3389/neuro.09.006.2010

Gifford-Smith, M. E., and Brownell, C. A. (2003). Childhood peer relationships: social acceptance, friendships, and peer networks. *J. Sch. Psychol.* 41, 235–284. doi: 10.1016/s0022-4405(03)00048-7

Ginsburg, G. S., La Greca, A. M., and Silverman, W. K. (1998). Social anxiety in children with anxiety disorders: relation with social and emotional functioning. *J. Abnorm. Child Psychol.* 26, 175–185. doi: 10.1023/A:1022668101048

Gladstone, G. L., Parker, G. B., and Malhi, G. S. (2006). Do bullied children become anxious and depressed adults?: a cross-sectional investigation of the

correlates of bullying and anxious depression. *J. Nerv. Ment. Dis.* 194, 201–208. doi: 10.1097/01.nmd.0000202491.99719.c3

Guyer, A. E., Choate, V. R., Detloff, A., Benson, B., Nelson, E. E., Perez-Edgar, K., et al. (2012). Striatal functional alteration during incentive anticipation in pediatric anxiety disorders. *Am. J. Psychiatry* 169, 205–212. doi: 10.1176/appi.ajp.2011.11010006

Guyer, A. E., Nelson, E. E., Perez-Edgar, K., Hardin, M. G., Roberson-Nay, R., Monk, C. S., et al. (2006). Striatal functional alteration in adolescents characterized by early childhood behavioral inhibition. *J. Neurosci.* 26, 6399–6405. doi: 10.1523/JNEUROSCI.0666-06.2006

Hale, W. W. III., Engels, R., and Meeus, W. (2006). Adolescent's perceptions of parenting behaviours and its relationship to adolescent Generalized Anxiety Disorder symptoms. *J. Adolesc.* 29, 407–417. doi: 10.1016/j.adolescence.2005.08.002

Haruno, M., and Kawato, M. (2006). Different neural correlates of reward expectation and reward expectation error in the putamen and caudate nucleus during stimulus-action-reward association learning. *J. Neurophysiol.* 95, 948–959. doi: 10.1152/jn.00382.2005

Hawker, D. S., and Boulton, M. J. (2000). Twenty years' research on peer victimization and psychosocial maladjustment: a meta-analytic review of cross-sectional studies. *J. Child Psychol. Psychiatry* 41, 441–455. doi: 10.1017/s0021963099005545

Hayes, A. F. (2018). Partial, conditional, and moderated moderated mediation: quantification, inference, and interpretation. *Commun. Monogr.* 85, 4–40. doi: 10.1080/03637751.2017.1352100

Hooley, J. M., Gruber, S. A., Parker, H. A., Guillaumot, J., Rogowska, J., and Yurgelun-Todd, D. A. (2009). Cortico-limbic response to personally challenging emotional stimuli after complete recovery from depression. *Psychiatry Res.* 171, 106–119. doi: 10.1016/j.pscychresns.2008.04.001

Hooley, J. M., Gruber, S. A., Scott, L. A., Hiller, J. B., and Yurgelun-Todd, D. A. (2005). Activation in dorsolateral prefrontal cortex in response to maternal criticism and praise in recovered depressed and healthy control participants. *Biol. Psychiatry* 57, 809–812. doi: 10.1016/j.biopsych.2005.01.012

Jarcho, J. M., Romer, A. L., Shechner, T., Galvan, A., Guyer, A. E., Leibenluft, E., et al. (2015). Forgetting the best when predicting the worst: preliminary observations on neural circuit function in adolescent social anxiety. *Dev. Cogn. Neurosci.* 13, 21–31. doi: 10.1016/j.dcn.2015.03.002

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., et al. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. *J. Am. Acad. Child Adolesc. Psychiatry* 36, 980–988. doi: 10.1097/00004583-199707000-00021

Kessler, R. C., Avenevoli, S., and Ries Merikangas, K. (2001). Mood disorders in children and adolescents: an epidemiologic perspective. *Biol. Psychiatry* 49, 1002–1014. doi: 10.1016/s0006-3223(01)01129-5

Kim, M. J., Hamilton, J. P., and Gotlib, I. H. (2008). Reduced caudate gray matter volume in women with major depressive disorder. *Psychiatry Res.* 164, 114–122. doi: 10.1016/j.pscychresns.2007.12.020

Koolschijn, P. C. M., Schel, M. A., de Rooij, M., Rombouts, S. A., and Crone, E. A. (2011). A three-year longitudinal functional magnetic resonance imaging study of performance monitoring and test-retest reliability from childhood to early adulthood. *J. Neurosci.* 31, 4204–4212. doi: 10.1523/JNEUROSCI.6415-10.2011

Krishnan, K. R. R., McDonald, W. M., Escalona, P. R., Doraiswamy, P. M., Na, C., Husain, M. M., et al. (1992). Magnetic resonance imaging of the caudate nuclei in depression: preliminary observations. *Arch. Gen. Psychiatry* 49, 553–557. doi: 10.1001/archpsyc.1992.01820070047007

Lee, K. H., Siegle, G. J., Dahl, R. E., Hooley, J. M., and Silk, J. S. (2014). Neural responses to maternal criticism in healthy youth. *Soc. Cogn. Affect. Neurosci.* 10, 902–912. doi: 10.1093/scan/nsu133

Lewinsohn, P. M., Hops, H., Roberts, R. E., Seeley, J. R., and Andrews, J. A. (1993). Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III—R disorders in high school students. *J. Abnorm. Psychol.* 102, 133–144. doi: 10.1037/0021-843x.102.4.517

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., and Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 19, 1233–1239. doi: 10.1016/s1053-8119(03)00169-1

Manuck, S. B., Brown, S. M., Forbes, E. E., and Hariri, A. R. (2007). Temporal stability of individual differences in amygdala reactivity. *Am. J. Psychiatry* 164, 1613–1614. doi: 10.1176/appi.ajp.2007.07040609

Merikangas, K. R., He, J., Burstein, M., Swanson, S. A., Avenevoli, S., Cui, L., et al. (2010). Lifetime prevalence of mental disorders in U.S. adolescents: results from the national comorbidity study—adolescent supplement (NCS-A). *J. Am. Acad. Child Adolesc. Psychiatry* 49, 980–989. doi: 10.1016/j.jaac.2010.05.017

Miller, E. M., Shankar, M. U., Knutson, B., and McClure, S. M. (2014). Dissociating motivation from reward in human striatal activity. *J. Cogn. Neurosci.* 26, 1075–1084. doi: 10.1162/jocn_a_00535

Monk, C. S., Klein, R. G., Telzer, E. H., Schroth, E. A., Mannuzza, S., Moulton, J. L. III., et al. (2008). Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. *Am. J. Psychiatry* 165, 90–98. doi: 10.1176/appi.ajp.2007.06111917

Morgan, J. K., Shaw, D. S., and Forbes, E. E. (2014). Maternal depression and warmth during childhood predict age 20 neural response to reward. *J. Am. Acad. Child Adolesc. Psychiatry* 53, 108–117. doi: 10.1016/j.jaac.2013.10.003

Nansel, T. R., Overpeck, M., Pilla, R. S., Ruan, W. J., Simons-Morton, B., and Scheidt, P. (2001). Bullying behaviors among US youth: prevalence and association with psychosocial adjustment. *JAMA* 285, 2094–2100. doi: 10.1001/jama.285.16.2094

Nelson, E. E., Leibenluft, E., McClure, E. B., and Pine, D. S. (2005). The social re-orientation of adolescence: a neuroscience perspective on the process and its relation to psychopathology. *Psychol. Med.* 35, 163–174. doi: 10.1017/s0033291704003915

O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., and Dolan, R. J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science* 304, 452–454. doi: 10.1126/science.1094285

Olino, T. M., Silk, J. S., Osterritter, C., and Forbes, E. E. (2015). Social reward in youth at risk for depression: a preliminary investigation of subjective and neural differences. *J. Child Adolesc. Psychopharmacol.* 25, 711–721. doi: 10.1089/cap.2014.0165

Olweus, D. (1993). "Victimization by peers: antecedents and long-term outcomes," in *Social Withdrawal, Inhibition, and Shyness in Childhood*, eds K. H. Rubin and J. B. Asendorf (Mahwah: Lawrence Erlbaum Associates, Inc.), 315–341.

Orvaschel, H., Lewinsohn, P. M., and Seeley, J. R. (1995). Continuity of psychopathology in a community sample of adolescents. *J. Am. Acad. Child Adolesc. Psychiatry* 34, 1525–1535. doi: 10.1097/00004583-199511000-00020

Pine, D. S., Cohen, P., Gurley, D., Brook, J., and Ma, Y. (1998). The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Arch. Gen. Psychiatry* 55, 56–64. doi: 10.1001/archpsyc.55.1.56

Reinherz, H. Z., Giaconia, R. M., Pakiz, B., Silverman, A. B., Frost, A. K., and Lefkowitz, E. S. (1993). Psychosocial risks for major depression in late adolescence: a longitudinal community study. *J. Am. Acad. Child Adolesc. Psychiatry* 32, 1155–1163. doi: 10.1097/00004583-199311000-00007

Rigby, K., and Slee, P. T. (1993). Dimensions of interpersonal relation among Australian children and implications for psychological well-being. *J. Soc. Psychol.* 133, 33–42. doi: 10.1080/00224545.1993.9712116

Rubin, K. H., Bukowski, W. M., and Parker, J. G. (2006). "Peer interactions, relationships, and groups," in *Handbook of Child Psychology Vol. 3. Social, Emotional, and Personality Development*, 6th Edn. eds W. Damon, R. M. Lerner and N. Eisenberg (Hoboken, NJ: Wiley), 571–645.

Rueger, S. Y., Malecki, C. K., and Demaray, M. K. (2010). Relationship between multiple sources of perceived social support and psychological and academic adjustment in early adolescence: comparisons across gender. *J. Youth Adolesc.* 39, 47–61. doi: 10.1007/s10964-008-9368-6

Schaefer, E. S. (1965). A configurational analysis of children's reports of parent behavior. *J. Consult. Psychol.* 29, 552–557. doi: 10.1037/h0022702

Schludermann, E., and Schludermann, S. (1970). Replicability of factors in children's report of parent behavior (CRPBI). *J. Psychol.* 76, 239–249. doi: 10.1080/00223980.1970.9916845

Schriber, R. A., and Guyer, A. E. (2016). Adolescent neurobiological susceptibility to social context. *Dev. Cogn. Neurosci.* 19, 1–18. doi: 10.1016/j.dcn.2015.12.009

Silk, J. S., Davis, S., McMakin, D. L., Dahl, R. E., and Forbes, E. E. (2012). Why do anxious children become depressed teenagers? The role of social

evaluative threat and reward processing. *Psychol. Med.* 42, 2095–2107. doi: 10.1017/s0033291712000207

Silk, J. S., Lee, K. H., Elliott, R. D., Hooley, J. M., Dahl, R. E., Barber, A., et al. (2017). 'Mom—I don't want to hear it': brain response to maternal praise and criticism in adolescents with major depressive disorder. *Soc. Cogn. Affect. Neurosci.* 12, 729–738. doi: 10.1093/scan/nsx014

Silk, J. S., Price, R. B., Rosen, D., Ryan, N. D., Forbes, E. E., Siegle, G. J., et al. (2019). A longitudinal follow-up study examining adolescent depressive symptoms as a function of prior anxiety treatment. *J. Am. Acad. Child Adolesc. Psychiatry* 58, 359–367. doi: 10.1016/j.jaac.2018.10.012

Silk, J. S., Siegle, G. J., Lee, K. H., Nelson, E. E., Stroud, L. R., and Dahl, R. E. (2014). Increased neural response to peer rejection associated with adolescent depression and pubertal development. *Soc. Cogn. Affect. Neurosci.* 9, 1798–1807. doi: 10.1093/scan/nst175

Silk, J. S., Tan, P. Z., Ladouceur, C. D., Meller, S., Siegle, G. J., McMakin, D. L., et al. (2018). A randomized clinical trial comparing individual cognitive behavioral therapy and child-centered therapy for child anxiety disorders. *J. Clin. Child Adolesc. Psychol.* 47, 542–554. doi: 10.1080/15374416.2016.1138408

Stadler, C., Feifel, J., Rohrmann, S., Vermeiren, R., and Poustka, F. (2010). Peer-victimization and mental health problems in adolescents: are parental and school support protective? *Child Psychiatry Hum. Dev.* 41, 371–386. doi: 10.1007/s10578-010-0174-5

Stapinski, L. A., Araya, R., Heron, J., Montgomery, A. A., and Stallard, P. (2015). Peer victimization during adolescence: concurrent and prospective impact on symptoms of depression and anxiety. *Anxiety Stress Coping* 28, 105–120. doi: 10.1080/10615806.2014.962023

Tan, P. Z., Lee, K. H., Dahl, R. E., Nelson, E. E., Stroud, L. J., Siegle, G. J., et al. (2014). Associations between maternal negative affect and adolescent's neural response to peer evaluation. *Dev. Cogn. Neurosci.* 8, 28–39. doi: 10.1016/j.dcn.2014.01.006

Ttofi, M. M., Farrington, D. P., Lösel, F., and Loeber, R. (2011). Do the victims of school bullies tend to become depressed later in life? A systematic review and meta-analysis of longitudinal studies. *J. Aggress. Confl. Peace Res.* 3, 63–73. doi: 10.1108/17596591111132873

Wechsler, D. (1997). *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: The Psychological Corporation.

Zimmerman, M. A., Ramirez-Valles, J., Zapert, K. M., and Maton, K. I. (2000). A longitudinal study of stress-buffering effects for urban African American male adolescent problem behaviors and mental health. *J. Commun. Psychol.* 28, 17–33. doi: 10.1002/(sici)1520-6629(200001)28:1<17::aid-jcop4>3.3.co;2-9

Zuo, X. N., Kelly, C., Adelstein, J. S., Klein, D. F., Castellanos, F. X., and Milham, M. P. (2010). Reliable intrinsic connectivity networks: test-retest evaluation using ICA and dual regression approach. *Neuroimage* 49, 2163–2177. doi: 10.1016/j.neuroimage.2009.10.080

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 02 October 2019
doi: 10.3389/fnbeh.2019.00219

I Knew You Weren't Going to Like Me! Neural Response to Accurately Predicting Rejection Is Associated With Anxiety and Depression

Megan E. Quarmley[1], Brady D. Nelson[2], Tessa Clarkson[1], Lauren K. White[3] and Johanna M. Jarcho[1]*

[1]Department of Psychology, Temple University, Philadelphia, PA, United States, [2]Department of Psychology, Stony Brook University, Stony Brook, NY, United States, [3]Department of Child and Adolescent Psychiatry and Behavioral Science, Children's Hospital of Philadelphia, Philadelphia, PA, United States

OPEN ACCESS

Edited by:
Walter Adriani, National Institute of Health (ISS), Italy

Reviewed by:
Julieta Ramos-Loyo, University of Guadalajara, Mexico
Anh Hai Tran, Vietnam Military Medical University, Vietnam

***Correspondence:**
Megan E. Quarmley
megan.quarmley@temple.edu

Specialty section:
This article was submitted to Emotion Regulation and Processing, a section of the journal Frontiers in Behavioral Neuroscience

Received: *31 March 2019*
Accepted: *05 September 2019*
Published: *02 October 2019*

Citation:
Quarmley ME, Nelson BD, Clarkson T, White LK and Jarcho JM (2019) I Knew You Weren't Going to Like Me! Neural Response to Accurately Predicting Rejection Is Associated With Anxiety and Depression. Front. Behav. Neurosci. 13:219. doi: 10.3389/fnbeh.2019.00219

Anxiety and depression often emerge in adolescence. A normative increase in the desire for peer acceptance may be one of many contributing factors. These shifts occur during a phase of development in which neural reward networks, including structures such as the ventral striatum, undergo critical changes. Despite the salience of peer feedback during adolescence, neural responses to reward have largely been examined in the monetary domain, leaving many open questions about responses to social rewards. Moreover, most paradigms do not tease apart different aspects of reward processing (e.g., receiving feedback, being correct). Anxiety and depression are also associated with alterations in reward networks; however, little is known about how anxiety and depression in adolescence relate to differences in social vs. non-social reward processing. In this study, adolescents (n = 28) underwent fMRI while completing novel monetary and social feedback tasks, which tease apart reward domain (social/monetary), valence (positive/negative), and outcome (correct/incorrect). Participants were shown a pair of stimuli (doors/age-matched peers) and asked to indicate which stimulus would provide positive (win money/social like) or negative (lose money/social dislike) feedback. Participants then received feedback about the purported accuracy of their response. Region-of-interest analyses showed that left ventral striatum response varied by domain (social/monetary), valence (positive/negative), and outcome (correct/incorrect) of reward. Additionally, unique associations between anxiety, depression, and brain function were observed for correct, but not for incorrect trials, in the social, but not monetary task. Specifically, adolescents with high anxiety symptoms, but low depression, displayed greater left ventral striatum activation when correctly identifying peers who gave dislike (vs. like) feedback. Thus, anxious youth exhibited enhanced activation in a brain region implicated in reward processing when

they accurately predicted someone was going to dislike them. Higher levels of both depression and anxiety symptoms were associated with greater striatal activation to correctly identifying peers who gave like (vs. dislike) feedback. These results suggest a neural mechanism by which negative prediction biases may be reinforced in anxious youth.

Keywords: ventral striatum, social reward, monetary reward, fMRI, anxiety, depression, peer evaluation

INTRODUCTION

The importance of peer relationships increases during adolescence as the brain undergoes changes in neural networks critical for processing reward (Nelson and Guyer, 2011). This network is composed of interconnected brain regions implicated in reward sensitivity, such as the striatum, orbitofrontal cortex and anterior cingulate cortex (Galvan, 2010; Richards et al., 2013), substantia nigra, and the ventral tegmental area (VTA; Haber and Knutson, 2010; Wang et al., 2016), as well as regions involved in self-regulation in rewarding contexts, such as the prefrontal cortex (Galvan, 2010; Richards et al., 2013; Wang et al., 2016). However, extensive human and animal studies have identified the dopamine-rich ventral striatum as a critical hub in this network (Galvan, 2010; Richards et al., 2013; Wang et al., 2016). Although social acceptance is a powerful reward for adolescents (Guyer et al., 2012), neural response to reward has largely been examined in the monetary domain. Testing reward processing in the social domain may be particularly important when considering the neural mechanisms that promote symptoms of anxiety (Beesdo-Baum et al., 2012) and depression (Thapar et al., 2012). These symptoms increase dramatically in adolescence and are associated with alterations in reward-related brain function (Kujawa et al., 2018). Although social stressors often potentiate symptoms of anxiety and depression, direct tests of the association between symptoms and neural responses across reward domains are rare. Moreover, most research examining relations between brain function and reward processing have confounded the intrinsically rewarding experience of being correct (Satterthwaite et al., 2012) with positively valenced outcomes (Rademacher et al., 2010; Meuwese et al., 2018). Yet, symptoms of adolescent anxiety and depression may be differentially associated with dysregulated processing of intrinsic (being correct) and extrinsic (receiving a positively valenced outcome) rewards across social and non-social domains. We tested these relations in adolescents with a range of anxiety and depression symptoms by implementing novel, well-matched fMRI tasks that disentangle the brain's response to the intrinsic reward of being correct from its response to positively and negatively valenced outcomes in social and non-social (i.e., monetary) domains.

Reward processing is commonly conceptualized as a uniform construct in which incentives elicit equivalent neural and behavioral responses regardless of domain (e.g., social, monetary; Ethridge et al., 2017). The few studies that have contrasted reward in social and monetary domains using fMRI have used monetary and social reward tasks with markedly different experimental designs (Delgado et al., 2008; Izuma et al., 2008; Wake and Izuma, 2017) or tasks in which the subjective value of monetary and social rewards differ (Rademacher et al., 2010). For example, Izuma et al. (2008) measured the relation between monetary and social reward by contrasting neural response during a monetary gambling task with neural response to reading positive self-descriptors (Izuma et al., 2008), while Delgado et al. (2008) utilized a solitary monetary bidding task and a social competition monetary bidding task. Despite the paucity of well-matched tasks, studies in adults demonstrate that the ventral striatum is engaged by both social and monetary rewards (Delgado et al., 2008; Izuma et al., 2008; Rademacher et al., 2010; Wake and Izuma, 2017). However, whether there are differences in the magnitude of ventral striatum activation to social and monetary rewards remains inconsistent in the literature. For example, while Delgado et al. (2008) found differences in right ventral striatum activation between conditions, Izuma et al. (2008) found no difference in ventral striatum activation between their social and monetary reward tasks. Thus, it is possible that the disparity in these findings could be due to methodological differences in the tasks themselves. Given that reward sensitivity (Ernst and Spear, 2009) and desire for social acceptance peak in adolescence, it is critical to delineate social vs. non-social reward processing during this developmental period.

Even fewer studies have sought to tease apart neural response to intrinsic and extrinsic rewards. Being correct is an intrinsically rewarding experience (Satterthwaite et al., 2012) that engages the ventral striatum in the absence of incentives or performance feedback (Han et al., 2010; Wolf et al., 2011). Although this effect is most pronounced during adolescence (Satterthwaite et al., 2012), most prior studies examining brain function during reward processing in adolescence fail to disentangle neural response to choosing correct outcomes (intrinsic reward) from winning money for having chosen those outcomes (extrinsic reward). Therefore, it is unclear whether prior findings that demonstrate adolescents have heightened ventral striatal engagement to rewards reflect a sensitivity to intrinsic or extrinsic rewards.

Prior fMRI studies of reward processing have also linked alterations in striatal activation to depression (Silk et al., 2014; Telzer et al., 2014) and anxiety (Guyer et al., 2006; Bar-Haim et al., 2009; Lago et al., 2017). Depression is associated with a blunted neural response to both social (Monk et al., 2008; Olino et al., 2015) and monetary (Gotlib et al., 2010; Sharp et al., 2014;

Weinberg et al., 2015; Nelson et al., 2016) rewards in adults and children, whereas anxiety is associated with enhanced neural response to social (Guyer et al., 2012; Spielberg et al., 2015) and monetary (Bar-Haim et al., 2009) rewards. We recently conducted an EEG study in young adults in which we examined relations between depression and the magnitude of the reward positivity (RewP), an event-related potential that indexes engagement of the reward system (Distefano et al., 2018), in response to social (being liked) and monetary (winning money) rewards. While both social and monetary rewards elicited the RewP, more severe symptoms of depression were associated with a blunted RewP to social, but not monetary, rewards. Specifically, women with more severe depressive symptoms had a blunted RewP in response to being liked by same-sex peers. This suggests that there are unique relations between depression and neural response to social, but not monetary, reward. However, given the poor spatial resolution of EEG, it is unclear whether the blunted RewP reflects diminished engagement in the ventral striatum. Moreover, extant work has not directly contrasted response to social and monetary rewards in individuals with a range of both depression and anxiety symptoms; thus, the interplay of symptoms of anxiety and depression on the brain's response to social vs. non-social reward, particularly in adolescents, remains unclear.

While our prior EEG study provides promising evidence for the relationship between depression and social reward, distinguishing neural response to receiving positively valenced social outcomes from the intrinsic experience of being correct was not tested. Given that alterations in brain regions implicated in reward processing are linked to symptoms of anxiety (Guyer et al., 2006; Bar-Haim et al., 2009) and depression (Silk et al., 2014; Telzer et al., 2014), it is critical to determine if these alterations are specific to intrinsic or extrinsic reward processing. Moreover, individuals with anxiety and depression often exhibit negative predictions about social outcomes (Beck et al., 1979; Clark and Wells, 1995; Joiner and Coyne, 1999; Smith et al., 2018). Given these biases and the role that social stressors often play in triggering symptoms of depression and anxiety, it is critical to test if relations between symptoms and brain function differ by reward domain.

In the present study, we used fMRI to isolate differences in ventral striatal response to correctly or incorrectly predicting positive and negative feedback in both social and monetary domains in adolescents. Well-matched social and monetary paradigms were employed to disentangle neural responses to positively valenced outcomes from the intrinsic reward of being correct. Additionally, we examined these neural responses in relation to anxiety and depression symptoms. We focus on ventral striatum because prior studies consistently find ventral striatum activation in response to monetary and social reward. We hypothesized that ventral striatal response to outcomes (correct or incorrect) would differ by reward valence (positive or negative) across reward domains (social or monetary). We also hypothesized that given the salience of peers to adolescents, altered neural response to social, but not monetary, reward would be associated with anxiety and depressive symptoms.

MATERIALS AND METHODS

Participants

Participants were adolescents (n = 37; females = 18) aged 11–15 (M = 13.32; SD = 1.28) who were free of psychotropic medication and had no contraindications for fMRI. Informed written parental consent and written participant assent were obtained prior to participation, and all procedures were approved by the Institutional Review Board at Stony Brook University and were conducted in accordance with the Helsinki Declaration.

Measures

Depression was measured using the Children's Depression Inventory (CDI; Kovacs, 1992), a 27-item self-report measure of depressive symptoms in school-aged children and adolescents. Anxiety was measured using the Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al., 1999), a 41-item self-report questionnaire that assesses severity of anxiety symptoms in youth aged 8–18. The self-report version of this measure was used because it has greater sensitivity for detecting symptoms of anxiety than parent-report (Rappaport et al., 2017).

Procedure

Prior to the experimental session, participants were told they were completing a social evaluation study and were asked to submit a digital picture of themselves that would be sent to other purported participants their age across the country. Participants believed that these peers would receive a text message asking them to view the photo and indicate whether they thought they would "like" or "dislike" the participant. The picture would then disappear after 5 min. At the beginning of the experimental session, participants were told that they would be asked to guess which peers "liked" or "disliked" them and that they would also be completing a monetary guessing task. Participants completed self-report questionnaires and underwent mock scanning to gain familiarity with the MRI environment. Participants then underwent fMRI while completing the monetary and social reward tasks in a counterbalanced order. At the end of the session, participants responded to questions about their experience with the task to ensure they were engaged and believed the credibility of the peer feedback. Nearly all (n = 35; 94%) participants had high levels of task engagement and believed they were receiving feedback from actual peers. Participants were then debriefed.

fMRI-Based Monetary and Social Reward Tasks

The monetary and social reward tasks were administered using Eprime software ["Psychology Software Tools Inc., 2016, (E-Prime 2.0). Retrieved from http://www.pstnet.com"]. There were four conditions (monetary win, monetary loss, social like, and social dislike) that were presented in a counterbalanced order. Each condition included 30 trials. Each task was completed across two, 4.55-min runs. Each run included two blocks: one block of monetary win or social like trials, and one block of monetary loss or social dislike trials (15 trials per block). Trials were separated by a variable duration intertrial interval (1,100–11,600 ms; M = 3,500 ms).

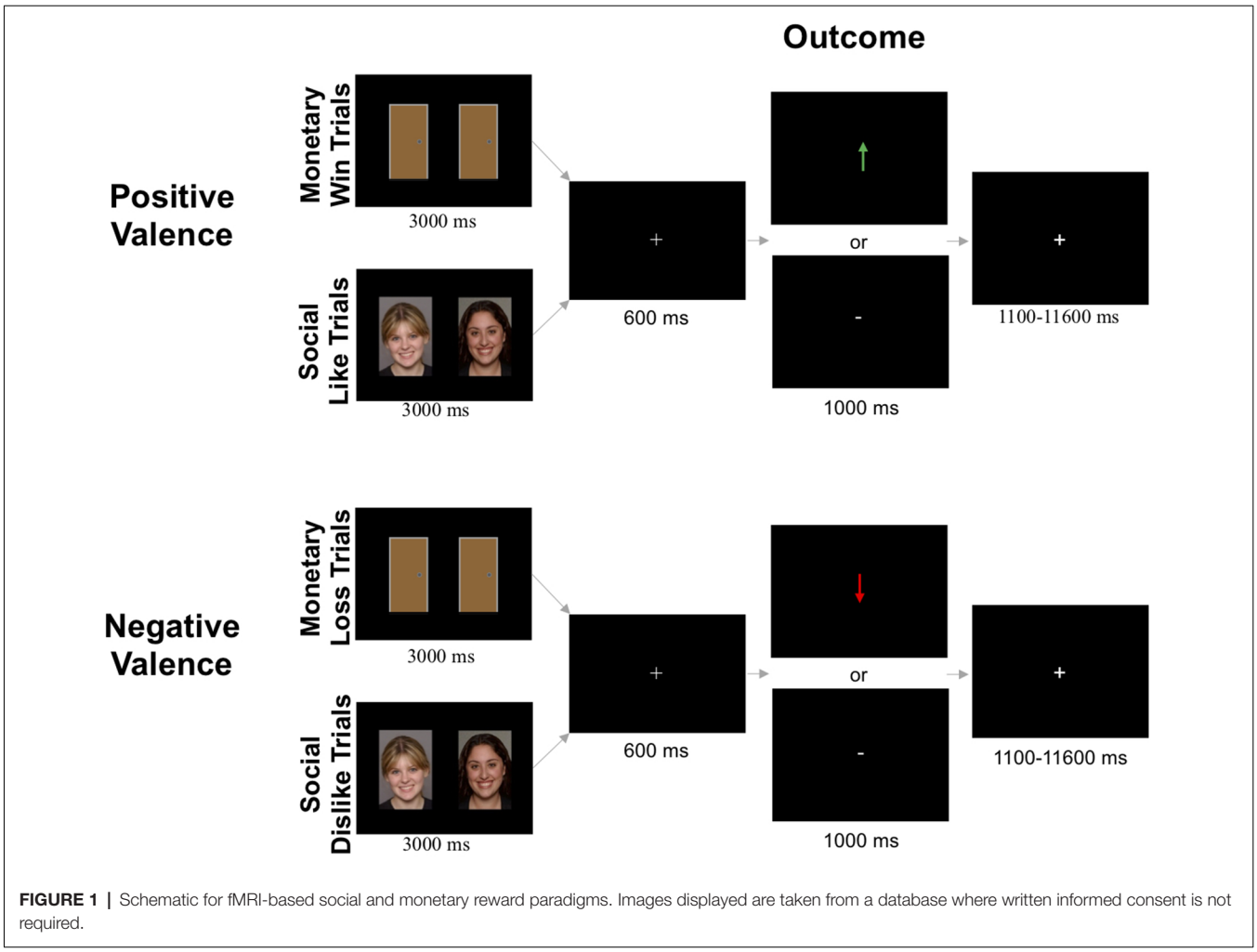


FIGURE 1 | Schematic for fMRI-based social and monetary reward paradigms. Images displayed are taken from a database where written informed consent is not required.

Monetary Reward Task (Figure 1)

At the beginning of each block, participants were informed if the block contained monetary win trials or monetary loss trials. In monetary win blocks, participants were instructed to choose the door behind which there was a $0.25 prize. In monetary loss blocks, participants were instructed to choose the door behind which there was a $0.25 monetary loss. Each trial began with the presentation of two identical doors (3,000 ms). Participants then used a button box to select either the left or right door on the screen. After stimulus offset, a fixation cross was presented for 600 ms before participants received feedback about the accuracy of their choice (1,000 ms). Participants were told that there were three possible scenarios for each monetary win/loss trial: (1) both doors contained a $0.25 monetary win/loss; (2) one door contained a $0.25 monetary win/loss while the other door resulted in a break-even outcome (i.e., neither win nor loss); or (3) both doors resulted in a break-even outcome. This ensured that the feedback the participant received would only be informative about the door they chose and not the door they *did not* choose. For example, if a participant chose a door and received feedback indicating a break-even result, the other door could have been a win/loss door (consistent with trial scenario [2] above) or it could have been another break-even door (consistent with trial scenario [3] above). In monetary win trials, feedback was either a green arrow pointing upward (↑) meaning the participant correctly selected the monetary win door, or a white horizontal dash (-), which indicated incorrect selection of the break-even door, resulting in no monetary win. In monetary loss trials, correct selection of the monetary loss door was indicated by a red arrow pointing downward (↓), while incorrect selection of the break-even door resulting in no monetary loss was indicated by a white horizontal dash (-).

Social Reward Task (Figure 1)

The social like and dislike tasks were identical to the monetary win and loss tasks, respectively, except pictures of gender-matched peers (i.e., two female faces or two male faces) were presented instead of doors. The social reward task consisted of 120 images of age-matched peers compiled from multiple sources [National Institute of Mental Health's Child Emotional Faces picture set (Egger et al., 2011) and internet databases of non-copyrighted images]. The pictures of purported peers had

positive facial expressions, were cropped so that individuals were pictured from their shoulders up, and were edited to have an identical solid gray background. Smiling faces were used because they are common in social reward tasks (Richards et al., 2013; Jarcho et al., 2015; Distefano et al., 2018), and are subject to less misinterpretation than neutral faces (Rapee and Heimberg, 1997; Davis et al., 2016). Images were constrained to a standard size (2.75 inch width × 4 inch height). There were an equal number of trials with male and female peers across the social like and dislike conditions (30 pairs each, 60 total).

At the beginning of each block of trials, participants were informed if the block contained social like trials or social dislike trials. In social like blocks, participants were instructed to choose the peer that liked them. In social dislike blocks, they were instructed to choose the peer that disliked them. Participants were told that there were three possible situations for each trial: (1) both people said they would like/dislike the participant; (2) one person said they would like/dislike the participant while the other person never rated the participant; or (3) neither person rated the participant. In social like trials, correct selection of the person who said they would like the participant was indicated by a green arrow pointing upward (↑). In social dislike trials, correct selection of the person who said they would dislike the participant was indicated by a red arrow pointing downward (↓). In both social like and dislike conditions, incorrect selection of the person who never rated the participant was indicated by a white horizontal dash (-).

fMRI Acquisition

Functional images were acquired using a 3T Siemens PRISMA MRI scanner. Blood Oxygenation Level-Dependent (BOLD) sensitive functional images were acquired using a gradient echo-planar imaging (EPI) sequence (224 mm in FOV, TR = 2,100 ms, TE = 23 ms, voxel size of 2.3 × 2.3 × 3.5 mm^3, flip angle = 83°, interleaved slice acquisition). Each run included 37 functional volumes. To facilitate anatomical localization and coregistration of functional data, a high-resolution structural scan was acquired (sagittal plane) with a T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (250 mm in FOV, TR = 1,900 ms, TE = 2.53 ms, voxel size of 1.0 × 1.0 × 1.0 mm^3, flip angle = 9°).

fMRI Preprocessing and Individual Level Analysis

Preprocessing and fMRI analyses were conducted using AFNI (Cox, 1996). Standard pre-processing steps were implemented with afni_proc.py; these steps included slice timing, coregistration, smoothing to 6-mm full-width half maximum (FWHM), spatial normalizing to standard Talairach space, and resampling, which resulted in 2-mm^3 voxels. Task-specific events (spanning the duration of each event) were modeled using a block function. An additional six regressors modeled motion residuals. Temporally adjacent repetition times (TRs) with a Euclidean-norm motion derivative greater than 1 mm were omitted from the model *via* censoring. Individual-level fMRI data were manually reviewed and subjects were excluded for motion and signal drop-out (n = 9), resulting in a final sample of 28 individuals. Results remained consistent when non-deceived participants were removed (n = 2). To retain power, these individuals were included in the final analyses.

Based on *a priori* hypotheses, we performed a region of interest (ROI) analysis on the ventral striatum. Ventral striatum was defined in MNI space using Neurosynth (Yarkoni et al., 2011). Left and right ventral striatum ROIs were derived using the meta-analytic search term "ventral striatum" (415 studies). Because a portion of the full cluster extended into ventricle and white matter, 6-mm sphere masks were created around central voxels (MNI left $x = -9$, $y = 6$, $z = -6$; right $x = 9$, $y = 6$, $z = 6$; see **Figure 2**). Individual-level data from these ROI masks were then extracted for each subject.

Data Analysis

Group level analyses were conducted in IBM SPSS Statistics, Version 25.0 ("Mac SPSS Statistics for Windows," IBM Corp, 2017). To investigate task effects, we conducted a Domain (monetary, social) × Valence (positive: monetary win/social like, negative: monetary loss/social dislike) × Outcome (correct, incorrect) analysis of variance (ANOVA). Next, to examine relations between the neural response to reward processing and anxiety and depression symptoms, we conducted a Domain (monetary, social) × Valence (positive: monetary win/social like, negative: monetary loss/social dislike) × Outcome (correct, incorrect) ANCOVA with depression and anxiety symptoms included as continuous covariates of interest. Decomposition analyses were performed for significant interactions related to task effects and *a priori* hypotheses regarding relations between ventral striatum response to reward domain, valence, and outcome to anxiety and depression.

RESULTS

A test of task effects demonstrated that while there was no Domain × Valence × Outcome interaction, a Valence × Outcome interaction emerged in the left ventral striatum ($F_{(1,27)} = 15.937$, $p < 0.001$, $\eta_p^2 = 0.371$). This interaction was driven by greater left ventral striatum response to correctly guessing positive outcomes (M = 0.0295), than to incorrectly guessing positive outcomes (M = −0.103; $t_{(27)}$ = 4.819, $p < 0.001$). There was no significant difference between correctly (M = −0.022) and incorrectly (M = −0.005) guessing negative outcomes ($t_{(27)}$ = 0.633, p = 0.532). There was also a main effect of Outcome ($F_{(1,27)}$ = 8.464, p = 0.007, η_p^2 = 0.239), such that there was greater left ventral striatum response to correctly (M = 0.004), relative to incorrectly (M = −0.054) guessing outcomes ($t_{(27)}$ = 2.909, p = 0.007). When anxiety and depression were included as covariates, a more complex task effect emerged. Specifically, a Domain × Valence × Outcome interaction was observed ($F_{(1,24)}$ = 5.064, p = 0.034, η_p^2 = 0.174; see **Figure 3**). A significant interaction emerged for correct trials ($F_{(1,24)}$ = 4.303, p = 0.049, η_p^2 = 0.152), but not for incorrect trials ($F_{(1,24)}$ = 1.642, p = 0.212, η_p^2 = 0.064). Although not significant, these effects were more prominent in the monetary domain.

The hypothesized Domain × Valence × Outcome × Anxiety × Depression interaction also emerged ($F_{(1,24)}$ = 5.043,

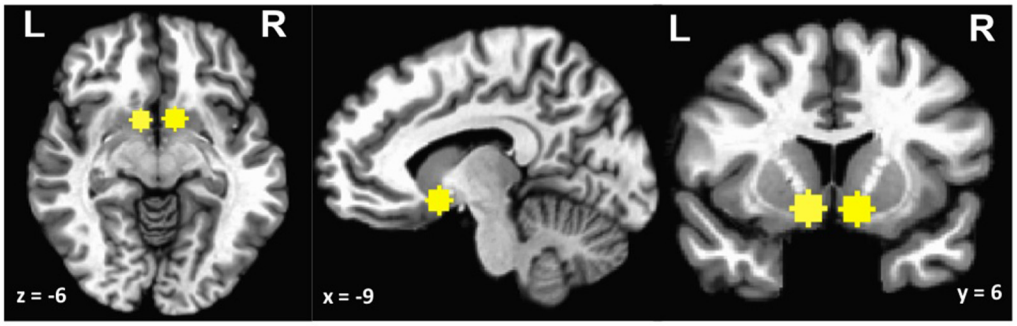


FIGURE 2 | Ventral striatum region of interest (ROI).

p = 0.034, η_p^2 = 0.174). The significant five-way interaction is decomposed in the below sections. Task effects with and without depression and anxiety were not observed in right ventral striatum. See **Table 1** for other main and interaction effects that do not directly relate to our *a priori* hypotheses.

Do Domain × Valence Effects Vary for Correct and Incorrect Outcomes Depending on Anxiety and Depression?

To determine if the interactive effects of domain, valence, and symptoms on brain function varied by outcome, we conducted two separate Domain (monetary, social) × Valence (monetary win/social like, monetary loss/social dislike) × Depression × Anxiety ANCOVAs, one for correct outcomes and one for incorrect outcomes. A significant interaction emerged for correct trials ($F_{(1,24)}$ = 7.195, p = 0.013, η_p^2 = 0.231), but not for incorrect trials ($F_{(1,24)}$ = 0.192, p = 0.665, η_p^2 = 0.008). Furthermore, there was a significant Domain × Valence interaction in correct ($F_{(1,24)}$ = 4.303, p = 0.049, η_p^2 = 0.152), but not incorrect trials ($F_{(1,24)}$ = 0.990, p = 0.330, η_p^2 = 0.040). Thus, further decomposition analyses focused on correct outcomes.

For Correct Outcomes, Do Valence Effects Vary by Domain Depending on Anxiety and Depression?

To determine if interaction effects for correct outcomes were specific to the domain of the reward (i.e., monetary or social), we next conducted two separate Valence (monetary win/monetary loss, social like/social dislike) × Depression × Anxiety ANCOVAs, one for correct trials in the social domain and one for correct trials in the monetary domain. For the social task, results indicated a Valence × Anxiety × Depression interaction ($F_{(1,24)}$ = 8.577, p = 0.007, η_p^2 = 0.263). However, these effects were not found in the monetary task ($F_{(1,24)}$ = 0.566, p = 0.459, η_p^2 = 0.023). Thus, the left ventral striatum differentially responds to social valence type (i.e., like vs. dislike) when an adolescent is correct, but activation varies based on severity of anxiety and depression symptoms.

For Correct Outcomes in the Social Domain, Do Valence Effects Differentially Relate to Anxiety and Depression?

While statistical analyses utilized fully dimensional measures, to facilitate the interpretation of this complex interaction and for illustrative purposes, participants were binned into low and high depression groups using a median split (low $<$ 9; high $\geq$ 9 on the CDI). See **Table 2** for group characteristics. Social Like and Dislike trials were also contrasted (dislike–like) for ease of interpretation (see **Figure 4**). In the low depression group (n = 17), there was a positive correlation between anxiety and ventral striatum activation to correct outcomes in dislike as compared to like trials (r = 0.472, p = 0.056). Specifically, among youth with *low* levels of depression, *more severe* anxiety symptoms were associated with *greater activation* in the striatum when participants learned they had correctly guessed that a peer *disliked* (vs. liked) them. The opposite relation was observed in the *high* depression group (n = 11; r = −0.617, p = 0.043). Specifically, among youth with higher levels of depression, *more severe* anxiety symptoms were associated with *greater activation* in the striatum to correctly guessing that a peer *liked* (vs. disliked) them. Furthermore, the association between brain activation and anxiety in the low-depression group was significantly different from this relation in the high-depression group (Fisher's r to z = 2.78, p = 0.005).

DISCUSSION

To our knowledge, this is the first study to utilize well-matched social and monetary reward paradigms to disentangle ventral striatal response to reward domain, valence, and outcome in adolescence. Importantly, the study design enabled us to tease apart striatal response to the intrinsic reward of being correct from the valence of social and monetary outcomes. Furthermore, we examined how depression and anxiety symptoms were associated with adolescents' striatal response in this paradigm. We found that activation in the left ventral striatum exhibited unique associations with symptoms of anxiety and depression depending on valence outcome, when receiving correctly predicted social feedback. These results support the idea that

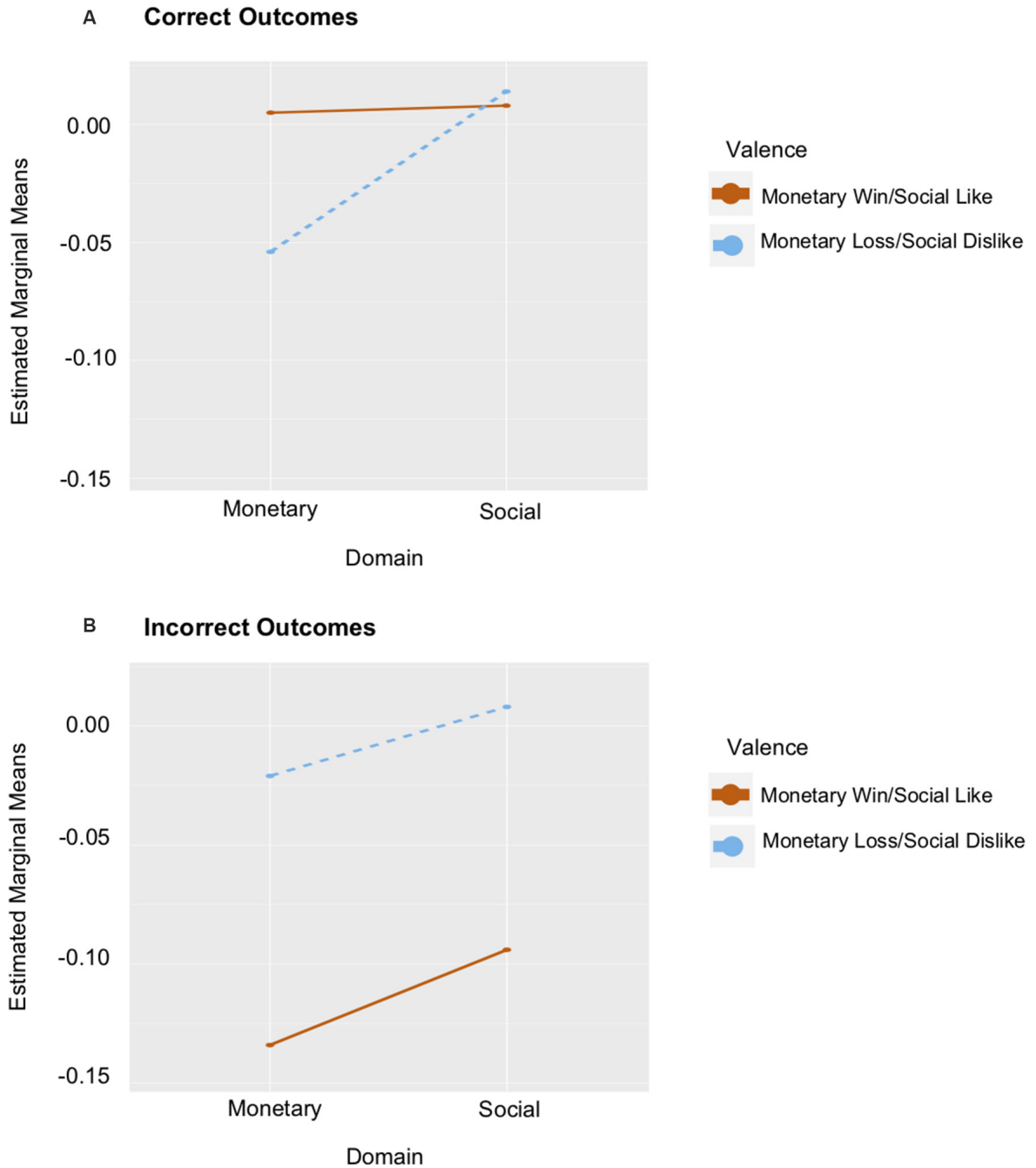


FIGURE 3 | Graphs of ventral striatum response to Domain × Valence controlling for Anxiety and Depression. **(A)** The red line depicts estimated marginal means of the monetary win and social like conditions for correct outcome trials. The dashed blue line depicts the estimated marginal means of the monetary loss and social dislike conditions for correct outcome trials. **(B)** The same relations are depicted for incorrect outcomes.

reward processing mechanisms are not uniform, but sensitive to contextual factors related to incentives. This sensitization may, in turn, be influenced by individual differences in anxiety and depression symptoms.

Considering task-based effects without the influence of symptoms of anxiety and depression revealed greater left ventral striatal response to correctly relative to incorrectly guessing outcomes. Thus, consistent with prior reports (Wolf et al., 2011; Satterthwaite et al., 2012), the intrinsic reward of being right engaged a critical hub in an appetitive processing circuit. However, this pattern of engagement was valence specific; greater activity was observed for positive, but not negative outcomes.

TABLE 1 | Results for the left ventral striatum Domain × Valence × Outcome × Anxiety × Depression ANCOVA.

Main effects	*F*	*p*	η_p^2
Domain	0.166	0.687	0.007
Valence	0.483	0.494	0.020
Outcome	4.289	0.049[a]	0.152
Interaction Effects			
Domain × Valence	0.390	0.538	0.016
Domain × Outcome	0.072	0.790	0.003
Valence × Outcome	4.551	0.043[b]	0.159
Domain × Valence × Outcome	5.064	0.034[c]	0.174
Domain × Anxiety × Depression	0.000	0.998	0.000
Valence × Anxiety × Depression	1.430	0.243	0.056
Outcome × Anxiety × Depression	0.175	0.680	0.007
Domain × Valence × Anxiety × Depression	1.978	0.172	0.076
Domain × Outcome × Anxiety × Depression	0.007	0.935	0.000
Valence × Outcome × Anxiety × Depression	1.430	0.243	0.056
Domain × Valence × Outcome × Anxiety × Depression	5.043	0.034	0.174

[a]*Correct Outcomes (M = −0.007; SE = 0.022); Incorrect Outcomes (M = −0.060; SE = 0.019).* [b]*Monetary Win/Social Like Correct Outcomes (M = 0.006; SE = 0.030); Monetary Win/Social Like Incorrect Outcomes (M = −0.114; SE = 0.028); Monetary Loss/Social Dislike Correct Outcomes (M = −0.020; SE = 0.029); Monetary Loss/Social Dislike Incorrect Outcomes (M = −0.006; SE = 0.025).* [c]*Social Like Correct Outcomes (M = 0.008; SE = 0.048); Social Like Incorrect Outcomes (M = −0.094; SE = 0.056); Social Dislike Correct Outcomes (M = 0.014; SE = 0.045); Social Dislike Incorrect Outcomes (M = 0.008; SE = 0.037); Monetary Win Correct Outcomes (M = 0.005; SE = 0.035); Monetary Win Incorrect Outcomes (M = −0.134; SE = 0.038); Monetary Loss Correct Outcomes (M = −0.054; SE = 0.039); Monetary Loss Incorrect Outcomes (M = −0.021; SE = 0.031).*

TABLE 2 | Characteristics of low and high depression groups used for illustrative purposes in decomposition analyses.

Characteristic	Low depression (*n* = 17)	High depression (*n* = 11)
Gender		
Female (*n*)	5	8
Male (*n*)	12	3
Age *M* (SD)	13.41 (1.33)	13.18 (1.25)
SCARED total anxiety *M* (SD)	12.94 (8.53)	28.09 (18.55)
CDI total depression *M* (SD)	4.29 (2.37)	15.91 (5.26)

These results underscore the importance of utilizing tasks that are sensitive to both the valence of appetitive outcomes and the intrinsic reward of being correct.

Interestingly, a more complex pattern of task effects emerged in the model controlling for anxiety and depression symptoms. The striatum responded differently to feedback depending on its domain (social/monetary), valence (positive/negative), and outcome (correct/incorrect). Specifically, when participants learned that they guessed correctly, there were differences in the striatal response depending on reward domain and valence. The same relation was not observed when participants learned that they guessed incorrectly. These effects were predominantly found in the monetary task, such that ventral striatum activation was greater to correctly guessing positively rather than negatively valenced outcomes. Surprisingly, similar relations were not observed in the social task. These findings are consistent with research demonstrating that the ventral striatum is closely linked to processing appetitive outcome and is engaged by being correct (Han et al., 2010; Wolf et al., 2011; Satterthwaite et al., 2012). Our findings support and extend this work by illustrating that ventral striatum activation to the intrinsically rewarding experience of being correct may also influence the way that other characteristics of reward, such as reward domain and valence, are processed.

Another unique feature of this study is that we contrast positively valenced outcomes and negatively valenced outcomes each with a null social condition (i.e., did not rate). Thus, we are able to examine the unique relation that each condition has with neural reward responsivity. Notably, this aim differs from most prior studies that directly contrast positive and negative social outcomes and are unable to tease apart unique effects for each condition. Therefore, prior work examining social reward in adolescence has not been able to disentangle ventral striatum response to positive (relative to null) vs. negative (relative to null) peer feedback. Our findings illustrate important differences in striatal function to the different feedback conditions. Specifically, the ventral striatum activates more to correctly guessing positive than negative monetary rewards; this pattern did not emerge for social rewards. Overall, these results highlight the importance of studying relations between neural activation to social rewards and of directly comparing reward domains.

We also found unique associations between anxiety and depression symptoms and ventral striatum activation to correctly guessing social outcomes. Among adolescents with low depressive symptoms, more severe anxiety was associated with greater striatal activation to correctly guessing if a peer *disliked* (vs. liked) them. Prior literature has shown that, separately, anxiety and depression are associated with altered neural responses to reward in different ways. For example, greater anxiety symptoms have been associated with an enhanced neural response to reward (Bar-Haim et al., 2009), an effect that we also found. However, these studies did not examine if relations were specific to social or monetary rewards, or intrinsic or extrinsic rewards. Our findings, therefore, extend prior work by showing that greater anxiety symptoms were associated with increased ventral striatum activation to correctly guessing about a negative social outcome. Predicting that social interactions will have a negative outcome is a common feature of anxiety (Clark and Wells, 1995; Smith et al., 2018). Therefore, our findings suggest that individuals with anxiety may find it rewarding to confirm their negative predictions about social experiences. These results may shed light on a possible mechanism by which negative social biases are reinforced and maintained. This is important because one of the central tenets of Cognitive Behavioral Therapy, the prevailing psychological treatment for anxiety (Chambless and Gillis, 1993), is to identify and change negative predictions, such as those about social outcomes (Hofmann, 2007). Therefore, elucidating neural mechanisms that underlie the reinforcement of these negative prediction biases may inform targets for interventions.

Conversely, among participants with high depressive symptoms, more severe anxiety was associated with greater striatal activation to correctly guessing if a peer *liked* (vs. disliked) them. Many studies have shown that depression is

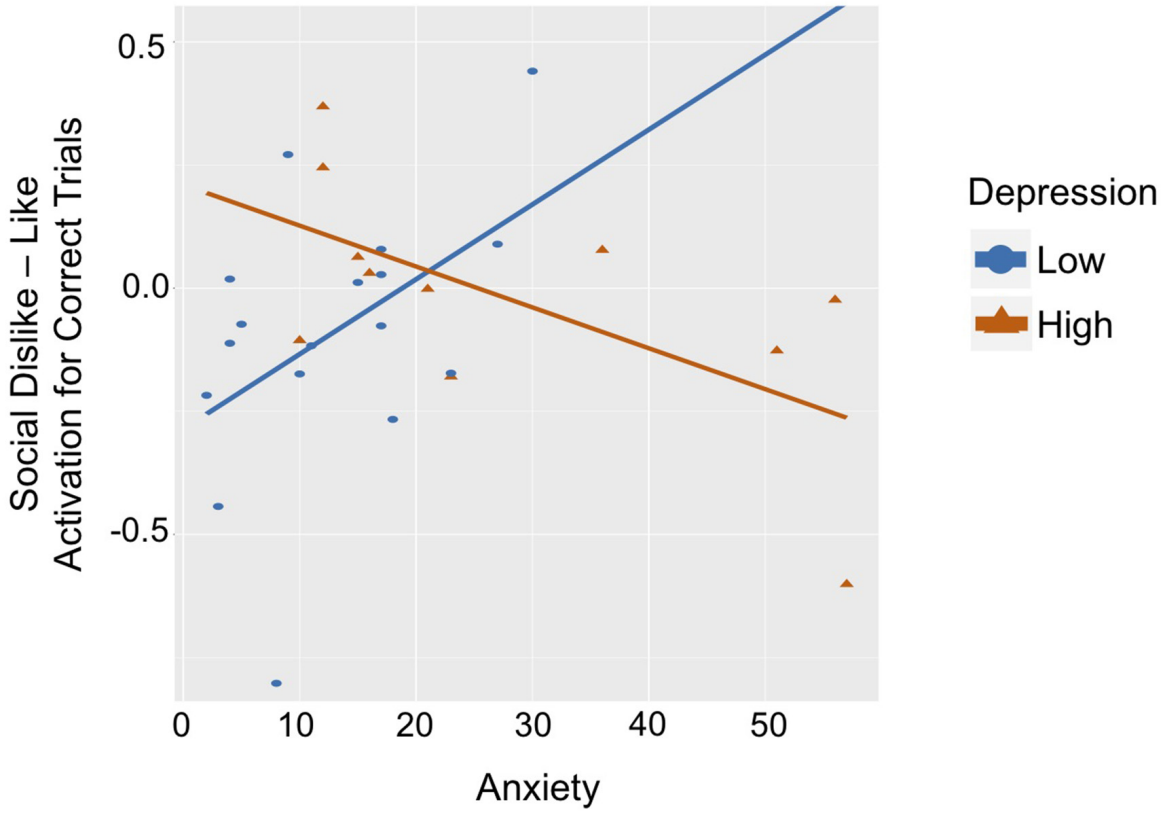


FIGURE 4 | Graph of correlation between ventral striatum response to Social Dislike–Like Correct Outcome Trials and anxiety for the low-depression group (blue line) and high-depression group (red line).

associated with a blunting of neural responsivity to reward (Landes et al., 2018). For example, our prior EEG study found that more severe symptoms of depression were associated with decreased RewP to social feedback (Distefano et al., 2018). These inconsistencies may be related to task-based features, but could also reflect an interplay between anxiety and depressive symptoms. Specifically, the brain's response to reward may vary depending on the level of symptom comorbidity. Thus, while depression and anxiety are both associated with negative prediction biases about social interactions (Beck et al., 1979; Clark and Wells, 1995; Joiner and Coyne, 1999; Smith et al., 2018), the neural mechanisms underlying the concurrent maintenance of these symptoms may be distinct.

Despite its strengths, this study is not without limitations. First, results need to be replicated in a larger sample. Moreover, because of the small sample size, we were unable to test for effects of participant and peer gender on brain function. Prior work has identified important sex differences in brain-based sensitivity to reward (Distefano et al., 2018; Greimel et al., 2018). For example, our prior EEG study found an association between depression and blunted RewP only in female participants when they were responding to same-sex peers. Thus, it is possible that present results may differ for adolescent males and females, or by the gender of the peer giving feedback. This study was also cross-sectional; thus, it is unclear whether altered neural response to social reward results in more symptoms of anxiety and depression or whether the presence of symptoms of anxiety and depression leads to altered neural response to social reward. Studies that leverage longitudinal designs are needed to test the predictive value and stability of neural response patterns to social reward and their relation to symptoms of psychopathology. Furthermore, longitudinal research could determine if relations between neural responses sensitive to reward domain, valence, outcome, and symptoms of psychopathology change across development. Indeed, children exhibit lower neural reward sensitivity than adolescents (Ernst and Spear, 2009), and socially anxious adolescents, but not adults, exhibit increased striatal activity to unexpected positive feedback from high-value peers (Jarcho et al., 2015). Lastly, the participants in this study were from an unselected community sample that had relatively low symptoms of anxiety and depression. It is possible that the association between ventral striatal engagement and symptoms of anxiety and depression may differ with more severe levels of psychopathology. However, the fact that these results emerged even in a subclinical sample suggests that reward to correctly guessing negative social predictions may be instantiated early in the course of a disorder and could promote symptoms.

In sum, this study begins to disentangle the complicated interplay between anxiety, depression, and neural activation to different characteristics of reward during adolescence. Results highlight that reward is not a unified construct. They suggest that engagement of neural mechanisms implicated in reward may depend on reward domain, valence, and the accuracy of the predicted outcome. Prior literature often conflates these different aspects of reward processing; however, results from the current study support the need to disentangle them in future work. Although tentative, our results also underscore complex relations between anxiety and depression and neural responses to reward in adolescence. Both anxiety and depression are associated with negative predictions about social interactions, yet there may be distinct, disorder-specific mechanisms that reinforce these negative predictions. Future work needs to directly connect these neural reward patterns to adolescents' adaptive and maladaptive behaviors in social interactions, as these relations likely play a critical role in forming strategies for navigating peer relationships. By understanding the mechanisms through which youth with and without psychopathology process different characteristics of reward, we may be able to inform treatment programs at this crucial stage of development.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Institutional Review Board of Stony Brook University with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Stony Brook University.

AUTHOR CONTRIBUTIONS

MQ, JJ and BN contributed to the conception and design of the study. MQ and JJ organized the database. MQ, JJ and LW performed the statistical analysis. MQ wrote the first draft of the manuscript. MQ, JJ and TC wrote sections of the manuscript. All authors contributed to manuscript revision, and read and approved the submitted version.

FUNDING

This study was supported by grants from the National Institute of Mental Health (K01 MH107808) to BN, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (R21HD093912) to JJ, and the Brain Research Foundation Young Investigator Award, Ellen Schapiro & Gerald Axelbaum Investigator (22441) to JJ.

REFERENCES

Bar-Haim, Y., Fox, N. A., Benson, B., Guyer, A. E., Williams, A., Nelson, E. E., et al. (2009). Neural correlates of reward processing in adolescents with a history of inhibited temperament. *Psychol. Sci.* 20, 1009–1018. doi: 10.1111/j.1467-9280.2009.02401.x

Beck, A. T., Rush, A. J., Shaw, B. F., and Emery, G. (1979). *Cognitive Therapy of Depression*. New York, NY: Wiley.

Beesdo-Baum, K., Knappe, S., Fehm, L., Höfler, M., Lieb, R., Hofmann, S. G., et al. (2012). The natural course of social anxiety disorder among adolescents and young adults. *Acta Psychiatr. Scand.* 126, 411–425. doi: 10.1111/j.1600-0447.2012.01886.x

Birmaher, B., Brent, D. A., Chiappetta, L., Bridge, J., Monga, S., and Baugher, M. (1999). Psychometric properties of the screen for child anxiety related emotional disorders (SCARED): a replication study. *J. Am. Acad. Child Adolesc. Psychiatry* 38, 1230–1236. doi: 10.1097/00004583-199910000-00011

Chambless, D. L., and Gillis, M. M. (1993). Cognitive therapy of anxiety disorders. *J. Consult. Clin. Psychol.* 61, 248–260. doi: 10.1037/0022-006x.61.2.248

Clark, D. M., and Wells, A. (1995). *A Cognitive Model of Social Phobia in Social Phobia: Diagnosis, Assessment, and Treatment*. New York, NY: The Guilford Press.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res.* 29, 162–173. doi: 10.1006/cbmr.1996.0014

Davis, F. C., Neta, M., Kim, M. J., Moran, J. M., and Whalen, P. J. (2016). Interpreting ambiguous social cues in unpredictable contexts. *Soc. Cogn. Affect. Neurosci.* 11, 775–782. doi: 10.1093/scan/nsw003

Delgado, M. R., Schotter, A., Ozbay, E. Y., and Phelps, E. A. (2008). Understanding overbidding: using the neural circuitry of reward to design economic auctions. *Science* 321, 1849–1852. doi: 10.1126/science.1158860

Distefano, A., Jackson, F., Levinson, A. R., Infantolino, Z. P., Jarcho, J. M., and Nelson, B. D. (2018). A comparison of the electrocortical response to monetary and social reward. *Soc. Cogn. Affect. Neurosci.* 13, 247–255. doi: 10.1093/scan/nsy006

Egger, H. L., Pine, D. S., Nelson, E. E., Leibenluft, E., Ernst, M., Towbin, K. E., et al. (2011). The NIMH child emotional faces picture set (NIMH-ChEFS): a new set of children's facial emotion stimuli. *Int. J. Methods Psychiatr. Res.* 20, 145–156. doi: 10.1002/mpr.343

Ernst, M., and Spear, L. P. (2009). "Reward systems," in *Handbook of Developmental Social Neuroscience*, ed. M. De Haan and M. R. Gunnar (New York, NY: Guilford Press), 558.

Ethridge, P., Kujawa, A., Dirks, M. A., Arfer, K. B., Kessel, E. M., Klein, D. N., et al. (2017). Neural responses to social and monetary reward in early adolescence and emerging adulthood. *Psychophysiology* 54, 1786–1799. doi: 10.1111/psyp.12957

Galvan, A. (2010). Adolescent development of the reward system. *Front. Hum. Neurosci.* 4:6. doi: 10.3389/neuro.09.006.2010

Gotlib, I. H., Hamilton, P., Cooney, R. E., Singh, M. K., Henry, M. L., and Joormann, J. (2010). Neural processing of reward and loss in girls at risk for major depression. *Arch. Gen. Psychiatry* 67, 380–387. doi: 10.1001/archgenpsychiatry.2010.13

Greimel, E., Bakos, S., Landes, I., Töllner, T., Bartling, J., Kohls, G., et al. (2018). Sex differences in the neural underpinnings of social and monetary incentive processing during adolescence. *Cogn. Affect. Behav. Neurosci.* 18, 296–312. doi: 10.3758/s13415-018-0570-z

Guyer, A. E., Choate, V. R., Pine, D. S., and Nelson, E. E. (2012). Neural circuitry underlying affective response to peer feedback in adolescence. *Soc. Cogn. Affect. Neurosci.* 7, 81–92. doi: 10.1093/scan/nsr043

Guyer, A. E., Nelson, E. E., Perez-Edgar, K., Hardin, M. G., Roberson-Nay, R., Monk, C. S., et al. (2006). Striatal functional alteration in adolescents

characterized by early childhood behavioral inhibition. *J. Neurosci.* 26, 6399–6405. doi: 10.1523/JNEUROSCI.0666-06.2006

Haber, S. N., and Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* 35, 4–26. doi: 10.1038/npp.2009.129

Han, S., Huettel, S. A., Raposo, A., Adckock, R. A., and Dobbins, I. G. (2010). Functional significance of striatal responses during episodic decisions: recovery or goal attainment? *J. Neurosci.* 30, 4767–4775. doi: 10.1523/JNEUROSCI.3077-09.2010

Hofmann, S. G. (2007). Cognitive factors that maintain social anxiety disorder: a comprehensive model and its treatment implications. *Cogn. Behav. Ther.* 36, 193–209. doi: 10.1080/16506070701421313

IBM Corp. (2017). *IBM SPSS Statistics for Windows.* Armonk, NY: IBM Corp.

Izuma, K., Saito, D. N., and Sadato, N. (2008). Processing of social and monetary rewards in the human striatum. *Neuron* 58, 284–294. doi: 10.1016/j.neuron.2008.03.020

Jarcho, J. M., Romer, A. L., Shechner, T., Galvan, A., Guyer, A. E., Leibenluft, E., et al. (2015). Forgetting the best when predicting the worst: preliminary observations on neural circuit function in adolescent social anxiety. *Dev. Cogn. Neurosci.* 13, 21–31. doi: 10.1016/j.dcn.2015.03.002

Joiner, T. E., and Coyne, K. C. (1999). *The Interactional Nature of Depression.* Washington, DC: American Psychological Association.

Kovacs, M. (1992). *The Children's Depression Inventory.* North Tonawanda, NY: Multi-Health Systems.

Kujawa, A., Carroll, A., Mumper, E., Mukherjee, D., Kessel, E. M., Olino, T., et al. (2018). A longitudinal examination of event-related potentials sensitive to monetary reward and loss feedback from late childhood to middle adolescence. *Int. J. Psychophysiol.* 132, 323–330. doi: 10.1016/j.ijpsycho.2017.11.001

Lago, T., Davis, A., Grillon, C., and Ernst, M. (2017). Striatum on the anxiety map: small detours into adolescence. *Brain Res.* 1654, 177–184. doi: 10.1016/j.brainres.2016.06.006

Landes, I., Bakos, S., Kohls, G., Bartling, J., Schulte-Körne, G., and Greimel, E. (2018). Altered neural processing of reward and punishment in adolescents with major depressive disorder. *J. Affect. Disord.* 232, 23–33. doi: 10.1016/j.jad.2018.01.017

Meuwese, R., Braams, B. R., and Güroğlu, B. (2018). What lies beneath peer acceptance in adolescence? Exploring the role of nucleus accumbens responsivity to self-serving and vicarious rewards. *Dev. Cogn. Neurosci.* 34, 124–129. doi: 10.1016/j.dcn.2018.07.004

Monk, C. S., Klein, R. G., Telzer, E. H., Schroth, E. A., Mannuzza, S., Moulton, J. L. III., et al. (2008). Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. *Am. J. Psychiatry* 165, 90–98. doi: 10.1176/appi.ajp.2007.06111917

Nelson, E. E., and Guyer, A. E. (2011). The development of the ventral prefrontal cortex and social flexibility. *Dev. Cogn. Neurosci.* 1, 233–245. doi: 10.1016/j.dcn.2011.01.002

Nelson, B. D., Perlman, G., Klein, D. N., Kotov, R., and Hajcak, G. (2016). Blunted neural response to rewards as a prospective predictor of the development of depression in adolescent girls. *Am. J. Psychiatry* 173, 1223–1230. doi: 10.1176/appi.ajp.2016.15121524

Olino, T. M., Silk, J. S., Osterritter, C., and Forbes, E. E. (2015). Social reward in youth at risk for depression: a preliminary investigation of subjective and neural differences. *J. Child Adolesc. Psychopharmacol.* 25, 711–721. doi: 10.1089/cap.2014.0165

Psychology Software Tools Inc. (2016). *[E-Prime 2.0].* Available online at: http://www.pstnet.com. Accessed January 02, 2019.

Rademacher, L., Krach, S., Kohls, G., Irmak, A., Gründer, G., and Spreckelmeyer, K. N. (2010). Dissociation of neural networks for anticipation and consumption of monetary and social rewards. *Neuroimage* 49, 3276–3285. doi: 10.1016/j.neuroimage.2009.10.089

Rapee, R. M., and Heimberg, R. G. (1997). A cognitive-behavioral model of anxiety in social phobia. *Behav. Res. Ther.* 35, 741–756. doi: 10.1016/s0005-7967(97)00022-3

Rappaport, B. I., Pagliaccio, D., Pine, D. S., Klein, D. N., and Jarcho, J. M. (2017). Discriminant validity, diagnostic utility, and parent-child agreement on the Screen for Child Anxiety Related Emotional Disorders (SCARED) in treatment- and non-treatment seeking youth. *J. Anxiety Disord.* 51, 22–31. doi: 10.1016/j.janxdis.2017.08.006

Richards, J. M., Plate, R. C., and Ernst, M. (2013). A systematic review of FMRI reward paradigms used in studies of adolescents vs. *Neurosci. Biobehav. Rev.* 37, 976–991. doi: 10.1016/j.neubiorev.2013.03.004

Satterthwaite, T. D., Ruparel, K., Loughead, J., Elliott, M. A., Gerraty, R. T., Calkins, M. E., et al. (2012). Being right is its own reward: load and performance related ventral striatum activation to correct responses during a working memory task in youth. *Neuroimage* 61, 723–729. doi: 10.1016/j.neuroimage.2012.03.060

Sharp, C., Sohye, K., Herman, L., Pane, H., Reuter, T., and Strathearn, L. (2014). Major depression in mothers predicts reduced ventral striatum activation in adolescent female offspring with and without depression. *J. Abnorm. Psychol.* 123, 298–309. doi: 10.1037/a0036191

Silk, J. S., Siegle, G. J., Lee, K. H., Nelson, E. E., Stroud, L. R., and Dahl, R. E. (2014). Increased neural response to peer rejection associated with adolescent depression and pubertal development. *Soc. Cogn. Affect. Neurosci.* 9, 1798–1807. doi: 10.1093/scan/nst175

Smith, E. M., Reynolds, S., Orchard, F., Whalley, H. C., and Chan, S. W. (2018). Cognitive biases predict symptoms of depression, anxiety and wellbeing above and beyond neuroticism in adolescence. *J. Affect. Disord.* 241, 446–453. doi: 10.1016/j.jad.2018.08.051

Spielberg, J. M., Jarcho, J. M., Dahl, R. E., Pine, D. S., Ernst, M., and Nelson, E. E. (2015). Anticipation of peer evaluation in anxious adolescents: divergence in neural activation and maturation. *Soc. Cogn. Affect. Neurosci.* 10, 1084–1091. doi: 10.1093/scan/nsu165

Telzer, E. H., Fuligni, A. J., Lieberman, M. D., and Galván, A. (2014). Neural sensitivity to eudaimonic and hedonic rewards differentially predict adolescent depressive symptoms over time. *Proc. Natl. Acad. Sci. U S A* 111, 6600–6605. doi: 10.1073/pnas.1323014111

Thapar, A., Collishaw, S., Pine, D. S., and Thapar, A. K. (2012). Depression in adolescence. *Lancet* 379, 1056–1067. doi: 10.1016/S0140-6736(11)60871-4

Wake, S. J., and Izuma, K. (2017). A common neural code for social and monetary rewards in the human striatum. *Soc. Cogn. Affect. Neurosci.* 12, 1558–1564. doi: 10.1093/scan/nsx092

Wang, K. S., Smith, D. V., and Delgado, M. R. (2016). Using FMRI to study reward processing in humans: past, present, and future. *J. Neurophysiol.* 115, 1664–1678. doi: 10.1152/jn.00333.2015

Weinberg, A., Liu, H., Hajcak, G., and Shankman, S. A. (2015). Blunted neural response to rewards as a vulnerability factor for depression: results from a family study. *J. Abnorm. Psychol.* 124, 878–879. doi: 10.1037/abn0000081

Wolf, D. H., Gerraty, R. T., Satterthwaite, T. D., Loughead, J., Campellone, T., Elliott, M. A., et al. (2011). Striatal intrinsic reinforcement signals during recognition memory: relationship to response bias and dysregulation in schizophrenia. *Front. Behav. Neurosci.* 5:81. doi: 10.3389/fnbeh.2011.00081

Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, V. C., and Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nat. Methods* 8, 665–670. doi: 10.1038/nmeth.1635

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 09 October 2019
doi: 10.3389/fnbeh.2019.00199

Neural Sensitivity to Social and Monetary Reward in Depression: Clarifying General and Domain-Specific Deficits

*Belel Ait Oumeziane *, Olivia Jones and Dan Foti*

Department of Psychological Sciences, Purdue University, West Lafayette, IN, United States

Reward dysfunction is thought to be play a critical role in the pathogenesis of depression. Multiple studies have linked depression to abnormal neural sensitivity to monetary rewards, but it remains unclear whether this reward dysfunction is generalizable to other rewards types. The current study begins to address this gap by assessing abnormal sensitivity to both monetary and social rewards in relation to depressive symptoms. We recorded event-related potentials (ERPs) during two incentive delay tasks, one with monetary reward and one with social reward. Both tasks were administered within the same sample, enabling a direct comparison of reward types. ERPs elicited by social and nonsocial rewards were morphologically similar across several stages of processing: cue salience, outcome anticipation, early outcome evaluation, outcome salience. Moderation analyses showed depression was linked with a pattern of general deficits across social and monetary rewards, specifically for the stages of outcome anticipation (stimulus-preceding negativity) and outcome salience (feedback-P3); self-reported reward sensitivity was generally associated with early outcome evaluation (reward positivity). Regression analyses modeling task-specific variance, however, showed a unique association between depression and outcome salience for social rewards, controlling for monetary rewards. The findings from this study underscore the importance of assessing neural sensitivity to multiple reward types in depression, particularly social reward. Characterizing the profile of reward functioning in depression across reward types may help to link laboratory-based deficits to relatively global vs. focal difficulties in real-world functioning.

Keywords: social reward, monetary reward, depression, reward processing, event-related potentials

OPEN ACCESS

Edited by:
Amanda E. Guyer, University of California, Davis, United States

Reviewed by:
Brady Nelson, Stony Brook University, United States
Yansong Li, Nanjing University, China

****Correspondence:***
Belel Ait Oumeziane
baitoume@purdue.edu

Specialty section:
This article was submitted to Motivation and Reward, a section of the journal Frontiers in Behavioral Neuroscience

Received: *15 March 2019*
Accepted: *13 August 2019*
Published: *09 October 2019*

Citation:
Ait Oumeziane B, Jones O and Foti D (2019) Neural Sensitivity to Social and Monetary Reward in Depression: Clarifying General and Domain-Specific Deficits. Front. Behav. Neurosci. 13:199. doi: 10.3389/fnbeh.2019.00199

INTRODUCTION

Major depressive disorder (MDD) ranks among the most prevalent and economically onerous medical conditions, having an estimated lifetime prevalence rate of 16% (Kessler et al., 2003) and an annual cost of more than $80 billion (Greenberg et al., 2015). Given these alarming statistics, there has been a growing focus on better understanding the core pathophysiological processes of depression. A cardinal symptom is anhedonia; a lack of motivation and enjoyment of activities that are pleasurable (American Psychiatric Association, 2013). There has been a growing interest in translating findings from basic cognitive and affective neuroscience research

to characterize anhedonia in depression in terms of quantitative deficits in reward functioning (Nestler and Carlezon, 2006; Pizzagalli et al., 2011; Russo and Nestler, 2013). In the current study, we focus on reward processing in the context of social and nonsocial domains across various stages of processing to better characterize the nature of the impairments in depression.

There has been converging evidence of reward dysfunction in depression across multiple units of analysis, including behavioral, neuroimaging, and electrophysiological research. Existing behavioral studies have linked depression with a rigid response style that is insensitive to reward contingencies (Henriques and Davidson, 2000; Pizzagalli et al., 2008), which is linked to anhedonia severity (Pizzagalli et al., 2005) and prospectively predicts poor treatment outcome (Vrieze et al., 2013). Building upon this behavioral data, functional magnetic resonance imaging (fMRI) studies have shed light on the pathophysiology of reward functioning in depression. For example, studies found decreased reactivity to rewards in the striatum, including the caudate, putamen, and nucleus accumbens (Steele et al., 2007; Knutson et al., 2008; Forbes et al., 2009; Pizzagalli et al., 2009; Moses-Kolko et al., 2011). These regions comprise the mesocorticolimbic dopamine system and are core areas involved in reward processing more broadly (Liu et al., 2011).

There is also converging evidence from event-related potential (ERP) research, particularly using the reward positivity [i.e., RewP; known previously as the feedback negativity (FN), or feedback-related negativity (FRN); Proudfit, 2015], as an index of reward dysfunction in depression. The RewP, which reflects the initial binary evaluation of outcomes as either better or worse than expected (Hajcak et al., 2007; Holroyd et al., 2008), is blunted in both clinical (Liu et al., 2014; Brush et al., 2018; Mulligan et al., 2018) and nonclinical samples (Bress et al., 2012; Mulligan et al., 2018), as well as among individuals with low self-reported reward sensitivity (Bress and Hajcak, 2013). Diminished RewP amplitude may also represent a neurobiological mechanism of risk for depression, such that it is more prevalent among people with a family history of depression (Foti et al., 2011; Kujawa et al., 2014) and has been shown to predict first episode onset of MDD (Bress et al., 2013; Nelson et al., 2016).

There are multiple reward stimuli types that can be leveraged for use in experimental research. For example, behavioral neuroscience studies typically use primary rewards or direct stimulation of reward-related regions to manipulate behavior (Salamone et al., 1994; Garris et al., 1999; Assadi et al., 2009). Yet, translational research of reward functioning in humans results in most studies conceptualizing reward narrowly, usually in terms of winning a nominal amount of money on laboratory tasks (i.e., monetary rewards; Liu et al., 2011). In fact, most reward processing studies in depression have used monetary contingencies to elicit reward-related behavior and neural activity (e.g., Knutson et al., 2008; Pizzagalli et al., 2008; Smoski et al., 2011; Ait Oumeziane and Foti, 2016). The emphasis on monetary rewards may in part be due to the relative ease of manipulating contingencies and eliciting neural responses. Nevertheless, findings based on a limited range of secondary rewards are then incorporated in general theories of reward dysfunction in depression. Monetary rewards are *assumed* to capture general reward functioning and studies have shown that primary (e.g., food) and secondary (e.g., money) rewards activate a common neural network (Sescousse et al., 2013). This focus on monetary rewards precludes a broader understanding of the role of social decision-making and reward functioning in depression (Forbes, 2009). Clarifying whether laboratory-based measures capture global or domain-specific reward deficits can have important implications for treatment. Global deficits may be indicative of efficient treatment targets with broad clinical utility (i.e., multiple psychopathologies, including substance use disorders, mood disorders, and schizophrenia), whereas deficits that are domain-specific may facilitate more targeted interventions based on the idiosyncratic profile of functional impairment at the individual level. A critical gap, however, is that studies of abnormal reward sensitivity in depression have largely assumed that laboratory-based based measures capture a global deficit, rather than directly comparing sensitivity to different reward types.

Far less is known about the regulation of neural responses to social stimuli than for other rewards (i.e., money), which is a key gap given the importance of social rewards in human functioning and their capacity to shape behavior (Fehr and Camerer, 2007; Gunaydin et al., 2014). However, there has been a growing focus in recent research to elucidate the neural correlates of social reward processing (Forbes and Dahl, 2012; Guyer et al., 2012; Bhanji and Delgado, 2014). Social rewards, such as stimuli indicating acceptance (Olino et al., 2015) and peer feedback (Guyer et al., 2012), elicit similar patterns of neural activity (e.g., striatum) as seen in studies examining money rewards. Other studies showed that receiving monetary rewards and another individual's positive opinion of oneself recruited similar striatal activity within the same sample (Izuma et al., 2008). Parallel findings from recent ERP studies showed that social and nonsocial reward elicited morphologically similar ERPs (Ait Oumeziane et al., 2017; Ethridge et al., 2017; Distefano et al., 2018). Together, these studies suggest different classes of rewards are underlined by an overlapping neural system or "common neural currency."

Recent work in the literature has also advanced the argument that social rewards may be particularly significant in depression (Forbes, 2009; Forbes and Dahl, 2012). Impairment in social functioning is a prominent feature of depression (Badcock and Allen, 2003) wherein individuals commonly display diminished motivation to engage in social interactions (Davey et al., 2008). Social contexts contribute to the development of depression. For example, a loss of an intimate partner is a common precipitating event for first episode onset (Monroe et al., 1999), whereas social factors in adolescence influence both the onset and course of depression (Sheeber et al., 2001; Davey et al., 2008). Although social withdrawal limits the likelihood of experiencing social rewards, it is also possible that reward responsiveness to social stimuli in depression is less sensitive thereby representing a potentially relevant sub-process for social functioning. To date, only a few studies have explicitly examined social reward deficits in depression. In one study, dysphoric individuals mobilized

less effort when expecting social approval (Brinkmann et al., 2014). Using a Chatroom Interaction task, youth at higher risk for depression displayed decreased reward-related striatal activity when being accepted by peers (Olino et al., 2015). Early findings implementing both social and monetary reward in ERP research shows dysphoric symptomatology was associated with diminished in RewP amplitude following female social feedback; participants completed the reward task under the pretense of receiving actual peer feedback (Distefano et al., 2018). Collectively, findings suggest depression is linked to impaired social and nonsocial reward functioning. A key gap, however, is that no study to date has evaluated social and nonsocial reward sensitivity across a broad range of processing (i.e., reward anticipation and receipt) in depression within the same sample. Indeed, the present study seeks to extend past research by clarifying whether reward dysfunctions in depression are general (i.e., spanning both monetary and social reward) or domain-specific (i.e., stronger for social or monetary reward).

In addition to evaluating different reward types, there is also growing interest in characterizing reward-related reactivity across different phases of processing. Findings from basic neuroscience literature suggest that reward processing reflects a set of interrelated processes that unfold over time across multiple stages (Schultz, 2007), which are neurobiologically and functionally distinct (Berridge et al., 2009). Using an established reward paradigm [i.e., monetary incentive delay (MID)] originally developed for fMRI research (Knutson et al., 2000, 2001), past research leveraged the millisecond temporal resolution of ERPs to capture a broad range of reward-related neural responses (Novak and Foti, 2015). Notably, the MID task refined for ERP research disentangles distinct sub-stages *within* both anticipatory and consummatory reward processing, providing additional precision of reward dynamics over the traditional magnetic resonance imaging (MRI) version of the task.

The task structure within the incentive delay framework is ideal for systematically capturing a broad range of reward processing. First, a cue signals the contingency for that trial (incentive vs. neutral), followed by a target stimulus that requires a behavioral response (e.g., button press). On incentive trials, fast button presses yield a reward (e.g., monetary gain) whereas slow responses yield a non-reward (e.g., monetary loss). On neutral trials, participants break-even regardless of reaction time. Neural response to rewards during the MID can be indexed by multiple candidate ERP components. First, reward-predicting cues elicit an increased P3 (cue-P3) compared to neutral cues (Broyd et al., 2012; Novak and Foti, 2015). The P3 is maximal at parietal sites approximately 300–500 ms. The cue-P3 is thought to track the allocation of attentional resources toward reward-predicting cues. Following the cue-P3, a contingent negative variation (CNV) is elicited to reflect a shift from initial reward cue detection toward approach-motivated action preparation (Novak and Foti, 2015). The CNV is a sustained, negative-going ERP that is maximal at central electrodes in anticipation of a cued motor response (Rohrbaugh et al., 1976; Brunia et al., 2012) and is increased for reward vs. neutral trials (Novak and Foti, 2015). Monetary reward contingencies can also modulate the anticipation of feedback. A promising index is the stimulus preceding negativity (SPN), which is a sustained centroparietal negativity that is maximal prior to feedback onset (Ohgami et al., 2006; Brunia et al., 2012; Foti and Hajcak, 2012; Novak et al., 2016). Collectively, these ERPs tease apart reward anticipation into discriminable stages.

Consummatory reward processing, meanwhile, is indexed by two ERPs elicited by reward delivery. First, a RewP is apparent at the frontocentral electrodes and peaks 250–300 ms following feedback. Although initially thought to be a loss-related signal (i.e., FN/FRN; Miltner et al., 1997; Gehring and Willoughby, 2002) recent findings suggest that the RewP is modulated by reward outcomes: a positivity that is increased for rewards vs. non-rewards (Holroyd et al., 2008; Foti et al., 2011). Immediately following the RewP is the feedback-P3 (fb-P3). Like the cue-P3, the fb-P3 is maximal at parietal sites and peaks between 300 and 500 ms following stimulus onset; whereas the cue-P3 tracks the salience of reward-predicting cues, the fb-P3 tracks the salience of uncertain outcomes (i.e., it is increased for uncertain monetary gains and losses vs. certain "break-even" outcomes). On our task, RewP tracks outcome valence (win vs. loss) and fb-P3 tracks outcome uncertainty (win/loss vs. neutral; Novak and Foti, 2015).

In our own work, we adapted the MID tasks in Novak and Foti (2015) to examine peoples' neural response to positive social feedback [i.e., Social Incentive Delay (SID); Ait Oumeziane et al., 2017]. Social rewards were defined positive performance feedback (i.e., "like") in a social/interpersonal context; people completed the SID under the pretense that feedback was delivered in real-time by a peer so that they would seemingly value receiving positive and negative feedback from others. That is, the pretense of stimulated live feedback regarding participants' performance was manipulated to be more evaluative than feedback generated automatically by a computer. This evaluative approach is in-line with a broader literature highlighting social-evaluative sensitivity in depression. For example, there is some evidence that depressed adults seek out excessive reassurance regarding their relationships and heavily rely on social approval for a sense of self-worth (Barnett and Gotlib, 1988; Joiner and Metalsky, 1995; Sheppard and Teasdale, 2004). Cognitive theories of depression have underlined the importance of sensitivity to feedback (e.g., social evaluation) as a potential vulnerability factor for depression (Beck, 1983; Mathews and MacLeod, 2005; Gotlib and Joormann, 2010). It is thought that depressed individuals may fail to utilize negative feedback to guide future performance (Elliott et al., 1997; Holmes and Pizzagalli, 2007; Steele et al., 2007), which could reflect underlying deficits in motivation (Eshel and Roiser, 2010). Other variants of the SID have utilized smiling faces as the feedback stimuli (Spreckelmeyer et al., 2009; Rademacher et al., 2010; Flores et al., 2015), which likely conflates reward and face processing. In addition, participants completing these tasks are cognizant of the notion that performance feedback was automated rather than determined by peers, thereby diminishing the social evaluative nature of the feedback. Here, we directly compare performance feedback in depression across multiple domains (social/nonsocial) and stage of processing.

Within this multi-faceted incentive delay framework, we demonstrated that social rewards on the SID elicited morphologically and psychometrically comparable ERPs as on the MID task in the same sample (Ait Oumeziane et al., 2017). Moreover, analogous ERPs across tasks (e.g., RewP on SID and MID) were moderately associated with one another (*r*'s 0.39–0.44), thereby highlighting the possibility of both a "common neural currency" and unique reward-type specific variance. That is, small correlations would suggest that these ERPs are primarily modulated by task-specific variability, whereas large correlations would indicate that there is little task-specific variability. The observed moderate correlations suggest the contribution of both general and task-specific reward sensitivity. Indeed, the combination of the SID and MID may have the potential of facilitating a more nuanced understanding of reward-related social and nonsocial neural dysfunctions in depression.

The current study seeks to systematically assess how depressive symptom severity relates to neural sensitivity to both social and monetary rewards within the same sample across a broad range of processing (reward anticipation and receipt). First, we aim to replicate our previous findings showing that ERPs elicited by social and monetary rewards on the SID and MID, respectively, are comparable across tasks (Ait Oumeziane et al., 2017). We expect that ERPs across tasks will exhibit a pattern of neural activity consistent with a common neural network (Izuma et al., 2008); that is, analogous ERPs on SID and MID will be morphologically similar and moderately correlated with one another (e.g., potentiated SPN on SID will be correlated with enhanced SPN on MID; Ait Oumeziane et al., 2017).

Next, we sought to evaluate the relationship between depressive symptoms with social and nonsocial reward-related brain activity. Although prior research suggests that depression is associated with deficits in both social (Olino et al., 2015; Distefano et al., 2018) and monetary rewards (Foti and Hajcak, 2012), no study has shown whether these deficits manifest within the same sample, particularly in the context of anticipatory (i.e., cue-P3, CNV, SPN) and consummatory ERPs (i.e., RewP, fb-P3). We expected that depression would exhibit deficits in abnormal consummatory (e.g., RewP; Brush et al., 2018; Mulligan et al., 2018) reward sensitivity. In order to distinguish the specificity of reward dysfunction across general depression severity as compared to the anhedonic features, we also tested whether blunted reward ERPs mapped on to diminished self-reported reward responsiveness (i.e., trait-like anhedonia). We expected that ERPs more uniquely map on to reward responsiveness rather than depression more generally (Pizzagalli et al., 2005; Foti et al., 2011; Bress and Hajcak, 2013).

Here, we formally tested whether reward-type (i.e., social, monetary) moderates the relationship with depressive symptoms and reward responsiveness, separately. Complementing these analyses, we sought to examine whether task-specific variability is uniquely associated with self-report symptoms. Task-specific effects were isolated using a series of exploratory regressions wherein analogous ERPs across tasks were entered as simultaneous predictors (i.e., social and nonsocial ERPs was controlled for in each regression model) of depressive symptoms and reward responsiveness.

MATERIALS AND METHODS

Participants

Demographic information is presented in **Table 1**. Participants were 121 adult volunteers. Participants were excluded due to past-month psychotropic medication use (N = 11). On SID, participants were excluded due to equipment failure (N = 2) and poor-quality ERP data (e.g., slow waves; N = 1), leaving 107 participants for the final analyses. On MID, participants were excluded for not completing the task (N = 4), equipment failure (N = 1), and poor-quality ERP data (N = 1), leaving 104 in the final analyses. There were 102 participants (M age = 19 years, SD = 1.15). with complete social and monetary reward ERP data in the final sample. Notably, participants in the current study represent a non-overlapping sample relative to our initial study comparing SID and MID ERPs (Ait Oumeziane et al., 2017).

Measures

Center for Epidemiological Studies—Depression Scale (CES-D; Radloff, 1977)

The Center for Epidemiological Studies-Depression Scale (CES-D) is a 20-item self-report questionnaire intended to measure current levels of depressive symptomatology in the general population (Radloff, 1977). Participants were asked to rate each question based on how frequently during the past week each item applied to them. Each item was scored on a 4-point Likert-type scale of 0 (*rarely or none of the time*) to 3 (*most or all of the time*). Higher scores on the scale denote greater depressive symptoms. In the current sample, Cronbach's α was 0.91.

Reward Responsiveness Scale (RR; Van den Berg et al., 2010)

The RR is an 8-item questionnaire used to quantify trait tendencies to engage in reward-related behavior (Van den Berg et al., 2010). This scale was developed as a means of providing a pure and more reliable measure of reward responsiveness than other self-report scales. Participants evaluate items on a Likert-scale from 1 (*strong disagreement*) to 4 (*strong agreement*). Higher scores denote greater reward responsiveness traits. In the current sample, Cronbach's α was 0.91.

TABLE 1 | Sample characteristics.

Variable	*N*	%
Gender		
Male	58	53.2
Female	51	46.8
Race		
Caucasian	81	74.3
Asian	21	19.3
African American	4	3.7
Native Hawaiian/Pacific Islander	1	0.9
Ethnicity		
Hispanic/Latino	11	10.1
Non-Hispanic/Latino	94	86.2

Laboratory Tasks

Social Incentive Delay

The SID task (Ait Oumeziane et al., 2017) was modeled after monetary reward tasks used in ERP research (Novak and Foti, 2015). An overview of the trial structure is shown in **Figure 1**. On each trial, participants were presented with one of two cues indicating the contingency for that trial: a blue circle with the letter "F," similar to the Facebook logo, indicated a social contingency (i.e., possible positive or negative social evaluation; $N = 50$) and an empty circle indicated a neutral trial (i.e., no social evaluation; $N = 20$). Cues were followed by an anticipatory interval that varied in length from 2,000 to 2,500 ms, during which a fixation mark ("+") was presented. The target stimulus (i.e., white box) was then presented; each participant was instructed to quickly click the left mouse button when the target appeared on the screen. After target offset, the fixation mark was presented for 1,300 ms while participants awaited feedback about their response. On incentive trials, successful responses resulted in a thumbs up (i.e., social media "like") indicating a positive social evaluation, while unsuccessful responses resulted in a thumbs down (i.e., social media "dislike" or "unlike") indicating a negative social evaluation. Neutral trials always resulted in no social evaluations "=." Here, we used "thumbs up" and "thumbs down" as social feedback stimuli to perceptually mirror the "up" and "down" arrow used as the monetary feedback stimuli in the MID task, respectively. Although feedback was mirrored perceptually across tasks, ultimately different stimuli were selected in order to ensure that task differences were salient. It is possible that participants who complete the monetary reward task first inadvertently believe that positive feedback on SID yields monetary rewards. Feedback stimuli were presented for 2,000 ms, and the inter-trial interval was 1,000 ms. Task difficulty was adjusted to keep performance at approximately 50%; the target presentation became easier (+10 ms) following each unsuccessful response and more difficult (−10 ms) after each successful response.

Prior to starting the SID, participants were told that research assistants would use a computer program outside of the EEG booth to evaluate their performance on "social rounds." To emphasize the role of the research assistants, participants were asked to treat the structure of the task similarly to how social media functions. For example, receiving a "like" by one's peers on Facebook for sharing content (e.g., status update, photos) parallels how they will receive "thumbs up" feedback if the research assistant approved or "liked" their performance on "social rounds." In reality, feedback stimuli were automated, and no real-time social evaluations were delivered. A practice block of 10 trials (eight incentives, two neutral) was used to determine initial task difficulty. Halfway through the task, participants received a short break. Ten consecutive incentive trials were added at the end of SID in order to allay any feelings of discomfort experienced from perceived negative social feedback; these trials were excluded from the analyses.

Monetary Incentive Delay

The overall trial structure, including the sequence and timing of all stimuli, was identical to the SID task; however, the cue and feedback stimuli differed (see **Figure 1**). On each trial, participants were presented with one of two cues indicating the contingency for that trial: a circle with a dollar symbol indicated a monetary incentive (i.e., possible gain or loss; $N = 50$ trials) and an empty circle indicated a neutral trial (i.e., certain break-even; $N = 20$ trials). On incentive trials, correct responses resulted in a green "↑" denoting a monetary gain of $0.40, while incorrect responses resulted in a red "↓" indicating a monetary loss of $0.20. Neutral trials always resulted in break-even feedback ($0). As before, a practice block of 10 trials (eight incentive, two neutral) was used to determine initial task difficulty. Halfway through the task, participants received a break; however, unlike SID they were informed of their cumulative winnings. Presentation software (Neurobehavioral Systems Inc., Berkeley, CA, USA) was used to control the timing and presentation of all stimuli for MID and SID.

Procedure

After a short description of the experiment, EEG sensors were attached. Participants performed the reward tasks (i.e., SID, MID) and other tasks unrelated to this study, with task order counterbalanced across participants. After the experiment, participants completed the CES-D and RR measures and were paid their winnings (i.e., $5.00).

Psychophysiological Recording and Data Reduction

The EEG was recorded *via* 32 Ag/AgCl active scalp electrodes using an actiCAP and the actiCHamp system (Brain Products, Munich, Germany). EEG signals were digitized at a 24-bit resolution with a sampling rate of 500 Hz. Impedances were maintained below 30 kOhm. Recordings were obtained from 32 scalp electrodes and a ground at Fpz. Vertical electrooculogram was recorded using two facial electrodes. Horizontal electrooculogram was recorded from electrodes FT9/10. Off-line analysis was performed using Brain Vision Analyzer software (Brain Products, Munich, Germany). All signals were re-referenced to the mastoid average (TP9/10) and band-pass filtered from 0.1 to 30 Hz. For the cue-P3 and CNV, the signal was segmented from −200 to 3,000 ms relative to cue onset. For the SPN, the signal was segmented from −1,700 to 100 ms relative to feedback onset (i.e., −200 to 1,600 relative to target onset). For the RewP and fb-P3, the signal was segmented from −200 to 1,000 ms relative to feedback onset. Each trial was corrected for blinks and eye movements (Gratton et al., 1983). Artifact rejection was conducted using a semi-automated procedure, with artifacts defined as: a step of 50 μV, >200 μV difference within 200-ms intervals, and <0.5 μV difference within 100-ms intervals. Additional artifacts were then identified using visual inspection.

ERPs were averaged separately for each condition on both tasks and corrected relative to their respective baseline windows (cue-P3 and CNV: −200 to 0 ms before cue onset; SPN: −1,200 to −1,000 ms before feedback onset; RewP and fb-P3: −200 to 0 ms before feedback onset). The average number of trials remaining for each condition after artifact rejection was as follows for SID: (1) social incentives for cue-P3 and CNV

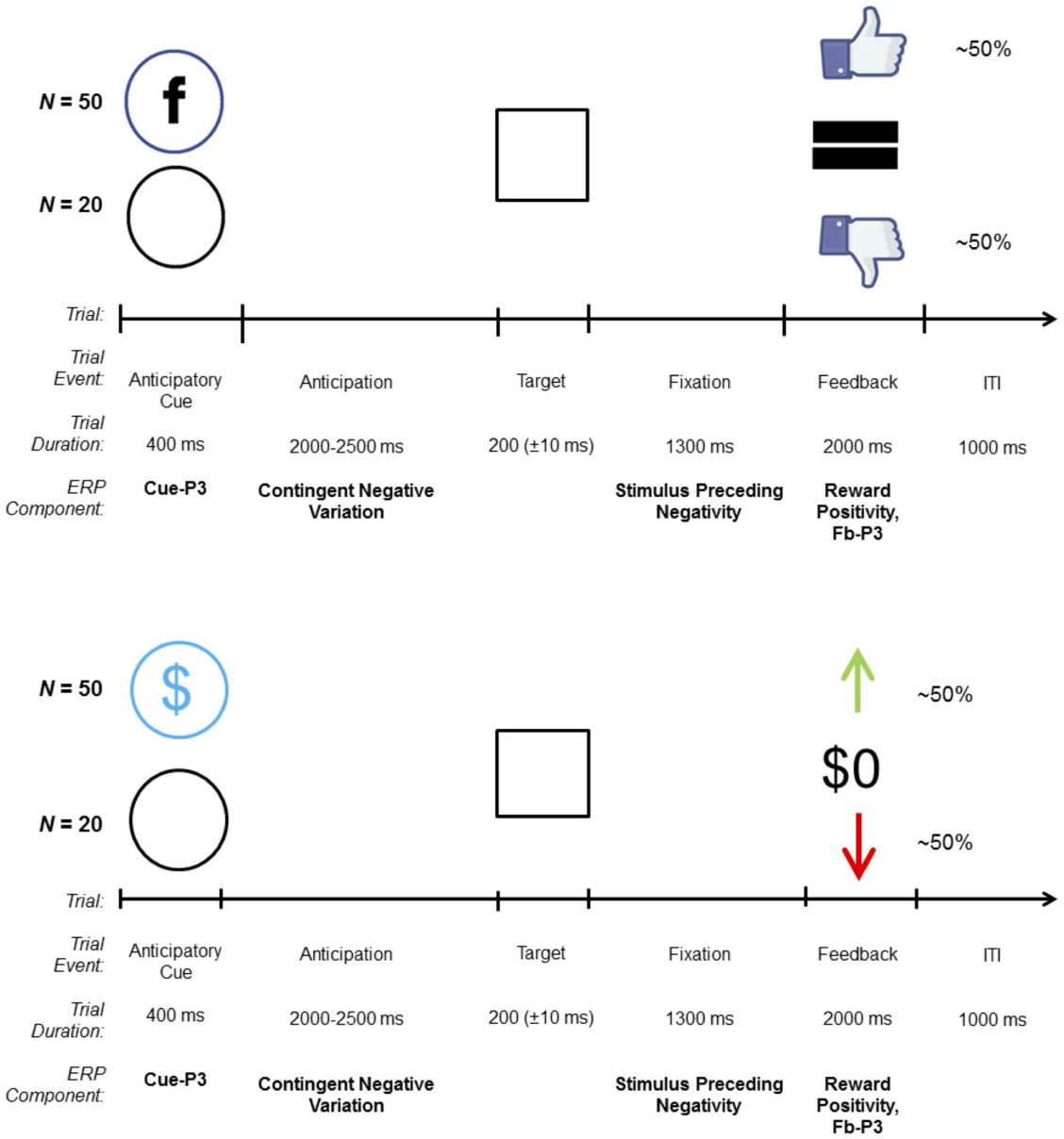


FIGURE 1 | Trial structure and related event-related potential (ERP) components for the social [top; social incentive delay (SID)] and monetary [bottom; monetary incentive delay (MID)] incentive delay tasks. On each trial, one of two possible cues was presented: incentive (SID, MID) or neutral (empty circle). Target duration began at 200 ms and was dynamically adjusted based on task performance. On incentive trials, win and loss feedback were uncertain and based on performance; on neutral trials, feedback [i.e., "=" (SID), "$0" (MID)], was certain and predictable. The total number of trials depicted do not factor in the practice trials (N = 10) on SID and MID, and the overinclusion trials (N = 10; always receive positive social feedback to allay discomfort) on SID, all of which were not included in the analyses.

(M = 42.41 trials, SD = 4.45); (2) neutral incentive condition for cue-P3 and CNV (M = 16.56 trials, SD = 2.59); (3) social (M = 44.27 trials, SD = 4.80) and neutral (M = 17.23 trials, SD = 2.64) conditions for SPN; (4) positive (M = 21.50 trials, SD = 3.48) and negative (M = 20.88 trials, SD = 3.55) social outcomes for the RewP and fb-P3; and (5) neutral social outcome condition for fb-P3 (M = 17.10 trials, SD = 2.67). The average number of trials for MID was as follows: (1) monetary incentives for cue-P3 and CNV (M = 42.05 trials, SD = 5.46); (2) neutral incentive condition for cue-P3 and CNV (M = 16.76 trials, SD = 2.49); (3) monetary (M = 44.50 trials, SD = 4.50) and neutral (M = 17.84 trials, SD = 1.90) incentive conditions for SPN; (4) monetary gain (M = 22.82 trials, SD = 2.87) and loss (M = 20.75 trials, SD = 3.20) conditions for the RewP and fb-P3; and (5) neutral monetary outcomes for fb-P3 (M = 17.72 trials, SD = 1.99).

ERPs were scored using time-window averages, which was determined based on peak of the difference wave for each

component within each task separately for the full sample. Given that we utilized distinct incentive cues and feedback stimuli across tasks, in addition to our findings from our development of the SID task (Ait Oumeziane et al., 2017), we expected that the time-window for the cue-P3, RewP, and fb-P3 may slightly differ across tasks. Thus, we scored each ERP surrounding the peak of relevant difference wave, regardless of their temporal properties of their counterpart component on the other task. Time windows and electrode poolings for MID ERPs were as follows: (1) cue-P3 from 390 to 440 ms after cue onset at Cz, CP1, CP2, Pz; (2) CNV from 2,200 to 2,400 ms after cue onset at FC1, Cz, C3, CP1; (3) SPN from −200 to 0 before feedback onset at Cz, CP1, CP2, Pz; (4) RewP from 250 to 300 ms post feedback at Fz, FC1, FC2, Cz; (5) fb-P3 from 340 to 490 ms post feedback at Cz, CP1, CP2, Pz. Time windows SID ERPs were as follows: (1) cue-P3 from 325 to 375 ms after cue onset; (2) the CNV from 2,200 to 2,400 ms after cue onset; (3) the SPN from −200 to 0 before feedback onset; (4) the RewP (i.e., positive minus negative outcome) from 290 to 340 ms post feedback; (5) the fb-P3 from 340 to 390 ms post feedback. The electrode poolings for SID ERPs were identical to MID.

Data Analysis

Effects of condition and task on behavioral performance were evaluated using 2 (Task: MID vs. SID) × 2 (Condition) repeated-measured analysis of variances (ANOVAs). Effects of condition on ERP amplitudes were evaluated using 2 (Task: MID vs. SID) × 2 (Condition) × 2 (Task Order) repeated-measured ANOVAs. For anticipatory ERPs (cue-P3, CNV, and SPN), the effect of condition was tested by comparing incentive and neutral trials. For the RewP, the relevant condition contrast was the effect outcome valence (i.e., positive vs. negative outcomes). For the fb-P3, the relevant contrast was the effect of outcome salience (i.e., positive vs. neutral outcome, negative vs. neutral outcome). Follow-up contrasts to test for within task-modulation were performed for ERPs that showed a significant Task × Condition interaction.

As an alternative to subtraction-based ERP difference scores, we also used linear regression to create residualized neural responses to rewards controlling for non-reward conditions. For example, cue-$P3_{resid}$ was created by saving the residual variance in a regression wherein cue-P3 on neutral trials was entered to predict cue-P3 on incentive trials. Other residualized anticipatory ERPs (i.e., CNV_{resid}, SPN_{resid}) followed the same steps (i.e., ERP on neutral trials predicting ERP on incentive trials). For $RewP_{resid}$, RewP on loss trials was entered predicting the RewP on win trials. For fb-$P3_{resid}$ to positive outcomes, fb-P3 on negative and neutral outcome trials were entered predicting fb-P3 on positive outcome trials. fb-$P3_{resid}$ to negative outcomes, fb-P3 on positive and neutral outcome trials were entered predicting fb-P3 on negative outcome trials[1]. Each residual ERP difference score was calculated separately for SID and MID (e.g., $RewP_{resid}$ on SID was calculated using only the relevant SID conditions).

To evaluate whether the association between depression symptoms and reward-related ERPs is moderated by reward type, we conducted a series of mixed-measure ANCOVAs. The within-subjects factor was Task (two levels; analogous SID and MID ERPs), whereas the between-subjects factor was self-report symptoms (i.e., CES-D and RR scores). In these models, the interaction between self-reported symptoms and task formally tests whether the strength of association differs across reward type. CES-D and RR scores were evaluated separated within each model. Next, a series of multiple linear regressions were performed to isolate task-specific variance in the instance of significant main effects of self-report symptoms and/or interaction between symptoms and task. These analyses complement the ANCOVAs, as regression is better suited to isolate unique task-specific variance in relation to depression. Within each regression model, analogous ERPs across tasks (e.g., $RewP_{resid}$ on MID and SID) were entered as simultaneous predictors of depression or reward responsiveness scores. Each regression analysis also included effects task order, age, gender, and ethnicity as covariates.

RESULTS

Sample Characteristics

Across the full sample, the average total CES-D score was 13.55 (SD = 10.01), with a range of 0–43. Approximately 108 (99%) participants in the sample reported at least some current symptoms (scores >0); 33 (30%) scored beyond the cut-off (>16) denoting higher risk for major depression. The average self-reported RR score was 26.83 (SD = 3.47), with a range of 18–32. RR and CES-D scores were not significantly correlated ($r = -0.10$, $p = 0.15$), likely due to the different time-frames of these scales.

Task Performance

The ANOVA revealed that reaction time varied as a function of Task ($F_{(1,104)} = 15.30$, $p < 0.001$, $\eta_p^2 = 0.13$). Overall, participants were quicker to respond on MID (M = 210.29 ms, SE = 2.83) compared to SID (M = 222.29 ms, SE = 3.56). There was also a significant main effect of Condition (incentive vs. neutral) across tasks ($F_{(1,104)} = 106.66$, $p < 0.001$, $\eta_p^2 = 0.51$). Participants were quicker to respond on incentive trials (M = 204.83 ms, SE = 2.57) compared to neutral trials (M = 227.75 ms, SE = 3.56). For SID, participants were significantly quicker on social (M = 211.95 ms, SD = 32.86) relative to neutral incentives (M = 232.02 ms, SD = 43.64; $t_{(106)} = 7.78$, $p < 0.001$, $d = 0.75$). For MID, reaction times were significant quicker on monetary (M = 197.68 ms, SD = 26.69) as compared to neutral incentives (M = 223.95 ms, SD = 37.85; $t_{(105)} = 8.47$, $p < 0.001$, $d = 0.83$). The Task × Condition interaction was not significant ($F_{(1,104)} = 2.39$, $p = 0.13$, $\eta_p^2 = 0.02$). As expected, participants were successful on 51.26% (SD = 3.00) and 50.39% (SD = 3.08) of all monetary and social incentive trials, respectively.

[1]Our analyses showed a significant Task × Condition interaction for the fb-P3, thus we calculated the residual difference score different than when using subtraction methods. This difference was important insofar as to disentangle reward magnitude (fb-P3) and potential overlapping valence effects typically associated with the RewP.

Reward ERPs

Reward Anticipation

Anticipatory ERPs are presented in **Figure 2**. Cues elicited a P3 that was maximal at centroparietal sites approximately 350 ms and 415 ms for SID and MID, respectively. The ANOVA yielded significant main effects of Task ($F_{(1,100)} = 15.42$, $p < 0.001$, $\eta_p^2 = 0.13$) and Condition ($F_{(1,100)} = 72.74$, $p < 0.001$, $\eta_p^2 = 0.42$); all other main effects, two-way, and three-way interactions were not significant ($p > 0.10$, $\eta_p^2 < 0.05$). Average cue-P3 amplitude (i.e., averaged across incentive and neutral conditions) was greater for MID ($M = 5.36$ μV, $SE = 0.39$) relative to SID ($M = 3.79$ μV, $SE = 0.40$). Furthermore, cue-P3 amplitude was more positive on incentive ($M = 5.78$ μV, $SE = 0.37$) compared to neutral cues ($M = 3.37$ μV, $SE = 0.39$).

Next, the CNV presented as a negative slow wave on MID and SID that was maximal immediately prior to target onset at left central electrodes. The CNV was sensitive to Condition ($F_{(1,100)} = 4.33$, $p < 0.05$, $\eta_p^2 = 0.04$); all other main effects, two-way, and three-way interactions were not significant ($p > 0.10$, $\eta_p^2 < 0.10$). The CNV was potentiated (i.e., more negative) on incentive ($M = -4.68$, $SE = 0.49$) compared to neutral trials ($M = -3.92$, $SE = 0.50$). Thus, CNV amplitude was modulated by incentive compared to neutral trials across tasks.

The SPN presented as a negative slow cortical wave immediately before feedback onset at the centroparietal sites. The ANOVA yielded a significant main effect of Condition ($F_{(1,100)} = 48.74$, $p < 0.001$, $\eta_p^2 = 0.33$) and Task × Condition interaction ($F_{(1,100)} = 10.20$, $p < 0.01$, $\eta_p^2 = 0.09$); all other main effects, two-way, and three-way interactions were not significant ($p > 0.10$, $\eta_p^2 < 0.10$). On MID, SPN amplitude was more negative on monetary incentive ($M = -5.90$ μV, $SD = 5.73$) compared to neutral trials ($M = -3.09$ μV, $SD = 4.78$), $t_{(101)} = 7.28$, $p < 0.001$, $d = 0.74$. Similarly, SPN amplitude was more negative on social incentive ($M = -4.59$ μV, $SD = 5.42$) relative to neutral trials ($M = -3.17$ μV, $SD = 5.22$) on SID, $t_{(101)} = 4.01$, $p < 0.001$, $d = 0.40$. SPN amplitude on incentive trials was more negative on MID compared to SID, $t_{(101)} = 2.85$, $p < 0.01$, $d = 0.28$. Thus, the SPN functioned similarly in anticipation of monetary and social reward outcomes, although reward-related anticipation was greater for monetary rewards.

Reward Receipt

ERPs evoked by feedback delivery are presented in **Figure 3**. The RewP was maximal at frontocentral sites approximately 275 ms and 315 ms for MID and SID, respectively. RewP amplitude was sensitive to Condition (positive vs. negative outcome; ($F_{(1,100)} = 108.41$, $p < 0.001$, $\eta_p^2 = 0.52$); all other main effects, two-way, and three-way interactions were not significant ($p > 0.05$, $\eta_p^2 < 0.05$). Across MID and SID, RewP amplitude was more positive on win trials ($M = 11.99$ μV, $SE = 0.60$) than loss trials ($M = 8.90$ μV, $SE = 0.60$)[2].

Following the RewP, the fb-P3 peaked at 365 ms with a centroparietal scalp distribution for MID and SID. Fb-P3 amplitude to positive and negative outcomes across MID and SID were analyzed as separate ANOVAs. For fb-P3 amplitude to positive outcomes (i.e., monetary and social), there was a significant main effect of Task ($F_{(1,100)} = 10.87$, $p < 0.01$, $\eta_p^2 = 0.10$) and Condition ($F_{(1,100)} = 520.21$, $p < 0.001$, $\eta_p^2 = 0.84$); all other main effects, two-way, and three-way interactions were not significant ($p > 0.10$, $\eta_p^2 < 0.05$). Fb-P3 amplitude to positive outcomes was greater on MID ($M = 12.08$ μV, $SE = 0.45$) compared to SID ($M = 10.75$ μV, $SE = 0.45$), whereas fb-P3 amplitude was greater on positive outcome conditions ($M = 17.45$ μV, $SE = 0.38$) relative to neutral conditions ($M = 5.38$ μV, $SE = 0.38$) across both tasks; all other main effects, two-way, and three-way interactions were not significant ($p > 0.05$, $\eta_p^2 < 0.05$).

Next, we were also interested in examining effects of fb-P3 amplitude to *negative* outcomes (i.e., monetary and social). There was a significant main effect of Task ($F_{(1,100)} = 35.67$, $p < 0.001$, $\eta_p^2 = 0.26$), Condition ($F_{(1,100)} = 369.02$ $p < 0.001$, $\eta_p^2 = 0.79$), and Task × Condition interaction ($F_{(1,100)} = 32.57$, $p < 0.001$, $\eta_p^2 = 0.25$); all other main effects, two-way, and three-way interactions were not significant ($p > 0.10$, $\eta_p^2 < 0.05$). Fb-P3 amplitude (i.e., ERP activity across negative and neutral outcome trials) was greater on MID ($M = 12.33$ μV, $SE = 0.51$) compared to SID ($M = 9.59$ μV, $SE = 0.49$), whereas fb-P3 amplitude was greater on negative outcome conditions ($M = 16.54$ μV, $SE = 0.65$) relative to neutral conditions ($M = 5.38$ μV, $SE = 0.38$) across both tasks. Unlike fb-P3 to positive outcomes, we performed follow-up contrasts for the significant Task × Condition interaction for the fb-P3 to negative outcomes. Results from *t*-test indicates that fb-P3 amplitude to monetary loss on MID ($M = 18.89$ μV, $SD = 7.67$) was significantly larger as compared to fb-P3 to negative social outcomes on SID ($M = 14.14$ μV, $SD = 6.85$), $t_{(101)} = 7.46$, $p < 0.001$, $d = 0.74$.

Links Between Social and Nonsocial Rewards

First, bivariate correlations were calculated between analogous residualized ERPs across tasks (e.g., $RewP_{Resid}$ on MID with $RewP_{Resid}$ on SID; see **Table 2**). The results indicated that residualized cue-P3, SPN, RewP and fb-P3 (i.e., positive and negative outcomes) amplitudes were significantly positively correlated across tasks. The cross-task correlation of CNV amplitude, however, was not significant.

Reward Processing and Internalizing Symptoms

ANCOVAs

Results across the ANCOVAs conducted are presented in **Tables 3**, **4**. Within each model, analogous SID and MID were entered as the within-subjects factor and self-report measures (CES-D, RR) were entered as between-subjects factor. Separate models were calculated for CES-D and RR scores for each ERP. First, there was a significant main effect of CES-D score when SPN ($F_{(1,100)} = 5.29$, $p < 0.05$, $\eta_p^2 = 0.05$) and fb-P3 amplitude to positive outcomes ($F_{(1,100)} = 4.56$, $p < 0.05$, $\eta_p^2 = 0.05$) were entered in the model. This indicates that the associations with

[2]We performed follow-up test to determine whether the effect of Condition for RewP amplitude remained significant when covarying for fb-P3 amplitude to positive and negative social feedback. This analysis was important insofar as to control for potential overlap between RewP and fb-P3 components in the waveform. The results revealed a significant effect of Condition (Win vs. Loss: $F_{(1,99)} = 5.09$ $p < 0.05$, $\eta_p^2 = 0.05$), adjusting for fb-P3 on SID.

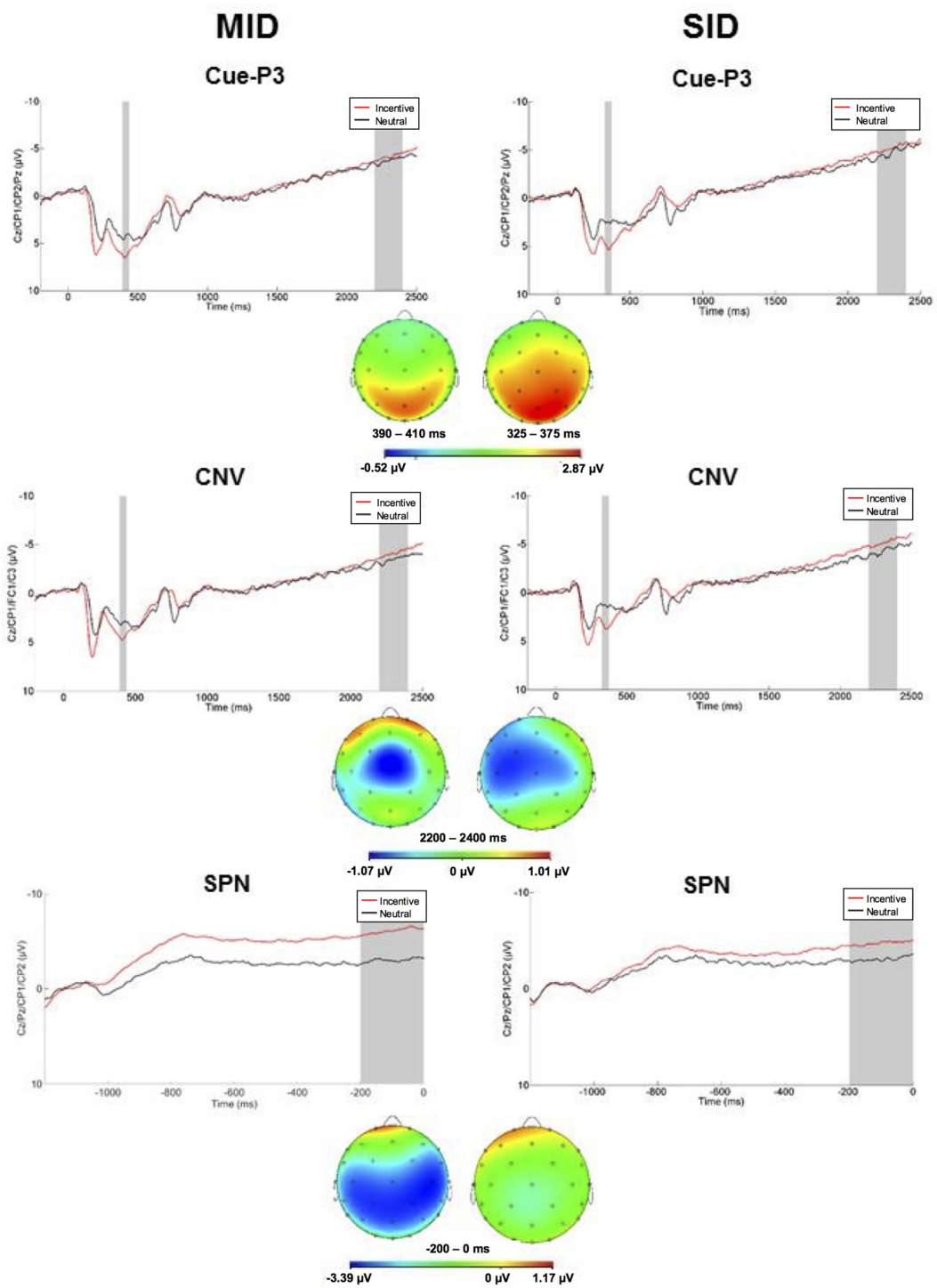


FIGURE 2 | Left column: anticipatory ERP responses to monetary incentive and neutral trial conditions on MID. The cue-P3 was scored as the average activity in the first shaded window (top row: 390–440 ms) and the contingent negative variation (CNV) in the second shaded window (middle row; 2,200–2,400 ms). The stimulus preceding negativity (SPN; bottom row; −200 to 0 ms prior to feedback onset) was scored as the average in the shaded window. Right column: anticipatory ERP responses to social incentive and neutral trial conditions on SID. The cue-P3 was scored as the average activity in the first shaded window (top row: 325–375 ms) and the CNV in the second shaded window (middle row; 2,200–2,400 ms). The SPN (bottom row; −200 to 0 ms prior to feedback onset) was scored as the average in the shaded window. Below each waveform is the scalp distributions of the difference between incentive and neutral trials for the cue-P3 (top), CNV (middle), and SPN (bottom) for MID and SID.

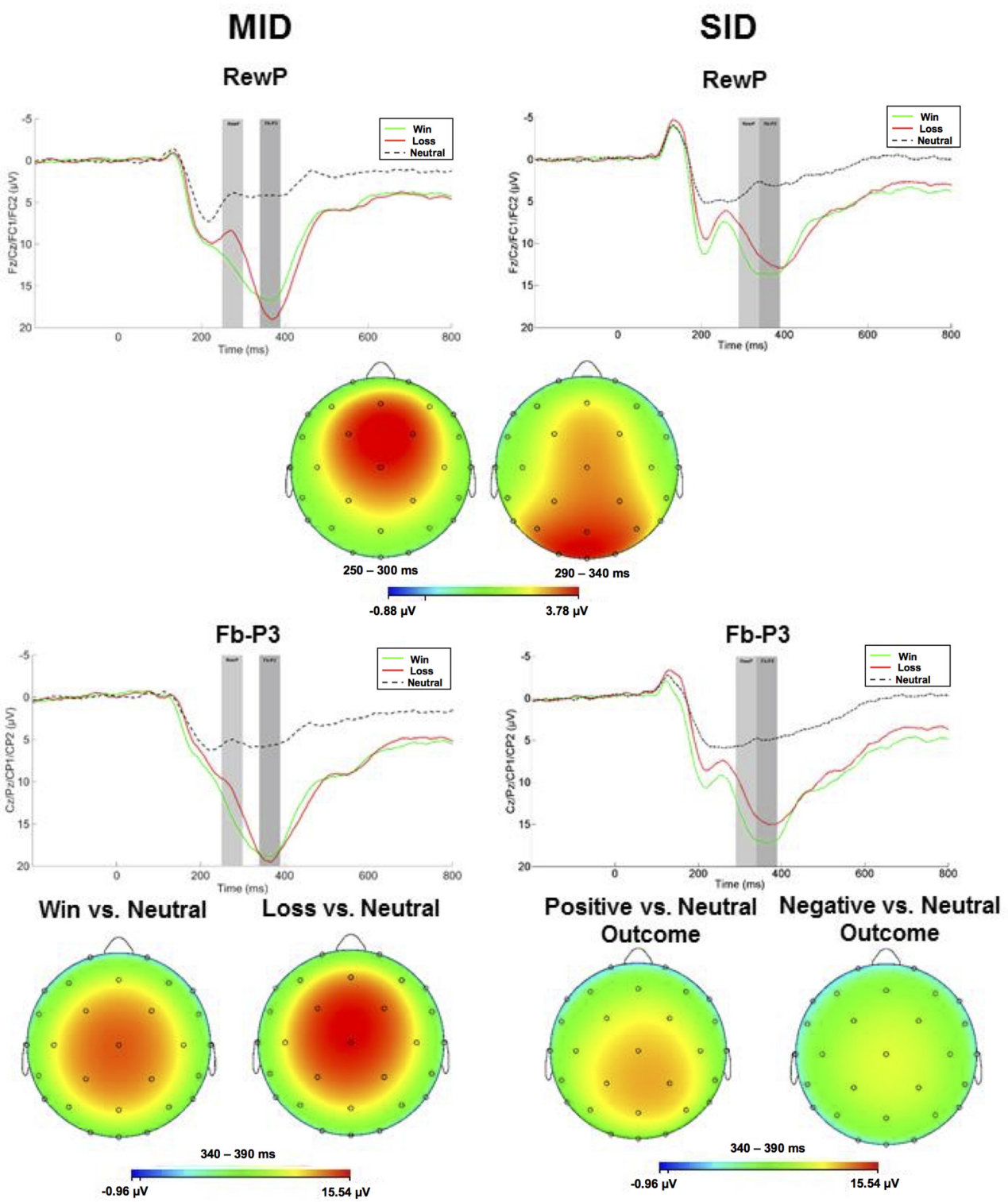


FIGURE 3 | Left column: ERP responses to monetary wins, losses, and neutral outcomes on MID. Feedback onset was at 0 ms. The RewP was scored as the average activity in the first shaded window (top row: 250–300 ms) and the fb-P3 in the second shaded window (bottom row 340–390 ms). Right column: ERP responses to positive, negative, and no social feedback on SID. The RewP was scored as the average activity in the first shaded window (top row: 290–340 ms) and the fb-P3 in the second shaded window (bottom row: 340–390 ms). Scalp distributions of the difference between conditions for the RewP (positive minus negative outcome) and fb-P3 (positive minus neutral; negative minus neutral) are depicted below each waveform for MID and SID.

TABLE 2 | Correlations of analogous social and nonsocial event-related potentials (ERPs).

	r
1. Cue-P3$_{resid}$	0.23*
2. CNV$_{resid}$	0.11
3. SPN$_{resid}$	0.41**
4. RewP$_{resid}$	0.28**
5. Fb-P3 positive outcome$_{resid}$	0.40***
6. Fb-P3 Negative outcome$_{resid}$	0.37***

*Note: correlations were calculated using residual ERP difference scores. The correlation coefficient (r) denote the relationship of analogous ERP components across social incentive delay (SID) and monetary incentive delay (MID). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.*

CES-D were statistically similar across MID and SID tasks for the SPN and the fb-P3 to positive outcomes. Main effects and interactions with Task were not statistically significant[3]. Next, there was a significant main effect of RR score ($F_{(1,98)} = 4.74$, $p < 0.05$, $\eta_p^2 = 0.05$) when RewP amplitude was entered in the model, indicating a statistically similar association between RR and RewP across MID and SID tasks; all other main effects and interactions were not statistically significant[4].

Regressions

Complementing these ANCOVAs, a series of multiple linear regressions were conducted to assess unique task-specific variability in depression (**Table 5**) and reward responsiveness (**Table 6**). Regressions analyses were performed only in instances where at least one main effect or interaction was significant in the ANCOVAs. Standardized analogous residualized ERPs across SID and MID were included as simultaneous predictors of CES-D and RR scores. Each regression model also contained the main effects of task order, age, gender, and ethnicity as covariates. In predicting CES-D scores, there was a significant main effect of fb-P3$_{resid}$ to positive outcomes on SID but not MID. Specifically, blunted fb-P3$_{resid}$ to positive social outcomes uniquely predicted higher depressive symptoms, over and above fb-P3 to monetary rewards. There were no significant effects for SPN amplitude on SID or MID. All covariate main effects were not statistically significant. Next, there was no significant effect of RewP$_{resid}$ amplitude on SID or MID in predicting RR scores.

DISCUSSION

The current study is the first to systematically examine social and nonsocial reward-related neural dysfunction in depression within the same sample. We successfully replicated our previous efforts to elicit parallel reward-related neural activity to social and monetary rewards. The SID and MID tasks elicited morphologically similar ERPs across different stages of reward processing (i.e., reward anticipation, reward receipt) and were moderately associated with one another. We also extended the literature by leveraging the social and nonsocial reward ERP framework to the study of individual differences in depressive symptomatology and self-reported trait reward sensitivity. We demonstrated that depressive symptomatology was characterized by broad reductions in anticipation of uncertain outcomes (i.e., reduced SPN across SID and MID) and in the salience of positive outcomes (i.e., fb-P3 to monetary gains and positive social feedback), across reward types. We also showed that blunted consummatory social reward processing in the time-window spanning the RewP and fb-P3 amplitudes (i.e., positive social outcomes) was associated with reward responsiveness. Complementing these findings, there was also evidence of a task-specific association between depressive symptoms and the fb-P3 to positive social outcomes, controlling for monetary outcomes. Overall, the current study provides early evidence of both general and domain-specific (social) reward deficits in depression.

Here, we replicated previous efforts to utilize the incentive delay framework for social (Ait Oumeziane et al., 2017) and nonsocial ERP research on reward processing (Novak and Foti, 2015). Consistent with previous studies, we found that anticipatory (cue-P3, SPN) and consummatory ERPs (RewP, fb-P3) were modulated by incentive and reward outcomes, respectively, regardless of reward type. Analogous reward ERPs across SID and MID were also morphologically similar and moderately associated, highlighting the possibility of a "common neural currency." Indeed, this finding is in concert with past fMRI (Izuma et al., 2008; Guyer et al., 2012) and ERP research (Ait Oumeziane et al., 2017; Ethridge et al., 2017; Distefano et al., 2018) that have suggested the social and monetary reward tap into an overlapping neural network.

These findings, however, are in light of evidence showing that ERP temporal onset was distinct across multiple stages of processing, including reward cue detection [i.e., cue-P3 (50 ms)] and initial evaluation of outcome valence [i.e., RewP (40 ms)]. Differences in stimuli properties may have contributed to these differences, as prior research has shown that stimulus complexity can impact the temporal properties of ERPs (Baker and Holroyd, 2011). Within each task, different ERP components were scored in non-overlapping time intervals; however, if stimuli properties impacted temporal onset, particularly in regard to RewP and fb-P3, then it is possible that the intervals scored may reflect a combination of distinct processes. Implementing distinct incentive and feedback stimuli was an important manipulation, in conjunction with participants completing the task under the pretense of live simulated peer feedback (Ait Oumeziane et al., 2017), insofar as to increase the social engagement and increase the value of receiving positive and negative feedback from others. It would be of interest for future research to explore the possibility of increasing the similarity in perceptual properties across SID and MID, although this may lead to other confounds. For example, it is possible that participants who complete the MID first may believe that SID feedback yield monetary rewards if identical stimuli are used across tasks.

[3]We also conducted identical analyses by dichotomizing our sample into "healthy controls" ($N = 76$) and "individuals at higher risk for depression" (i.e., CES-D scores greater than 16; $N = 33$). We found a significant main effect of CES-D when SPN was entered for healthy controls ($F_{(1,68)} = 7.96$, $p < 0.01$, $\eta_p^2 = 0.11$) but not individuals at risk for depression ($F_{(1,30)} = 0.57$, p = 0.46, $\eta_p^2 = 0.02$). All other main effects and interactions were not statistically significant (i.e., $p > 0.05$).

[4]We also evaluated identical ANCOVAs for RR across "healthy controls" and "individuals at risk for depression." Results showed no significant main effects or interactions for either group (i.e., p's > 0.05).

TABLE 3 | Summary of ANCOVA analysis for anticipatory reward ERPs.

	Cue P3			CNV			SPN		
	Depression								
	$F_{(1,100)}$	p	η_p^2	$F_{(1,100)}$	p	η_p^2	$F_{(1,100)}$	p	η_p^2
Task	0.04	0.85	0.00	0.19	0.66	0.00	0.61	0.44	0.01
CES-D	0.95	0.33	0.01	0.15	0.70	0.00	5.29*	0.02	0.05
Task CES-D	0.04	0.84	0.00	0.36	0.55	0.00	0.70	0.41	0.01
	Reward responsiveness								
	$F_{(1,98)}$	p	η_p^2	$F_{(1,98)}$	p	η_p^2	$F_{(1,98)}$	p	η_p^2
Task	1.66	0.20	0.02	0.08	0.78	0.00	0.52	0.47	0.01
RR	0.06	0.81	0.00	1.47	0.23	0.02	0.33	0.56	0.00
Task RR	1.73	0.19	0.02	0.07	0.79	0.00	0.60	0.44	0.01

*Note: CES-D denotes Center for Epidemiologic Studies Depression Scale. RR denotes reward. *$p < 0.05$.*

TABLE 4 | Summary of ANCOVA analysis for consummatory reward ERPs.

	RewP			Fb-P3 positive outcome			Fb-P3 negative outcome		
	Depression								
	$F_{(1,100)}$	p	η_p^2	$F_{(1,100)}$	p	η_p^2	$F_{(1,100)}$	p	η_p^2
Task	0.00	0.96	0.00	0.31	0.58	0.00	0.01	0.94	0.00
CES-D	1.51	0.22	0.02	4.56*	0.04	0.04	3.03	0.09	0.03
Task × CES-D	0.09	0.76	0.00	0.63	0.43	0.01	0.03	0.85	0.00
	Reward responsiveness								
	$F_{(1,98)}$	p	η_p^2	$F_{(1,98)}$	p	η_p^2	$F_{(1,98)}$	p	η_p^2
Task	0.02	0.90	0.00	0.78	0.38	0.01	0.34	0.56	0.00
RR	4.74*	0.03	0.05	3.00	0.09	0.03	0.22	0.22	0.02
Task × RR	0.03	0.87	0.00	0.80	0.37	0.01	0.35	0.56	0.00

*Note: CES-D denotes Center for Epidemiologic Studies Depression Scale. RR denotes reward. *$p < 0.05$.*

The current study highlights that depression may be associated broadly with anticipatory and consummatory processing across social and nonsocial rewards. Specifically, depressive symptoms were linked to both reduced anticipation of uncertain outcomes (SPN across MID and SID) and blunted salience of positive feedback (fb-P3 to positive social feedback and monetary gains). The moderating effect of reward type was not significant, suggesting a generalizable effect across tasks. These parallel findings for the SPN and fb-P3 are consistent with past findings demonstrated that these two ERP components are intertwined, such that greater feedback anticipation predicts higher feedback salience (Novak et al., 2016). However, we extend the literature by highlighting that depression is broadly implicated by neural deficits to reward (social and monetary). Interestingly, unlike previous studies we did not find significant associations between depression and RewP amplitude, both in regards to general and domain-specific deficits. Past studies have shown that an attenuated RewP amplitude is associated with depression (Liu et al., 2014; Umemoto and Holroyd, 2017; Brush et al., 2018). The relationship between RewP amplitude is less direct and more nuanced than previously considered. For example, blunted RewP amplitude and depression may operate through other clinically related dimensions (Ait Oumeziane and Foti, 2016; Nelson et al., 2016; Novak et al., 2016). Alternatively, diminished RewP amplitude may be associated with a trait-like depression vulnerability rather than current symptom severity (Bowyer et al., 2019). In contrast to depression, our findings showed that reward lower reward responsiveness was associated with reduced RewP amplitude across social and monetary rewards. These differences may be due to the way positive affect is conceptualized; that is, RewP may be more sensitive to trait (RR) rather than state levels of positive affect (CES-D).

These findings provide preliminary evidence of general patterns of reward reactivity (i.e., both social and nonsocial) reward reactivity in depression. To further contextualize these results, we performed a series of multiple linear regressions to isolate task-specific MID and SID variance in relation to self-report symptoms. Our findings suggest that blunted salience to positive social feedback uniquely predicted depressive symptoms, over and above one's fb-P3 amplitude to nonsocial rewards. Whereas blunted fb-P3 in our sample appears to be sensitive to social contexts, there was no significant effect from isolating task-specific variance for anticipation of outcomes (i.e., SPN) in predicting depression. Consistent with the ANVOCAs findings, depression may be characterized by general deficits in anticipation of uncertain outcomes (i.e., both social and

TABLE 5 | Predicting unique reward-related neural deficits in depression.

	Outcome: depression score	
	Model 1: SPN_{resid}	**Model 2: Fb-$P3_{resid}$**
Covariates		
Task order	−0.04	−0.06
Age	−0.11	−0.07
Gender	−0.06	−0.04
Ethnicity	0.14	0.13
SID ERPs		
SPN_{resid}	0.20	-
Fb-$P3_{resid}$ positive Social Outcomes	-	−0.25*
MID ERPs		
SPN_{resid}	0.06	-
Fb-$P3_{resid}$ monetary gains	-	0.00

*Note: columns represent separate regression models wherein analogous ERPs across MID and SID were entered as simultaneous predicts of depression. Gender was coded as 0 = Male, 1 = Female. Ethnicity was coded as 0 = Hispanic, 1 = Other. Regression coefficients are denoted using standardized beta weights. SPN amplitude reflects a slow, sustained negativity; therefore, a positive beta weight with CES-D denotes the reverse association. *$p < 0.05$.*

TABLE 6 | Predicting unique reward-related neural deficits in self-report reward responsiveness.

	Outcome: reward responsiveness
	$RewP_{resid}$
Covariates	
Task order	−0.04
Age	−0.09
Gender	0.15
Ethnicity	−0.11
SID ERPs	
$RewP_{resid}$	0.13
MID ERPs	
$RewP_{resid}$	0.14

Note: gender was coded as 0 = Male, 1 = Female. Ethnicity was coded as 0 = Hispanic, 1 = Other. Regression coefficients are denoted using standardized beta weights.

nonsocial). It would be of interest for future research to evaluate this possibility of a latent reward dimension using advanced statistical technique such as structural equation modeling.

There is growing interest in assessing the role of social reward dysfunction in depression (Forbes, 2009; Forbes and Dahl, 2012). Past studies have demonstrated that depressed individuals exhibit blunted neural activation to social rewards (Olino et al., 2015); however, we addressed a key gap by showing that symptoms of depression may be uniquely related to diminished salience of positive social feedback, over and above other reward types. Interestingly, we did not observe any significant effect of monetary reward-related neural activity, which is in contrast with a multitude of studies implicating monetary reward processing deficits in depression (e.g., Liu et al., 2014; Umemoto and Holroyd, 2017; Brush et al., 2018). One possible explanation is that the SID task impacted the interrelationship between monetary reward sensitivity and depression in some manner; however, there was no significant effect of task order across our analyses. Alternatively, many ERP studies in depression have used simple guessing tasks (e.g., Foti and Hajcak, 2012; Ait Oumeziane and Foti, 2016), whereas the current study utilizes an active, performance-based task. It would be of interest for future studies to evaluate whether active vs. passive task properties within the same sample mediates the relationship between monetary ERPs and depression.

Nevertheless, gaining a more nuanced understanding of the neural correlates of reward processing in depression, beyond monetary contingencies, can have important treatment considerations. For example, recent work describes interventions [e.g., Positive Affect Treatment (PAT; Craske et al., 2016)] specifically designed to target deficits in reward sensitivity. Within this framework, blunted fb-P3 to positive social feedback may represent a novel target for treatment wherein attention is guided towards important in-the-moment factors (physical sensations, thoughts, behaviors, mood) during social contexts to facilitate increased engagement with reward. This notion, however, is speculative in nature as more research linking the therapeutic benefits on neural measures is required. Nevertheless, it does highlight the potential clinical utility of gaining a better understanding of the pathophysiological processes of depression, as doing so may shed light on more effective and targeted treatments (Forbes, 2009).

A strength of the current study is the use of theoretically distinct reward paradigms within a large sample (N = 107). The strengths should be considered in light of the limitations. First, the current study did not assess whether participants believed that peers were evaluating them in real-time; however, existing studies show imagined social feedback is sufficient in eliciting striatal activity (Hsu et al., 2013). Second, although we found evidence of task-specific (i.e., social) and general reward-related abnormalities in depression, it is that it is unclear how these effects extend to more severe populations. Nevertheless, subclinical depressive symptomology is highly prevalent (Cuijpers et al., 2004) and represents a significant risk factor for the onset of a major depressive episode (Cuijpers et al., 2004). These findings enhance our understanding of reward-related dysfunction in mood disorders by extending dimensional approaches of classification to subthreshold and healthy populations (Insel et al., 2010; Cuthbert and Insel, 2013). A second limitation is that the incentive delay framework is effective for capturing anticipatory and consummatory neural activity, but it cannot isolate other relevant reward processing, particularly reward learning. Previous research has linked depression with an impaired capacity to acquire reward contingencies (Pizzagalli et al., 2008; Herzallah et al., 2013; Vrieze et al., 2013). It would be of interest to apply the present framework in conjunction with existing reward learning paradigms to improve understanding of the full range of reward processing. Indeed, a more fine-grain understanding of reward dysfunction may help lay the foundation for identifying meaningful subgroups in depression characterized by disruptions in reward type (social, nonsocial), phase (reward anticipation, receipt, learning), or a combination of these factors.

Disruptions in reward-related functioning may play an important role in the pathophysiology of depression. The current study extends the literature by examining whether reward dysfunction in depression is general and/or domain-specific using theoretically distinct paradigms of social and nonsocial rewards. We demonstrated found that depression was characterized by deficits across two stages of processing: blunted anticipation of unexpected outcomes and salience of positive feedback. When simultaneously accounting for analogous neural activity, only blunted salience of positive social feedback was a significant predictor of depressive symptoms. Blunted anticipation to unexpected outcomes appeared to reflect general rather than task-specific reward variance. Overall, social reward sensitivity appears to be an important neural correlate that may enhance our understanding of the pathophysiology of depression. This study underscores the importance of a multi-faceted assessment of reward functioning toward the goal of understanding psychopathology, particularly in the context of depression.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was approved by Purdue University's Human Research Protection Program. All participants gave full study consent prior to any research procedures.

AUTHOR CONTRIBUTIONS

BA and DF contributed to the conception and design of the study. BA collected the data, organized the database and performed the statistical analyses. BA, OJ, and DF contributed to writing and revision of the manuscript. All authors read and approved the submitted version.

REFERENCES

Ait Oumeziane, B., and Foti, D. (2016). Reward-related neural dysfunction across depression and impulsivity: a dimensional approach. *Psychophysiology* 53, 1174–1184. doi: 10.1111/psyp.12672

Ait Oumeziane, B., Schryer-Praga, J., and Foti, D. (2017). "Why don't they 'like' me more?": comparing the time courses of social and monetary reward processing. *Neuropsychologia* 107, 48–59. doi: 10.1016/j.neuropsychologia.2017.11.001

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5).* Arlington, VA: American Psychiatric Pub.

Assadi, S. M., Yücel, M., and Pantelis, C. (2009). Dopamine modulates neural networks involved in effort-based decision-making. *Neurosci. Biobehav. Rev.* 33, 383–393. doi: 10.1016/j.neubiorev.2008.10.010

Badcock, P., and Allen, N. (2003). Adaptive social reasoning in depressed mood and depressive vulnerability. *Cogn. Emot.* 17, 647–670. doi: 10.1080/02699930302299

Baker, T. E., and Holroyd, C. B. (2011). Dissociated roles of the anterior cingulate cortex in reward and conflict processing as revealed by the feedback error-related negativity and N200. *Biol. Psychol.* 87, 25–34. doi: 10.1016/j.biopsycho.2011.01.010

Barnett, P. A., and Gotlib, I. H. (1988). Psychosocial functioning and depression: distinguishing among antecedents, concomitants and consequences. *Psychol. Bull.* 104, 97–126. doi: 10.1037/0033-2909.104.1.97

Beck, A. T. (1983). "Cognitive therapy of depression: new perspectives," in *Treatment for Depression: Old Controversies and New Approaches*, eds P. J. Clayton and J. E. Barnett (New York, NY: Raven Press), 265–290.

Berridge, K. C., Robinson, T. E., and Aldridge, J. W. (2009). Dissecting components of reward: "liking," "wanting" and learning. *Curr. Opin. Pharmacol.* 9, 65–73. doi: 10.1016/j.coph.2008.12.014

Bhanji, J. P., and Delgado, M. R. (2014). The social brain and reward: social information processing in the human striatum. *Wiley Interdiscip. Rev. Cogn. Sci.* 5, 61–73. doi: 10.1002/wcs.1266

Bowyer, C. B., Joyner, K. J., Yancey, J. R., Venables, N. C., Hajcak, G., and Patrick, C. J. (2019). Toward a neurobehavioral trait conceptualization of depression proneness. *Psychophysiology* 56:e13367. doi: 10.1111/psyp.13367

Bress, J. N., Foti, D., Kotov, R., Klein, D. N., and Hajcak, G. (2013). Blunted neural response to rewards prospectively predicts depression in adolescent girls. *Psychophysiology* 50, 74–81. doi: 10.1111/j.1469-8986.2012.01485.x

Bress, J. N., and Hajcak, G. (2013). Self-report and behavioral measures of reward sensitivity predict the feedback negativity. *Psychophysiology* 50, 610–616. doi: 10.1111/psyp.12053

Bress, J. N., Smith, E., Foti, D., Klein, D. N., and Hajcak, G. (2012). Neural response to reward and depressive symptoms in late childhood to early adolescence. *Biol. Psychol.* 89, 156–162. doi: 10.1016/j.biopsycho.2011.10.004

Brinkmann, K., Franzen, J., Rossier, C., and Gendolla, G. H. E. (2014). I don't care about others' approval: dysphoric individuals show reduced effort mobilization for obtaining a social reward. *Motiv. Emot.* 38, 790–801. doi: 10.1007/s11031-014-9437-y

Broyd, S., Richards, H., Helps, S., Chronaki, G., Bamford, S., and Sonuga-Barke, E. (2012). An electrophysiological monetary incentive delay (e-mid) task: a way to decompose the different components of neural response to positive and negative monetary reinforcement. *J. Neurosci. Methods* 209, 40–49. doi: 10.1016/j.jneumeth.2012.05.015

Brunia, C., Van Boxtel, G., and Bocker, K. (2012). "Negative slow waves as indices of anticipation: the bereitschaftspotential, the contingent negative variation and the stimulus-preceding negativity," in *The Oxford Handbook of Event-Related Potential Components*, eds S. Luck and E. Kappenman (New York, NY: Oxford University Press, Inc.), 196–199.

Brush, C. J., Ehmann, P. J., Hajcak, G., Selby, E. A., and Alderman, B. L. (2018). Using multilevel modeling to examine blunted neural responses to reward in major depression. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 3, 1032–1039. doi: 10.1016/j.bpsc.2018.04.003

Craske, M. G., Meuret, A. E., Ritz, T., Treanor, M., and Dour, H. J. (2016). Treatment for anhedonia: a neuroscience driven approach. *Depress. Anxiety* 33, 927–938. doi: 10.1002/da.22490

Cuijpers, P., de Graaf, R., and van Dorsselaer, S. (2004). Minor depression: risk profiles, functional disability, health care use and risk of developing major depression. *J. Affect. Disord.* 79, 71–79. doi: 10.1016/s0165-0327(02)00348-8

Cuthbert, B. N., and Insel, T. R. (2013). Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med.* 11:126. doi: 10.1186/1741-7015-11-126

Davey, C. G., Yücel, M., and Allen, N. B. (2008). The emergence of depression in adolescence: development of the prefrontal cortex and the representation of reward. *Neurosci. Biobehav. Rev.* 32, 1–19. doi: 10.1016/j.neubiorev.2007.04.016

Distefano, A., Jackson, F., Levinson, A. R., Infantolino, Z. P., Jarcho, J. M., and Nelson, B. D. (2018). A comparison of the electrocortical response to monetary and social reward. *Soc. Cogn. Affect. Neurosci.* 13, 247–255. doi: 10.1093/scan/nsy006

Elliott, R., Sahakian, B. J., Herrod, J. J., Robbins, T. W., and Paykel, E. S. (1997). Abnormal response to negative feedback in unipolar depression: evidence for a diagnosis specific impairment. *J. Neurol. Neurosurg. Psychiatry* 63, 74–82. doi: 10.1136/jnnp.63.1.74

Eshel, N., and Roiser, J. P. (2010). Reward and punishment processing in depression. *Biol. Psychiatry* 68, 118–124. doi: 10.1016/j.biopsych.2010.01.027

Ethridge, P., Kujawa, A., Dirks, M. A., Arfer, K. B., Kessel, E. M., Klein, D. N., et al. (2017). Neural responses to social and monetary reward in early adolescence and emerging adulthood. *Psychophysiology* 54, 1786–1799. doi: 10.1111/psyp.12957

Fehr, E., and Camerer, C. F. (2007). Social neuroeconomics: the neural circuitry of social preferences. *Trends Cogn. Sci.* 11, 419–427. doi: 10.1016/j.tics.2007.09.002

Flores, A., Münte, T. F., and Doñamayor, N. (2015). Event-related EEG responses to anticipation and delivery of monetary and social reward. *Biol. Psychol.* 109, 10–19. doi: 10.1016/j.biopsycho.2015.04.005

Forbes, E. E. (2009). Where's the fun in that? Broadening the focus on reward function in depression. *Biol. Psychiatry* 66, 199–200. doi: 10.1016/j.biopsych.2009.05.001

Forbes, E. E., and Dahl, R. E. (2012). Research review: altered reward function in adolescent depression: what, when and how? *J. Child Psychol. Psychiatry* 53, 3–15. doi: 10.1111/j.1469-7610.2011.02477.x

Forbes, E. E., Hariri, A. R., Martin, S. L., Silk, J. S., Moyles, D. L., Fisher, P. M., et al. (2009). Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *Am. J. Psychiatry* 166, 64–73. doi: 10.1176/appi.ajp.2008.07081336

Foti, D., and Hajcak, G. (2012). Genetic variation in dopamine moderates neural response during reward anticipation and delivery: evidence from event-related potentials. *Psychophysiology* 49, 617–626. doi: 10.1111/j.1469-8986.2011.01343.x

Foti, D., Kotov, R., Klein, D. N., and Hajcak, G. (2011). Abnormal neural sensitivity to monetary gains versus losses among adolescents at risk for depression. *J. Abnorm. Child Psychol.* 39, 913–924. doi: 10.1007/s10802-011-9503-9

Garris, P. A., Kilpatrick, M., Bunin, M. A., Michael, D., Walker, Q. D., and Wightman, R. M. (1999). Dissociation of dopamine release in the nucleus accumbens from intracranial self-stimulation. *Nature* 398, 67–69. doi: 10.1038/18019

Gehring, W. J., and Willoughby, A. R. (2002). The medial frontal cortex and the rapid processing of monetary gains and losses. *Science* 295, 2279–2282. doi: 10.1126/science.1066893

Gotlib, I. H., and Joormann, J. (2010). Cognition and depression: current status and future directions. *Annu. Rev. Clin. Psychol.* 6, 285–312. doi: 10.1146/annurev.clinpsy.121208.131305

Gratton, G., Coles, M., and Donchin, E. (1983). A new method for offline removal of ocular artifact. *Electroencephalogr. Clin. Neurophysiol.* 55, 468–484. doi: 10.1016/0013-4694(83)90135-9

Greenberg, P. E., Fournier, A.-A., Sisitsky, T., Pike, C. T., and Kessler, R. C. (2015). The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J. Clin. Psychiatry* 76, 155–162. doi: 10.4088/JCP.14m09298

Gunaydin, L. A., Grosenick, L., Finkelstein, J. C., Kauvar, I. V., Fenno, L. E., Adhikari, A., et al. (2014). Natural neural projection dynamics underlying social behavior. *Cell* 157, 1535–1551. doi: 10.1016/j.cell.2014.05.017

Guyer, A. E., Choate, V. R., Pine, D. S., and Nelson, E. E. (2012). Neural circuitry underlying affective response to peer feedback in adolescence. *Soc. Cogn. Affect. Neurosci.* 7, 81–92. doi: 10.1093/scan/nsr043

Hajcak, G., Moser, J., Holroyd, C., and Simons, R. (2007). It's worse than you thought: the feedback negativity and violations of reward prediction in gambling tasks. *Psychophysiology* 44, 905–912. doi: 10.1111/j.1469-8986.2007.00567.x

Henriques, J. B., and Davidson, R. J. (2000). Decreased responsiveness to reward in depression. *Cogn. Emot.* 14, 711–724. doi: 10.1080/026999300501176 84

Herzallah, M. M., Moustafa, A. A., Natsheh, J. Y., Abdellatif, S. M., Taha, M. B., Tayem, Y. I., et al. (2013). Learning from negative feedback in patients with major depressive disorder is attenuated by SSRI antidepressants. *Front. Integr. Neurosci.* 7:67. doi: 10.3389/fnint.2013.00067

Holmes, A. J., and Pizzagalli, D. A. (2007). Task feedback effects on conflict monitoring and executive control: relationship to subclinical measures of depression. *Emotion* 7, 68–76. doi: 10.1037/1528-3542.7.1.68

Holroyd, C. B., Pakzad-Vaezi, K. L., and Krigolson, O. E. (2008). The feedback correct-related positivity: sensitivity of the event-related brain potential to unexpected positive feedback. *Psychophysiology* 45, 688–697. doi: 10.1111/j.1469-8986.2008.00668.x

Hsu, D. T., Sanford, B. J., Meyers, K. K., Love, T. M., Hazlett, K. E., Wang, H., et al. (2013). Response of the μ-opioid system to social rejection and acceptance. *Mol. Psychiatry* 18, 1211–1217. doi: 10.1038/mp.2013.96

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., et al. (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am. J. Psychiatry* 167, 748–751. doi: 10.1176/appi.ajp.2010.09091379

Izuma, K., Saito, D. N., and Sadato, N. (2008). Processing of social and monetary rewards in the human striatum. *Neuron* 58, 284–294. doi: 10.1016/j.neuron.2008.03.020

Joiner, T. E., and Metalsky, G. I. (1995). A prospective test of an integrative interpersonal theory of depression: a naturalistic study of college roommates. *J. Pers. Soc. Psychol.* 69, 778–788. doi: 10.1037/0022-3514.69.4.778

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., et al. (2003). The epidemiology of major depressive disorder. *JAMA* 289, 3095–3105. doi: 10.1001/jama.289.23.3095

Knutson, B., Bhanji, J. P., Cooney, R. E., Atlas, L. Y., and Gotlib, I. H. (2008). Neural responses to monetary incentives in major depression. *Biol. Psychiatry* 63, 686–692. doi: 10.1016/j.biopsych.2007.07.023

Knutson, B., Fong, G. W., Adams, C. M., Varner, J. L., and Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport* 12, 3683–3687. doi: 10.1097/00001756-200112040-00016

Knutson, B., Westdorp, A., Kaiser, E., and Hommer, D. (2000). FMRI visualization of brain activity during a monetary incentive delay task. *Neuroimage* 12, 20–27. doi: 10.1006/nimg.2000.0593

Kujawa, A., Proudfit, G. H., and Klein, D. N. (2014). Neural reactivity to rewards and losses in offspring of mothers and fathers with histories of depressive and anxiety disorders. *J. Abnorm. Psychol.* 123, 287–297. doi: 10.1037/a0036285

Liu, X., Hairston, J., Schrier, M., and Fan, J. (2011). Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. *Neurosci. Biobehav. Rev.* 35, 1219–1236. doi: 10.1016/j.neubiorev.2010.12.012

Liu, W. H., Wang, L. Z., Shang, H. R., Shen, Y., Li, Z., Cheung, E. F., et al. (2014). The influence of anhedonia on feedback negativity in major depressive disorder. *Neuropsychologia* 53, 213–220. doi: 10.1016/j.neuropsychologia.2013.11.023

Mathews, A., and MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annu. Rev. Clin. Psychol.* 1, 167–195. doi: 10.1146/annurev.clinpsy.1.102803.143916

Miltner, W. H. R., Braun, C. H., and Coles, M. G. H. (1997). Event-related brain potentials following incorrect feedback in a time-estimation task: evidence for a "generic" neural system for error detection. *J. Cogn. Neurosci.* 9, 788–798. doi: 10.1162/jocn.1997.9.6.788

Monroe, S. M., Rohde, P., Seeley, J. R., and Lewinsohn, P. M. (1999). Life events and depression in adolescence: relationship loss as a prospective risk factor for first onset of major depressive disorder. *J. Abnorm. Psychol.* 108, 606–614. doi: 10.1037/0021-843x.108.4.606

Moses-Kolko, E. L., Fraser, D., Wisner, K. L., James, J. A., Saul, A. T., Fiez, J. A., et al. (2011). Rapid habituation of ventral striatal response to reward receipt in postpartum depression. *Biol. Psychiatry* 70, 395–399. doi: 10.1016/j.biopsych.2011.02.021

Mulligan, E. M., Flynn, H., and Hajcak, G. (2018). Neural response to reward and psychosocial risk factors independently predict antenatal depressive symptoms. *Biol. Psychol.* doi: 10.1016/j.biopsycho.2018.11.008 [Epub ahead of print].

Nelson, B. D., Kessel, E. M., Jackson, F., and Hajcak, G. (2016). The impact of an unpredictable context and intolerance of uncertainty on the electrocortical response to monetary gains and losses. *Cogn. Affect. Behav. Neurosci.* 16, 153–163. doi: 10.3758/s13415-015-0382-3

Nestler, E. J., and Carlezon, W. A. Jr. (2006). The mesolimbic dopamine reward circuit in depression. *Biol. Psychiatry* 59, 1151–1159. doi: 10.1016/j.biopsych.2005.09.018

Novak, B. K., Novak, K. D., Lynam, D. R., and Foti, D. (2016). Individual differences in the time course of reward processing: stage-specific links with depression and impulsivity. *Biol. Psychol.* 119, 79–90. doi: 10.1016/j.biopsycho.2016.07.008

Novak, K. D., and Foti, D. (2015). Teasing apart the anticipatory and consummatory processing of monetary incentives: an event-related potential

study of reward dynamics. *Psychophysiology* 52, 1470–1482. doi: 10.1111/psyp.12504

Ohgami, Y., Kotani, Y., Tsukamoto, T., Omura, K., Inoue, Y., Aihara, Y., et al. (2006). Effects of monetary reward and punishment on stimulus-preceding negativity. *Psychophysiology* 43, 227–236. doi: 10.1111/j.1469-8986.2006.00396.x

Olino, T. M., Silk, J. S., Osterritter, C., and Forbes, E. E. (2015). Social reward in youth at risk for depression: a preliminary investigation of subjective and neural differences. *J. Child Adolesc. Psychopharmacol.* 25, 711–721. doi: 10.1089/cap.2014.0165

Pizzagalli, D. A., Dillon, D. G., Bogdan, R., and Holmes, A. J. (2011). "Reward and punishment processing in the human brain: clues from affective neuroscience and implications for depression research," in *Contemporary Topics in Cognitive Neuroscience Series. Neuroscience of Decision Making*, eds O. Vartanian and D. R. Mandel (New York, NY: Psychology Press), 199–220.

Pizzagalli, D., Holmes, A. J., Dillon, D. G., Goetz, E. L., Birk, J. L., Bogdan, R., et al. (2009). Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am. J. Psychiatry* 166, 702–710. doi: 10.1176/appi.ajp.2008.08081201

Pizzagalli, D. A., Iosifescu, D., Hallett, L. A., Ratner, K. G., and Fava, M. (2008). Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *J. Psychiatr. Res.* 43, 76–87. doi: 10.1016/j.jpsychires.2008.03.001

Pizzagalli, D. A., Jahn, A. L., and O'Shea, J. P. (2005). Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. *Biol. Psychiatry* 57, 319–327. doi: 10.1016/j.biopsych.2004.11.026

Proudfit, G. H. (2015). The reward positivity: from basic research on reward to a biomarker for depression. *Psychophysiology* 52, 449–459. doi: 10.1111/psyp.12370

Rademacher, L., Krach, S., Kohls, G., Irmak, A., Gründer, G., and Spreckelmeyer, K. N. (2010). Dissociation of neural networks for anticipation and consumption of monetary and social rewards. *Neuroimage* 49, 3276–3285. doi: 10.1016/j.neuroimage.2009.10.089

Radloff, L. S. (1977). The CES-D scale. *Appl. Psychol. Meas.* 1, 385–401. doi: 10.1177/014662167700100306

Rohrbaugh, J. W., Syndulko, K., and Lindsley, D. B. (1976). Brain wave components of the contingent negative variation in humans. *Science* 191, 1055–1057. doi: 10.1126/science.1251217

Russo, S. J., and Nestler, E. J. (2013). The brain reward circuitry in mood disorders. *Nat. Rev. Neurosci.* 14, 609–625. doi: 10.1038/nrn3381

Salamone, J. D., Cousins, M. S., and Bucher, S. (1994). Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. *Behav. Brain Res.* 65, 221–229. doi: 10.1016/0166-4328(94)90108-2

Schultz, W. (2007). Behavioral dopamine signals. *Trends Neurosci.* 30, 203–210. doi: 10.1016/j.tins.2007.03.007

Sescousse, G., Caldú, X., Segura, B., and Dreher, J.-C. (2013). Processing of primary and secondary rewards: a quantitative meta-analysis and review of human functional neuroimaging studies. *Neurosci. Biobehav. Rev.* 37, 681–696. doi: 10.1016/j.neubiorev.2013.02.002

Sheeber, L., Hops, H., and Davis, B. (2001). Family processes in adolescent depression. *Clin. Child Fam. Psychol. Rev.* 4, 19–35. doi: 10.1023/A:1009524626436

Sheppard, L. C., and Teasdale, J. D. (2004). How does dysfunctional thinking decrease during recovery from major depression? *J. Abnorm. Psychol.* 113, 64–71. doi: 10.1037/0021-843x.113.1.64

Smoski, M. J., Rittenberg, A., and Dichter, G. S. (2011). Major depressive disorder is characterized by greater reward network activation to monetary than pleasant image rewards. *Psychiatry Res.* 194, 263–270. doi: 10.1016/j.pscychresns.2011.06.012

Spreckelmeyer, K. N., Krach, S., Kohls, G., Rademacher, L., Irmak, A., Konrad, K., et al. (2009). Anticipation of monetary and social reward differently activates mesolimbic brain structures in men and women. *Soc. Cogn. Affect. Neurosci.* 4, 158–165. doi: 10.1093/scan/nsn051

Steele, J. D., Kumar, P., and Ebmeier, K. P. (2007). Blunted response to feedback information in depressive illness. *Brain* 130, 2367–2374. doi: 10.1093/brain/awm150

Umemoto, A., and Holroyd, C. B. (2017). Neural mechanisms of reward processing associated with depression-related personality traits. *Clin. Neurophysiol.* 128, 1184–1196. doi: 10.1016/j.clinph.2017.03.049

Van den Berg, I., Franken, I. H. A., and Muris, P. (2010). Reward responsiveness scale. *Front. Psychol.* 1:239. doi: 10.3389/fpsyg.2010.00239

Vrieze, E., Pizzagalli, D. A., Demyttenaere, K., Hompes, T., Sienaert, P., de Boer, P., et al. (2013). Reduced reward learning predicts outcome in major depressive disorder. *Biol. Psychiatry* 73, 639–645. doi: 10.1016/j.biopsych.2012.10.014

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: info@frontiersin.org | +41 21 510 17 00

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership