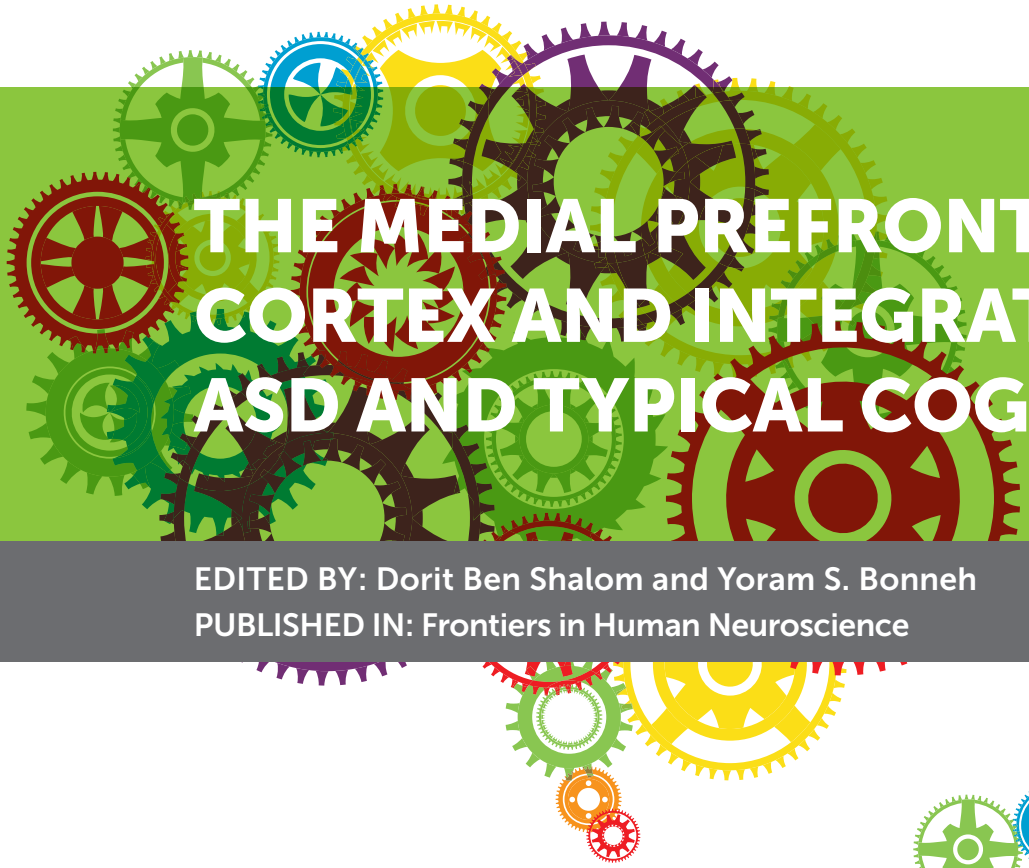

THE MEDIAL PREFRONTAL CORTEX AND INTEGRATION IN ASD AND TYPICAL COGNITION

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THE MEDIAL PREFRONTAL CORTEX AND INTEGRATION IN ASD AND TYPICAL COGNITION

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This eBook explores within-discipline implications and and across-discipline connections of the Ben Shalom (2009) model. The 12 papers hail from psychology, neuroscience, psychiatry, philosophy, and biology.

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EDITORIAL
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Editorial: The Medial Prefrontal Cortex and Integration in ASD and Typical Cognition

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Keywords: emotion, memory, sensory, motor, prefrontal cortex

Editorial on Research Topic

The Medial Prefrontal Cortex and Integration in ASD and Typical Cognition

A long standing theme in the study of ASD is the lack of, or atypicality, of cognitive integration. Despite its intuitive power, there have been very few attempts to specify the specific type of integration, that would allow for a systematic investigation of its neural basis. A recent paper in the Neuroscientist has attempted to do just that, in terms of a connection between subareas of the medial prefrontal cortex and the integration of familiar cognitive objects (albeit often under different names): perceptual objects, memory episodes, emotional states, and motor actions. The model suggested that in each of these four domains, three levels of processing can be identified: a basic pre-integrative level, an integrative level which produces the above mentioned cognitive objects, and a "logical" or higher-order level that performs selection/inhibition and perhaps combination on these basic type of objects. It further suggests that a lack of or atypicality of these objects is the source of some core difficulties in ASD.

This Research Topic explores within-discipline and across-discipline implications of the Ben Shalom (2009) model. The 12 papers hail from psychology, neuroscience, psychiatry, philosophy, and biology.

Broadly speaking, this Research Topic is divided into two sections: one that explores within-discipline implications of the model, and one that explores across-discipline connections.

This Research Topic includes 7 papers discussing the 4 cognitive domains contained in the model: emotion, memory, sensory-perceptual, and motor. There are 2 papers about each, apart from motor, probably reflecting our relative lack of knowledge about the processing of this domain in ASD.

Our initial hope was to have, within each domain, one paper that talks about difficulties in the integration *within* objects, and one about difficulties in the integration *between* objects, because we believe we see these two types of difficulties in different subgroups in the ASD population. This hope was partially fulfilled.

In the *emotion* domain, South and Rodgers mention alexithymia, which, although comorbid to ASD (e.g., Bird et al., 2010), is probably always present (although can be compensated for) in the subgroup with difficulties integrating typical *emotional states*, because these atypical states are inherently harder to identify and label.

The Komeda paper discusses how, based on mutual understanding, individuals with ASD respond empathically to others with these disorders. Being a high-level social cognition paper, it necessarily involves integration *between* emotional states, rather than the integration *within* the emotional states themselves.

In the *memory* domain, Lecouvey et al. talk about the ability to create a unified representation of the individual features of an event, i.e., the integration *within* memory events.

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The Brezis paper discusses memory integration in the autobiographical narratives of individuals with autism. Being a high-level autobiographical narratives paper, necessarily involves integration *between* memory events, rather than the integration *within* the memory events themselves.

In the sensory domain, Smith et al. discusses the influence of both low-level features and information from meaningful context on the final percept, so in this sense it is about the integration *within* sensory objects.

The Martínez-Sanchis paper discusses difficulties in multisensory integration in people with autism spectrum disorders. Being a high-level multisensory integration paper, it necessarily involves integration *between* sensory objects, rather than *within* the sensory objects themselves.

In the motor domain, Fukui et al. discusses difficulties in the chaining of motor acts in adolescents and young adults with autism spectrum disorder. Being a high-level chaining paper, it necessarily involves integration *between* motor actions, rather than *within* the motor actions themselves.

The between-discipline section includes 5 papers, which are intended to connect the current functional neuroanatomical work with other disciplines.

The first paper, by Yao et al. is intended as a connection to *other* areas of cognitive neuroscience, specifically functional connectivity. It showed decreased functional connectivity between the precuneus/posterior cingulate gyrus and the medial prefrontal cortex in the default mode network.

The second paper, by Tzur, is intended as a connection to *psychiatry*. Perhaps most notably, it manages to establish a connection between Ben Shalom's (2009) model of the medial prefrontal cortex and integration in ASD and Schore (2013) regulation theory in which mother-infant mutual interpersonal emotion-regulation processes help the infant develop holistically integrated regulatory processes, that are supported by the prefrontal cortex.

The third paper, by Ferguson and Gao, is intended as a connection to *biology*, discussing the development of the thalamocortical connections between mediodorsal thalamus and prefrontal cortex, and its implication in cognition. Perhaps most notable in the present context, following just days behind the arrival and subsequent increase in the density of mediodorsal afferent terminals, the medial prefrontal cortex undergoes a vast increase in volume further suggesting that the mediodorsal thalamus plays a critical regulatory role over prefrontal cortical development.

The fourth paper, by Yatziv and Jacobson, is intended as a connection to *philosophy*. Specifically, they argue against the view that autistic subjects have a deficiency in the most basic form of perceptual consciousness namely, phenomenal consciousness. Instead, they maintain, the perceptual atypicality of individuals with autism is of a more conceptual and cognitive sort. Thus, the basic experiences of individuals with autism are likely to be similar to typical subjects experiences; the main difference lies in the sort of cognitive access the subjects have to their experiences, specifically the *_integration_* of perceptual objects and concepts.

The fifth paper, by Ronel, is intended as a connection to *neurology*. It is the lateral prefrontal counterpart of Ben Shalom (2009), which suggested that the medial prefrontal cortex (including the medial orbital prefrontal cortex) is involved in the *integration* of perceptual objects (medial BA 11), memory episodes (medial BA 10), emotional states (medial BA9), and motor actions (medial BA 8). The current paper suggests that the corresponding *lateral* prefrontal areas (including the lateral orbital prefrontal cortex), re involved in the *selection/inhibition* of the same cognitive objects: perceptual objects (lateral BA 11), memory episodes (lateral BA 10), emotional states (lateral BA9), and motor actions (lateral BA 8).

At the core functional neuroanatomical level, these papers suggest a full model of the prefrontal cortex in terms of 4 streams of information (from ventral to dorsal): perceptual, memory, emotion, and motor. Within each stream, the medial prefrontal cortex is predicted to perform the *integration* of the associated cognitive objects, and the lateral prefrontal cortex their *selection/inhibition* (and perhaps also combination). On a more functional level, these papers go a long way toward describing how atypicality of medial prefrontal integration contributes to behavioral difficulties in ASD (such as agnosias, episodic memory difficulties, alexithymia, and dyspraxia). What is less clear, perhaps because the medial prefrontal cortex does not, in general, support any type of introspection *on its own workings*, is how this integration functions in typical cognition: in object recognition, in the creation of memory episodes, in the integration of one's own and perhaps others' emotional states, or in the construction of smooth, integrated motor actions. In that sense, the medial prefrontal cortex is perhaps the ultimate "cognitive black box", as it shapes our own reality, and as such, should be a prime target for future work in both the neurosciences and cognitive psychology.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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MINI REVIEW
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Sensory, Emotional and Cognitive Contributions to Anxiety in Autism Spectrum Disorders

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Severe symptoms of anxiety add substantial additional burden to many individuals diagnosed with Autism Spectrum Disorder (ASD). Improved understanding of specific factors that contribute to anxiety in ASD can aid research regarding the causes of autism and also provide targets for more effective intervention. This mini-review article focuses on emerging evidence for three concepts that appear to be related to each other and which also strongly predict anxiety in ASD samples. *Atypical sensory function* is included in the diagnostic criteria for ASD and is likely an important contributor to anxiety. Difficulties in understanding and labeling emotions (*alexithymia*), although a co-morbidity, may arise in part from atypical sensory function and can lead to confusion and uncertainty about how to respond to social and emotional situations. *Intolerance of uncertainty (IU)* describes people who have a particularly hard time with ambiguity and is known to be a key mechanism underlying some anxiety disorders. While evidence for linking these ideas is to date incomplete, we put forward a model including each concept as a framework for future studies. Specifically, we propose that IU is a critical mediator for anxiety in ASD, and explore the relationships between sensory function, alexithymia and IU. We further explore the role of the medial prefrontal cortex (mPFC) in regulating emotional response, in connection with limbic and insula-based networks, and suggest that disrupted integration in these networks underlies difficulties with habituation to strong emotional stimuli, which results in an enhanced perception of threat in many people with ASD. Behavioral and biologically-based treatments for anxiety in ASD will benefit from attending to these specific mechanisms as adjunct to traditional interventions.

Keywords: autism spectrum disorder, anxiety, medial prefrontal cortex, intolerance of uncertainty, alexithymia, mindfulness, sensory function

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INTRODUCTION: ANXIETY IN AUTISM SPECTRUM DISORDERS

Severe symptoms of anxiety co-occur frequently in autism spectrum disorder (ASD; Kerns and Kendall, 2014). Kerns et al. (2014) identified several aspects of anxious presentation in ASD that are similar to those found in standard diagnostic systems, but also a number of atypical expressions that seem specific to ASD, including social discomfort not associated with a fear of negative evaluation; compulsive behavior that does not seem motivated by distress relief, and highly unusual phobias. Improved understanding of the cognitive and emotional mechanisms which underlie anxiety in ASD may provide insight regarding the neurobiology

of both conditions and create more specific targets for biological and behavioral intervention (Hashemi et al., 2016; Kerns et al., 2016; Rodgers et al., 2016b).

Targeting Specificity

This review examines three ideas that may have particular salience for understanding the development and maintenance of anxiety in ASD: (1) atypical sensory function, which is included in the diagnostic criteria for ASD; (2) difficulty identifying/labeling emotions (alexithymia), which has been shown to be frequently severe in ASD; and (3) intolerance of uncertainty (IU), which has been suggested as a critical pathway to anxiety in ASD. While these ideas come from very different backgrounds, existing research shows that they are closely related, at least as measured with current instruments. A critical challenge is to define how these ideas diverge biologically and behaviorally.

ATYPICAL SENSORY FUNCTION AND ANXIETY IN ASD

Sensory function in ASD samples may be marked by both over-responsivity (e.g., experiencing various sounds as painful) and under-responsivity (e.g., repeated touching of objects). Both extremes may occur in the same children (Green and Ben-Sasson, 2010; Wigham et al., 2015; Watts et al., 2016). Green and Ben-Sasson (2010) proposed separate causal models for sensory over-responsivity and anxiety in ASD that moves in both directions. This seminal article suggested three guidelines for future studies: (1) using questionnaires and also psychophysiological challenge; (2) the need for prospective/longitudinal studies and also intervention studies; and (3) the development of animal studies.

Several aspects of the Green and Ben-Sasson (2010) framework are finding empirical support. Rodgers et al. (2016b) collected data from parent focus groups and factor analysis to modify an existing anxiety questionnaire in pursuit of increased relevance for both clinical and research use with ASD children. Sensory-based anxiety is a critical subscale along with subscales for difficulty with uncertainty and performance anxiety. Sensory concerns appear to be more prevalent in ASD samples than in control groups with developmental concerns, including special educational needs (Green et al., 2016) and adults with intellectual disabilities (Gillott and Standen, 2007). In ASD samples, severity of anxiety appears to be higher in individuals with more severe sensory dysfunction (Gillott and Standen, 2007; Uljarević et al., 2016).

There are now a few studies using psychophysiological methods to study sensory function. Green et al. (2013, 2015) reported two fMRI studies in high-functioning ASD youth during a challenge of mildly aversive sensory stimuli. In general, ASD participants showed more activation than controls in primary sensory areas, amygdala and orbitofrontal cortex in response to auditory stimuli. This activation was correlated with parent-reported anxiety and also with sensory over-responsiveness beyond the association with anxiety. Brain activity in the ASD samples was especially heightened when multiple sensory modalities (auditory and tactile) appeared simultaneously. The authors highlighted difficulties with habituation as a key underlying feature of this overresponsiveness. Corbett et al. (2016) reported that cortisol response to stress was higher for ASD children than controls during an ecologically-relevant peer interaction. Greater sensory dysfunction was associated with increased stress, and diagnosis was a significant moderator of the relationship between sensory function and stress response.

Animal researchers likewise have developed increased awareness of the importance of sensory function as a dependent variable (Kas et al., 2014). Adult mice whose whiskers had been trimmed at 10 days old (which causes pronounced tactile deficits) exhibited both social deficits and profound changes in amygdala activation, including hypersensitivity to stress (Soumiya et al., 2016).

UNDERSTANDING EMOTIONS: ALEXITHYMIA AND MINDFULNESS IN ASD

Alexithymia is a term used to characterize difficulties with emotional awareness, especially referring difficulty in identifying and describing internal emotional states (Cameron et al., 2014). Alexithymia cuts across diagnostic boundaries including associations with anxiety, depression and autism (Grabe et al., 2004; Mennin and Fresco, 2009; Bird and Cook, 2013). Whereas alexithymia is generally thought of as a psychological trait, *psychological mindfulness* is a term used to describe the skill to attend to one's experience in the present moment in a non-judgmental way (Kabat-Zinn, 2015). Our previous work (Maisel et al., 2016) has highlighted the contribution of emotional acceptance, which describes the ability to allow one's internal experience to be as it is and not to push feelings away, to anxiety in ASD. Decreased emotional awareness associated with alexithymia may impair the ability to develop emotional acceptance.

Some cognitive and emotional difficulties frequently seen in autism may be more related to alexithymia than to core autism symptoms (Caria et al., 2011; Allen et al., 2013; Bird and Cook, 2013). For example, Bird et al. (2011) reported that overall, a small sample of ASD adults showed less attention to faces compared to controls; importantly, the balance of time spent looking at the mouth rather than the eyes was predicted by alexithymia scores and not autism severity. An fMRI study from the same group (Bird et al., 2010) reported that alexithymia predicts brain response to empathy-generating situations in both ASD and control groups and that alexithymia, not autism symptoms, seems to account for between-group differences in empathy symptoms.

Maisel et al. (2016) reviewed symptom questionnaires completed by adults diagnosed with ASD (n = 76) and neurotypical controls (n = 75), showing strong correlations between dimensional measures of autism symptoms and several measures of anxiety. Structural equation modeling demonstrated that this relationship was almost completely accounted for by a

combination factor of alexithymia, emotional acceptance and IU. High alexithymia levels are also seen in young children diagnosed with ASD (Griffin et al., 2015).

INTOLERANCE OF UNCERTAINTY IN ASD

IU is a cognitive construct referring to decreased thresholds for the perception of ambiguity and enhanced discomfort with ambiguity (Dugas et al., 1998). The negative affect associated with IU is seen in generalized anxiety disorder but also other anxiety disorders, depression and autism (McEvoy and Mahoney, 2012; Einstein, 2014).

Boulter et al. (2014) reported on the relationship between IU and anxiety in ASD using both parent and child reports on the Intolerance of Uncertainty Scale for Children (IUS-C) and Spence Children's Anxiety Scale (SCAS). They found significantly higher IUS-C and SCAS scores for ASD children and adolescents than a typical comparison group, a finding recently replicated by Neil et al. (2016) with similarly large samples. Importantly, Boulter et al. (2014) report a "causal mediational model" in which IU almost completely mediated the relationship between diagnostic group and anxiety scores.

Wigham et al. (2015) reported that IUS-C and SCAS-P anxiety scores were significant mediators of the relationship between sensory function and core symptoms of repetitive/restricted behaviors in ASD children, with somewhat different pathways associating under- or over-responsive sensory function with category of repetitive behavior (motor behaviors or sameness behaviors). This was also replicated and extended by Neil et al. (2016), who included a large group of typically developing children. Parent-report scores were higher for the ASD than control group for sensory sensitivities, IU and anxiety scales. Hierarchical regression analysis indicated that IU significantly predicted sensory sensitivity in both ASD and typical groups, but the predictive power of IU was much greater in the ASD group. Links between sensory sensitivity, IU and anxiety have also been reported in mothers of ASD children (Uljarevic et al., 2015).

Hodgson et al. (2016) conducted focus groups of nine parents of ASD children without intellectual disabilities. The parents easily differentiated IU from a general dislike of change, including discomfort with unknown situations such as delayed flights on a planned trip; and discomfort with uncertainty even in known situations, when a child moves to middle school and is required to use a pen instead of a pencil but is afraid she might make a mistake and not be able to erase it. Keefer et al. (2016) reported that ASD children completing the *Face Your Fears* cognitive behavioral therapy (CBT) protocol had significantly reduced parent-reported anxiety symptoms. Importantly, pre-treatment IU scores significantly mediated the change in anxiety scores such that children with higher pre-treatment IU showed less improvement of their anxiety symptoms.

BUILDING MODELS

We have presented evidence for associations between anxiety in ASD with atypical sensory function, emotion recognition and regulation (trait alexithymia and mindfulness skills), and cognitive (IU) difficulties. While these represent just a few among many possible pathways to emotion dysregulation in autism (Mazefsky et al., 2013; White et al., 2014), recent clinical- and measurement-based research studies have highlighted the relevance of each of these ideas for future study. We propose the following exploratory model as a framework for future studies to develop areas of overlap and causal links among these constructs (see **Figure 1**). For example,

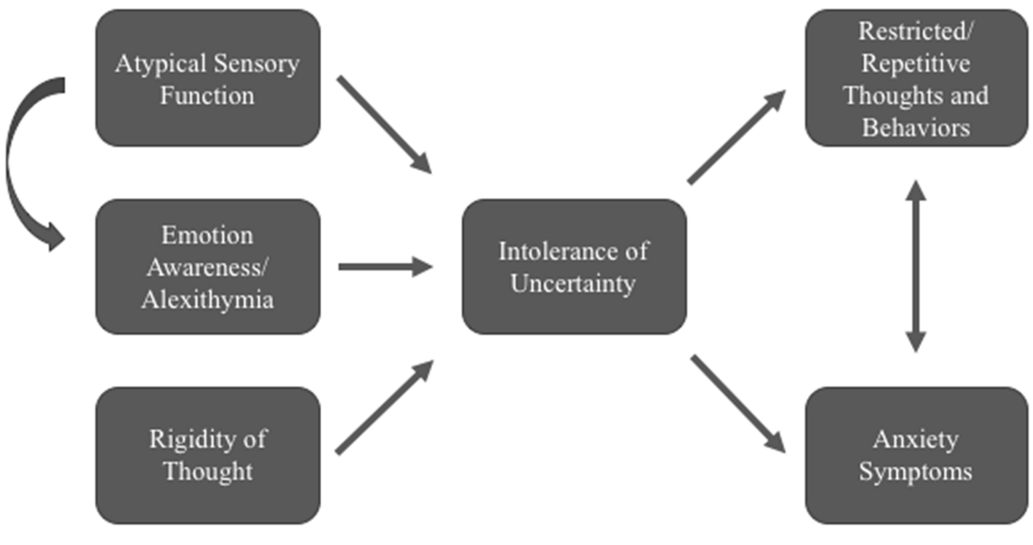

FIGURE 1 | Exploratory model of possible pathways related to Intolerance of uncertainty (IU) and anxiety in Autism Spectrum Disorder (ASD). Evidence is growing for IU as a significant mediator of anxiety in ASD samples.

atypical sensory functioning may exacerbate uncertainty for both external and internal (interoceptive) stimuli. Our model includes related ideas that have not yet received adequate research attention but may also provide explanatory power. For example, cognitive and behavioral rigidity may create enhanced uncertainty about whether exact rules will be followed, and may also be associated with repetitive and restricted behaviors (see e.g., Wigham et al., 2015; Neil et al., 2016).

A major difficulty for many of the studies reviewed here is how to separate the underlying theoretical mechanisms from each other. While this model arose from clinical observation, other factors such as methods bias (e.g., questionnaires completed by the same raters) make it difficult to tease them apart using only survey data. It is likewise difficult to understand relationships between behavioral data and psychophysiological data (Geurts et al., 2009; Watts et al., 2016).

There is an urgent need for experimental and ecologically-valid paradigms to address these questions. One question is how valid are existing measures of these constructs for autism samples. This has so far been taken up in the autism and anxiety literature, mostly for pediatric samples. Several studies suggest some relevance for existing measures but also recognize autism-unique aspects of anxiety that require additional attention (Kerns et al., 2014; Rodgers et al., 2016b). Standard measures for alexithymia include the Toronto Alexithymia Scale-20 (Bagby et al., 1994) and the Bermond-Vorst Alexithymia Questionnaire (Vorst and Bermond, 2001). Mindfulness is most frequently measured using the Five Facet Mindfulness Questionnaire (Baer et al., 2006) though there are many others. IU is captured using the IU Scale, often the short, 12-item version (Carleton et al., 2007). While these measures demonstrated more-than-typical levels of each construct in a self-reporting sample of ASD adults (Maisel et al., 2016), formal studies of validity and factor structure have not been undertaken in autism populations. Such studies are clearly necessary for forwarding work in this field.

AUTISM, ANXIETY AND INTEGRATION OF mPFC

Shalom (2009) and others have highlighted the potential contributions of disrupted integration in medial prefrontal cortex (mPFC) function across a variety of abilities in ASD, including memory and visual processing (Lecouvey et al., 2015; Smith et al., 2015; Tzur, 2015). To date, however, there has been little published research specifically related to the mechanisms that link mPFC, anxiety and autism symptoms (though see possible relationships in rodent models, Truitt et al., 2007).

Fear and anxiety critically depend on medial aspects of prefrontal cortex including mPFC and anterior cingulate cortex (ACC), with key connections to amygdala, hippocampus and insula regions among others (Giustino and Maren, 2015). Essentially, it is thought that prefrontal cortex functions to provide top-down regulation of emotional response to incoming signals, and disruption in this network leads to difficulty managing that emotional response and the subsequent development of maladaptive emotional states including excessive anxiety. For example, Herry et al. (2007) found that unpredictability in sequences of sound pulses was associated with anxiety-like behavior in both mice and humans, with enhanced/sustained amygdala activity in both species. The authors conclude (p. 5964) that "habituation of neuronal activity in the amygdala represents an evolutionary conserved mechanism by which temporal predictability of perceptual input leads to adaptive changes in emotional behavior". That is, difficulties with uncertainty at a primitive level (the amygdala) seem to be related to difficulties in flexible emotional response.

Several studies of mPFC dysfunction in ASD samples have focused on social disabilities such as face processing (Kleinhans et al., 2009; Swartz et al., 2013) conclude that decreased regulation of amygdala by ventromedial PFC (vmPFC) underlies reduced habituation of amygdala in ASD, resulting in decreased modulation of response to social stimuli. This same reasoning applies just as well to explanations for anxiety: reduced modulation of limbic activity via higher cortical systems may result in chronic, unchecked perception of threat and subsequent anxiety (Amaral et al., 2003). Top et al. (2016) conducted an fMRI study of fear conditioning and extinction in adults with ASD, concluding that the ASD group failed to recognize safety cues, and thus were delayed in responding to changes between threat to safety contexts.

One key question is how much these difficulties with adaptation/flexibility arise from bottom-up or top-down integration (Shalom, 2009). For example, experience with ambiguity may be increased in ASD through multiple channels. Computational models created by Pellicano and others (Pellicano and Burr, 2012; Lawson et al., 2014; Sinha et al., 2014; Van de Cruys et al., 2014) suggest that people with ASD are unable to effectively modulate current experience with information from prior experience, leading to an overwhelming experience for new information. While Pellicano and Burr (2012) have mostly focused this account on sensory and perceptual stimuli, others have noted the relevance of such a model for explaining other aspects of autism including social difficulties based on more top-down approaches (Brock, 2012; Sinha et al., 2014). Disrupted connectivity between other regions of mPFC (including ACC) and the limbic system (including hippocampus) may also affect emotion regulation and anxiety.

Insula cortex is critical for integration of interoceptive and sensory information and regulating emotional response (Gasquoine, 2014). Alexithymia and empathy are associated with insula activity in ASD and controls (Bird et al., 2010). A seminal article on the neurobiology of IU (Grupe and Nitschke, 2013) suggests that medial orbitofrontal cortex and insula provide information about the subjective value of potential events, balancing an individual's feelings of probable risk separate from a reasoned consideration of risk. Disruptions to this network may then lead to "more vivid or visceral simulations of potential events" (p. 492) and heighten a bias towards threat especially in uncertain situations. Future research should continue to examine the interplay between specific aspects of reduced mPFC integration in ASD.

IMPLICATIONS FOR TREATMENT

Traditional CBT approaches may focus on mechanisms of anxiety that are less relevant for ASD youth and adults (Kerns et al., 2014). Rapidly emerging data suggests that standard behavioral and pharmacological mental health interventions will benefit from understanding and targeting highly-specific underlying mechanisms (Keefer et al., 2016; Walsh et al., 2016). For example, interventions directed at improving sensory integration could potentially reduce anxiety in ASD, although little research in this area has been done to date (Watts et al., 2016). Mindfulness based treatments (MBT)—aimed at increasing emotional awareness as well as the ability to cope with strong emotions–have been adapted for ASD in several trials with encouraging success in reducing anxiety and increasing positive affect (Spek et al., 2013; Dykens et al., 2014; Jones et al., 2014; de Bruin et al., 2015). Difficulties with habituation and flexibility, associated with disrupted integration between mPFC and limbic regions, can also be treated directly with benefits for anxiety and depression (Kenworthy et al., 2014; Lawson et al., 2015; Wallace et al., 2016). IU is a critical target for future research in both causes and treatment for anxiety in some individuals diagnosed with ASD. Keefer et al. (2016) suggest that directly targeting IU in ASD may be a helpful adjunct to usual CBT approaches. Rodgers et al. (2016a) developed a manualized, parent group based treatment program for young people with ASD which focused specifically on IU, which preliminary evaluation indicates has promise as a treatment option for young people with ASD and anxiety.

Individual differences provide essential context for any treatment implications. For instance, we propose here that difficulties with habituation contribute to atypical sensory function in ASD. However, Schoen et al. (2008) identified two habituation subgroups within a sample of 40 children with ASD, one characterized by slower latency and faster habituation and the other by faster latency and slower habituation in response to sensory stimuli. Similar findings have been reported by Hirstein et al. (2001). It may be that the link between sensory function and anxiety holds only for those with difficulty habituating to new stimuli. As noted by Grupe and Nitschke (2013), limited habituation in mPFC biases information processing towards negative/threatening frameworks; individuals for whom this system is working more typically may be less susceptible to anxiety even if they are diagnosed with ASD.

SUMMARY

There is an urgent need to investigate the relevance of many possible underlying mechanisms related to emotion dysregulation in ASD. This mini-review article has focused on three such mechanisms—atypical sensory function, alexithymia and IU–that appear to be closely related to each other and that strongly predict anxiety in ASD. Although support for each of these concepts is emerging, evidence linking the three constructs together remains incomplete. Thus, this model is speculative, but we believe it builds a helpful framework for future studies. Such difficulty integrating cognitive and emotional information putatively arises at least in part from disruptions in neural systems involving mPFC and limbic structures, in conjunction with insula cortex. Improved understanding of the contribution of these and other mechanisms should lead to better, more specific interventions for anxiety in ASD.

AUTHOR CONTRIBUTIONS

Both authors conceived the project. MS wrote the preliminary draft and both authors edited and approved the final manuscript.

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Similarity hypothesis: understanding of others with autism spectrum disorders by individuals with autism spectrum disorders

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Individuals with an autism spectrum disorder (ASD) are generally thought to lack empathy. However, according to recent empirical and self-advocacy studies, individuals with ASD identify with others with ASD. Based on mutual understanding, individuals with ASD respond empathically to others with these disorders. Results have shown that typically developing (TD) adults identify with TD fictional characters, and that such identification plays a critical role in social cognition. TD individuals retrieve episodes involving TD individuals faster than they retrieve episodes involving ASD individuals. Individuals with ASD also show a "similarity effect" whereby they retrieve stories involving ASD individuals more effectively when the stories have consistent outcomes than when they have inconsistent outcomes. In this context, I hypothesized that similarities between a perceiver and a target facilitate cognitive processing. This hypothesis was named the "similarity hypothesis". Perceivers empathize with targets similar to themselves, which facilitates subsequent cognitive processing. Behavioral and neuroimaging studies are reviewed based on the similarity hypothesis.

Keywords: similarity, self, other, empathy, autism spectrum disorder, vmPFC, fMRI

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Introduction

Autism spectrum disorder (ASD) is diagnosed based on behaviors such as difficulties with communication and social development, repetitive behaviors, and narrowly focused but strong interests (American Psychiatric Association, 2013). Individuals with ASD have difficulty understanding other people's inner states, and they are generally thought to lack empathy (Baron-Cohen, 1995; Lombardo et al., 2007). However, according to recent empirical (Komeda et al., 2013a) and self-advocacy studies (Dern, 2008; Ayaya and Kumagaya, 2010), individuals with ASD understand others with ASD. Indeed, individuals with ASD have intact empathy if they do not have alexithymic traits (Bird et al., 2010). Moreover, they show empathic responses toward individuals with ASD (Komeda et al., 2015). The APA dictionary (VandenBos, 2007) defines empathy as understanding a person from that person's frame of reference rather than from one's own frame of reference so that the other's perceptions and thoughts are experienced vicariously. Empathy includes at least two aspects: cognitive and affective (Blair, 2005; Shamay-Tsoory et al., 2005, 2007; Shamay-Tsoory and Aharon-Peretz, 2007; Jones et al., 2010; Schwenck et al., 2012). Cognitive empathy involves perspective taking (Eslinger, 1998) and theory of mind (Premack and Woodruff, 1978; Baron-Cohen et al., 1985) and is dependent on several cognitive capacities.

Affective empathy refers to the capacity to experience affective reactions in response to the observed experience of others (Davis, 1994; Shamay-Tsoory, 2011).

Humans often have preferences and feel affinity for their in-group over an out-group (Turner, 1982). For example, people tend to be attracted to and more satisfied with interactions involving individuals similar to them (Byrne and Griffitt, 1969; Carli et al., 1991). People also prefer individuals with personality traits similar to their own (Griffitt, 1966, 1969; Deutsch et al., 1991). Additionally, we preferentially remember other people with whom we share an identity (Sporer, 2001), which is called the in-group memory advantage (Rule et al., 2010).

Recent studies on typically developing (TD) adults have shown that similarities between readers and characters in a story play a critical role in social cognition. For example, it is easier for extraverted participants to understand stories about other extraverted people (Komeda et al., 2009). Additionally, extraverted individuals are able to predict the outcomes of other extraverted people's actions more easily, and neurotic individuals are able to predict the outcomes of other neurotic people's actions more easily (Komeda et al., 2013b). TD individuals retrieved target sentences about a TD character's context faster than they retrieved target sentences about an ASD character's context (Komeda et al., 2013a).

Individuals with ASD also showed a "similarity effect" in that they retrieved ASD-consistent outcomes more efficiently than they retrieved ASD-inconsistent outcomes if the episodes were about individuals with ASD, whereas they did not respond differentially in response to TD-consistent and TD-inconsistent outcomes of episodes about TD individuals (Komeda et al., 2013a). Therefore, similarities between a perceiver and a target facilitate cognitive processing. This prediction is called the *similarity hypothesis*. The similarity hypothesis was originally part of the *reader-protagonist interaction model* in narrative comprehension (Komeda and Kusumi, 2007).

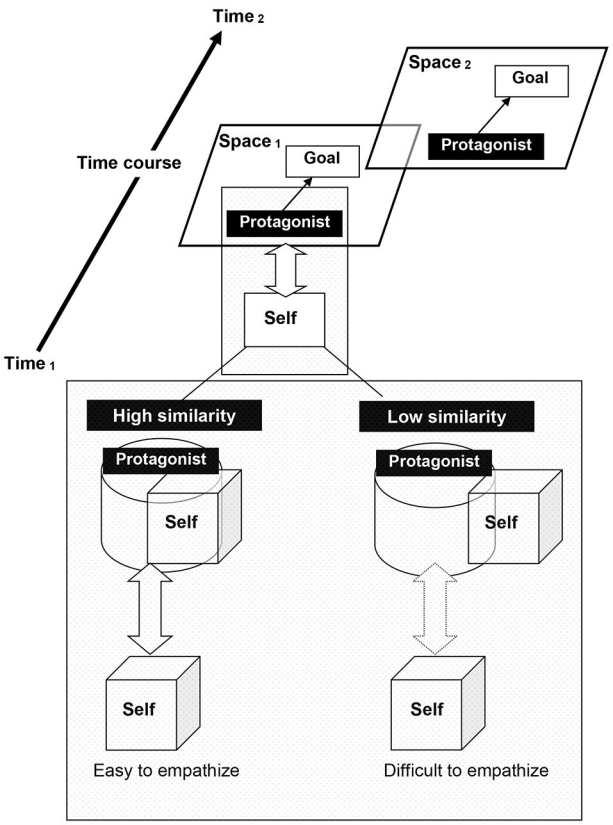

FIGURE 1 | Reader-protagonist interaction model. "Self" corresponds to "reader" or "listener" during discourse comprehension. The more the characteristics between self and story protagonists or characters overlap, the greater the similarity.

Reader-Protagonist Interaction Model

We proposed the reader-protagonist interaction model as a framework to integrate discourse comprehension studies with social cognitive neuroscience studies (Komeda and Kusumi, 2007; Komeda, 2010). This model builds a connection between empathy as a virtual experience during story reading and empathy during social interactions as a real experience.

As shown in **Figure 1**, mental representations are updated during discourse comprehension when ongoing sentences are mapped on previous contexts (Zwaan and Radvansky, 1998). This mental representation includes spatial and temporal information, story protagonists or characters (or conversational partners), and their goals, motivations, and intentions (Zwaan et al., 1995a,b; Zwaan and Radvansky, 1998; Komeda and Kusumi, 2006). Readers infer and predict the actions of story characters using causal clues described in the situation to understand these actions (van den Broek and Gustafson, 1999; van den Broek et al., 1999). When readers experience causal discontinuities, they feel a sense of strangeness and strive to predict the behavior and mental states of the story character, such as desires, motivations, and feelings (Miall, 1989; Komeda et al., 2005).

Similarity Hypothesis

The similarity hypothesis states that perceivers empathize with targets similar to themselves, and, as a consequence, subsequent cognitive processing is facilitated. Although all types of similarity—including body posture (Dijkstra et al., 2007), political opinions (Mitchell et al., 2006), and cultural backgrounds (Chiao et al., 2008)—are considered, this paper focuses on similarities in a perceiver's personality traits (extraversion and neuroticism) and ASD-related characteristics.

The bi-directional white arrow in **Figure 1** indicates the interaction between self, or the reader/listener, and the story protagonist during discourse comprehension. The bottom segment of **Figure 1** shows the degree of similarity between the readers/listeners and the story protagonist. Readers tend to overestimate the protagonist's happiness, presumably due to their empathy for characteristics similar to themselves

(Komeda et al., 2009). Self (reader) and other (protagonist) overlap when readers are similar to the protagonist and feel empathy for them in a virtual situation (Komeda et al., 2013b). Alternatively, self and other do not overlap when readers (listeners) do not see themselves as similar to the protagonists (speakers) (Komeda et al., 2009, 2013b). In the latter situation, it is difficult to feel empathy (Komeda and Kusumi, 2007). In other words, the degree of overlap represents a possibility for mental simulation (Oatley, 2002; Mar and Oatley, 2008).

The perception of similarity is implicitly evoked via empathy with a target (Stotland, 1969). If the perceiver empathizes with the target, the cognitive processing related to the target is enhanced. For example, reading comprehension is facilitated (e.g., reading accelerates and the outcome-judgment task is performed rapidly and accurately) and memory is enhanced (recognition time is fast and accuracy is better). If the perceiver does not empathize with the target, a perception of dissimilarity is evoked. As a result, cognitive processing is not enhanced (Tversky and Kahneman, 1974; Epley and Gilovich, 2001; Epley et al., 2004).

The next section will discuss empirical evidence obtained from behavioral and neuroimaging studies that supports the similarity hypothesis.

Evidence Supporting the Similarity Hypothesis

All levels of similarity, from the lowest (e.g., sensation or perception) to the highest (e.g., cognitions regarding politics or social perceptions), are covered by the similarity hypothesis. However, this paper focuses on behavioral and neuroimaging approaches to higher-level cognitive functions.

Evidence from Behavioral Findings

Similarities in personalities between a reader and characters facilitate reading comprehension (Komeda et al., 2009). Highly extraverted participants judge the outcomes of stories with extraverted protagonists more rapidly than do less extraverted participants, whereas highly neurotic participants judge the outcomes of stories with neurotic protagonists more rapidly than do participants with low levels of neuroticism (Komeda et al., 2013b). Furthermore, a participant's personality traits predict their empathy for the protagonist: The higher a participant's extraversion or neuroticism score, the greater their empathy with the extraverted or neurotic protagonist (Komeda et al., 2013b).

Evidence from Functional Brain Imaging Findings

Discriminating between similar and dissimilar others is performed in the medial prefrontal cortex (mPFC). Activation of the ventral part of the mPFC (vmPFC) is related to processing similar others on a socio–emotional preference task (participants viewed faces with various emotional expressions and made appraisals of whether they liked the face or not) (Chen et al., 2010), judgment of another person's opinion (Mitchell et al., 2006), and preference for another person's and their own preference (Tamir and Mitchell, 2010). vmPFC activation during a decision-making task reflects a choice that is executed (no simulation), whereas dmPFC reflects a choice that is modeled but not executed (involving simulation) (Nicolle et al., 2012).

Perceptions of similarity are also based on implicit and automatic processes. According to Lieberman (2007) model of social cognition, the control system (C-system) engages in reflective social cognition (controlled cognitive processing), and the reflexive system (X-system) engages in reflexive social cognition (automatic cognitive processing). The C-system includes the dorsal part of the mPFC (dmPFC), whereas the X-system includes the vmPFC.

Based on the similarity hypothesis, if perceivers empathize with a similar target, the perception of similarity is automatically elicited. These automatic cognitive processes lead to activation of the vmPFC (Mitchell et al., 2006; Jenkins et al., 2008; Komeda et al., 2015). For example, vmPFC activation was significantly greater when making appraisals of self than other (familiar but dissimilar character to the participants, Harry Potter) in TD children and adolescents (Pfeifer et al., 2013).

Alternatively, if perceivers do not empathize with a dissimilar target, a perception of dissimilarity is explicitly elicited. Differences between perceivers and targets are processed explicitly, and the gap between perceivers and targets is resolved through social cognition processes. These effortful cognitive processes lead to activation of the dmPFC (Ferstl and von Cramon, 2002; Ferstl et al., 2005; Mason et al., 2008; Mano et al., 2011). For example, psychophysiological interactions (PPI) analyses showed that dmPFC is a hub of resolutions of social conflict, which is a type of effortful cognitive processes (Watanabe et al., 2014).

Application of the Similarity Hypothesis to Understand and Support Individuals with ASD

The similarity hypothesis provides the following three predictions to understand the characteristics of individuals with ASD. First, individuals with ASD empathize with others with ASD. Second, individuals with ASD retrieve others with ASD more easily from their memory representation. Third, individuals with ASD support others with ASD.

Empathy in Individuals with ASD

Although deficits including lack of social reference and difficulty empathizing have been demonstrated in previous studies (Baron-Cohen, 1995; Lombardo et al., 2007; Pfeifer et al., 2013), most target stimuli are oriented at TD individuals. For example, Pfeifer et al. (2013) compared brain activations while making appraisals of one's self and a familiar but distant other (Harry Potter). Harry Potter do not show a defining characteristics with ASD. As a comparison, brain activations are worth investigating while making appraisal of another character who has the characteristics with ASD. It is probably difficult for individuals with ASD to understand TD individuals, just as it tends to be difficult for TD individuals to understand those

with ASD. Komeda et al. (2015) used functional magnetic resonance imaging to examine whether individuals with ASD experience empathy toward other people with ASD. Fifteen high-functioning Japanese participants with ASD (17–41 years of age) and 15 TD Japanese participants (22–40 years of age) matched for age and full and verbal intelligence quotient scores with the participants with ASD were enrolled in this study.

The participants performed social judgment tasks that required reading a sentence related to an autistic character (e.g., "I would rather be alone than with others") and answering the following question: "Do you agree with the sentence?" Judgments involving a non-autistic character involved reading a sentence (e.g., "Yuya (Japanese male name) would rather be with others than alone") and answering the following question: "Do you think you are similar to him?"

Interestingly, the results showed that the vmPFC was significantly activated in individuals with ASD in response to characters with ASD and in TD individuals in response to characters without ASD. We found no differences between self- and other-judgments; that is, the vmPFC of individuals with ASD was activated during the self- and other-judgments in response to ASD sentences, whereas the vmPFC of TD individuals was activated during the self- and other-judgments in response to TD sentences. Because the reaction times of other-judgments were longer than those of self-judgments in both the ASD and TD groups, the other-judgments were processed differently from the self-judgments. Nonetheless, it is important that the brain-imaging data showed that the vmPFC was activated during both the self- and other-judgments made by the ASD group in response to ASD sentences and during both the self- and other-judgments made by the TD group in response to TD sentences.

Additionally, higher autism-spectrum quotient scores (Baron-Cohen et al., 2001) in individuals with ASD and TD were significantly correlated with greater activation in the vmPFC while judging characters with ASD traits. Thus, individuals with high levels of ASD traits tend to empathize with others with high levels of ASD, at least on an explicit social judgment task (Komeda et al., 2015).

However, the behavioral results did not support the similarity hypothesis in that the self-reports in the social judgment tasks were not consistent with the diagnostic status of individuals with ASD. Thus, the similarity hypothesis was supported by the implicit measure (vmPFC activation as a physiological measure) but not by the explicit measure (number of agreements as a subjective measure), perhaps in agreement with the distinction between cognitive and emotional empathy (Blair, 2005; Shamay-Tsoory et al., 2005; Saxe, 2006; Völlm et al., 2006; Shamay-Tsoory and Aharon-Peretz, 2007; Jones et al., 2010; Schwenck et al., 2012).

Memory Retrieval in Individuals with ASD

The similarity hypothesis predicts that individuals with ASD should retrieve others with ASD more easily from their memory representation. Based on this hypothesis, I predicted that ASD individuals would demonstrate superior memory for the ASD characters in stories and that TD individuals would demonstrate superior memory for the TD characters in stories. Komeda et al. (2013a) examined differences in episodic memory retrieval between individuals with ASD and TD. Eighteen individuals with ASD (age, 17–40 years) and 17 age- and IQ-matched TD participants (age, 22–40 years) read 24 stories; 12 stories featured protagonists with ASD characteristics, and the other 12 featured TD protagonists. After reading all 24 stories, the participants were asked to complete a recognition task about a target sentence in each story. Although no differences were observed between the ASD and TD groups for encoding processes, they did reveal group differences in memory retrieval. Although individuals with ASD demonstrated the same level of accuracy as did TD individuals, their memory-retrieval patterns differed with respect to response times; individuals with ASD more effectively retrieved ASD-consistent than ASD-inconsistent sentences (**Figure 2**), and TD individuals retrieved stories with TD more effectively than they retrieved stories with ASD protagonists. Thus, similarities between the reader and the story characters had different effects on memory retrieval in the ASD and TD groups.

Possibility of ASD Peer Support Based on the Similarity Hypothesis

The similarity hypothesis suggests that individuals with ASD characteristics can help people with ASD. Individuals with ASD can support others with ASD based on empathy toward similar others.

Zercher et al. (2001) examined the effect of peer support using a measure of eye contact and found that participation in an integrated play group was associated with an increase in the joint attention, symbolic play acts, and verbal utterances of two children with ASD. Peer support was provided by a group consisting of 6-year-old boys with ASD and 5-, 6-, and 11-year-old TD boys. As far as I know, scant empirical evidence that children with ASD support other children with ASD is available. Data related to tests of the similarity hypothesis among individuals with ASD may contribute to the effectiveness of

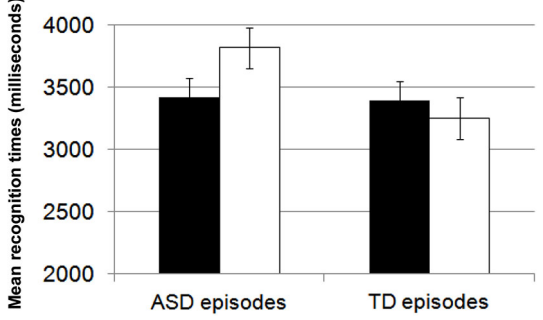

FIGURE 2 | Comparison of consistent and inconsistent episodes in individuals with ASD. Black bar shows consistent episodes. White bar shows inconsistent episodes. Individuals with ASD retrieved ASD-consistent episodes faster than they retrieved ASD-inconsistent episodes.

self-advocacy groups for these individuals as well as to peer support for children with ASD. For example, Bauminger et al. (2003) reported that many children with ASD reported feelings of loneliness. In this context, children with ASD who have experienced loneliness may be able to support other children with ASD who share similar experiences or feelings.

Finally, the similarity hypothesis is closely related to the "assortative mating" theory, which holds that "like marries like" (Baron-Cohen, 2008). Parents of children who have ASD may not have autism but may have characteristics associated with the condition. Thus, children with ASD have superior attention to detail in terms of perception and memory, and they are strongly attracted to systems (Baron-Cohen, 2006). The assortative mating theory is very useful for thinking about the origins of ASD. However, why "like marries like" occurs remains unclear. The similarity hypothesis can fill the gap. According to the similarity hypothesis, people with ASD empathize with others with ASD. Thus, a preference toward similar others arises. This preference may elicit romantic love and lead to marriage. It will be necessary to investigate genetic backgrounds based on the similarity hypothesis. If the project is completed, we might be able to organize peer (and/or family) support for individuals with ASD based on integrating genetic approaches and similarity-based empathy.

Conclusions

Behavioral and neuroimaging studies were reviewed based on the similarity hypothesis, which asserts that perceivers empathize with targets similar to themselves. When perceivers empathize with similar targets, a perception of similarity is automatically elicited. This process facilitates cognitive processing, including reading comprehension and memory retrieval. Alternatively, if perceivers do not empathize with dissimilar targets, a perception of dissimilarity is explicitly elicited, and differences between perceivers and targets should be addressed and resolved, as these effortful cognitive processes inhibit cognitive processing.

Potentially, the similarity hypothesis can be applied to the development of educational curricula, such as those for special-needs classes, minority education, and cross-cultural education in order to overcome the effort involved in understanding dissimilar others.

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Binding in working memory and frontal lobe in normal aging: is there any similarity with autism?

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Some studies highlight similarities between Autism Spectrum Disorder (ASD) and healthy aging. Indeed, the decline in older individuals' ability to create a unified representation of the individual features of an event is thought to arise from a disruption of binding within the episodic buffer of working memory (WM) as the same way as observed in ASD. In both cases, this deficit may result from an abnormal engagement of a frontohippocampal network. The objective of the present study is to identify both cognitive processes and neural substrates associated with the deficit of binding in WM in healthy aging. We studied the capacity of binding and the cognitive processes that might subtend its decline in 72 healthy participants aged 18–84 years. We examined the behavioral data in relation to the changes in brain metabolism associated with the age-related decline in a subgroup of 34 healthy participants aged 20–77 years using the resting-state [^{18}F] fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET). Forward stepwise regression analyses showed that the age-related decline in binding was partially explained by a decline in inhibition and processing speed. PET correlation analyses indicated that metabolism of the frontal regions, anterior and middle cingulate cortices is implicated in this phenomenon. These data suggest that executive functions and processing speed may play a crucial role in the capacity to integrate unified representations in memory in aging. Possible implications are discussed in ASD.

Keywords: aging, binding, executive functions, processing speed, brain metabolism, frontal lobes

INTRODUCTION

Episodic memory refers to a memory system that stores memories of personal events located in space and time, associated to self-referential and contextual environment. Encoding and recollecting episodic memories imply to create multimodal traces that will be achieved by binding mechanisms. This very complex memory system is impaired in Autism. There is growing evidence that individuals with high-functioning Autism Spectrum Disorder (ASD) show impaired contextual memory (Bowler et al., 2008; Gaigg et al., 2008; Souchay et al., 2013b) and relational memory (Southwick et al., 2011; Maister et al., 2013). In addition, other studies reported difficulties in the capacity to mentally re-experience or recollect the personal event with all associated phenomenological details (Bowler et al., 2000; Souchay et al., 2013a). Overall, these results lead some authors to compare these memory difficulties in ASD with the memory decline observed in healthy aging (Bowler et al., 2004). This "aging analogy" refers to difficulties in processing complex stimuli and binding together the different features that define an episodic memory trace in Working Memory (WM; Baddeley, 2000). WM is a memory system comprising two slave systems (i.e., the phonological loop and the visuospatial sketchpad) responsible for the processing and temporary storage of information useful for understanding, learning and reasoning (Eustache and Desgranges, 2008). This suggests a dysfunction of the episodic buffer that refers to a working space where information from different sources is bound into a unitary representation and stored as a multimodal one for several seconds in WM. It is conceptualized as an interface between the central executive which supervises and coordinates the information supplied by the slave systems and long-term memory (Baddeley et al., 2011). The *episodic* label refers to the hypothetical role it plays during encoding and conscious recollection of events in episodic memory, whereby it integrates information that becomes accessible to conscious awareness (Eustache and Desgranges, 2008).

Indeed, it has been suggested that an associative deficit disturbing the creation of associations (and equivalent to a binding deficit) is one of factors contributing to diminished

episodic memory both in older adults (Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2003) and in ASD (Bowler et al., 2010; Maister et al., 2013). Using a task where individuals were shown 30 colored objects within a 7 × 7 array for 90 s and had to immediately recognize these objects and their location, Chalfonte and Johnson (1996) were the first to show that while memory for individual features (objects, colors and locations) is preserved in aging, memory for bound features (e.g., object + color and object + location) suffers from an age-related decline. These results in support of a general age-related decline in binding have since been replicated (Mitchell et al., 2000a,b; Plancher et al., 2010). Interestingly, the same task was recently used by Bowler et al. (2014) in a group of adults with ASD and the same pattern of performances was found: relatively undiminished performances for individual features contrasting with significant difficulties in combination conditions. These results suggest that processing steps from perceptual analysis to item-based memory are broadly spared in contrast with an impairment of the binding process *per se*.

The cognitive substrates of binding have been studied in various populations. Baddeley and Wilson (2002) found positive correlations between immediate prose recall, a task that involves the binding of verbal information into meaningful units, and both executive (shifting and inhibition processes) and intellectual (Wechsler Adult Intelligence Scale; Wechsler, 1987) performances, in densely amnesic patients. In the context of ASD and aging, binding difficulties are thought to result from difficulties in the executive processes (Maister et al., 2013). For instance, Mitchell et al. (2000b) hypothesized that the age-related binding decline stems from an age-related decline in the executive processes involved in WM (e.g., shifting of attention from one stimulus to another, implementation and maintenance of a cumulative rehearsal strategy). To test their hypothesis, they asked young and older individuals to recognize objects, locations or object-location combinations after an 8-s unfilled interval. While young and older adults performed at the same level when it came to recognizing individual features or targets in the combination condition, the older adults produced more false alarms in the latter condition. They were also slower than the young adults at rejecting lures in the combination condition, either in an attempt to improve their accuracy, or because of an age-related processing speed decrement which has been suggested to account for some of the age-related differences reported in measures of cognition (Salthouse, 1996). Mitchell et al. concluded that the older individuals may have experienced difficulties using an efficient rehearsal strategy, possibly owing to a decline in reflective and executive processes. Following up on this study, Naveh-Benjamin found that older individuals performed more poorly during the incidental encoding of associative information (i.e., learning a list of word-nonword pairs and recognizing them after a 90-s interval) and exhibited an even greater deficit in the use of strategic behavior when they directed their attention to the relevant associative information (Naveh-Benjamin, 2000). In other words, older adults exhibit a greater deficit when strategic processing involving executive functions (inhibition of irrelevant information, shifting between strategies) is required.

Neuroimaging studies in young adults have revealed the involvement of a frontohippocampal network during feature binding (Mitchell et al., 2000a), and several hypotheses have been put forward as to the respective roles of these two structures. Damage to the hippocampus is typically associated with massive impairment of long-term episodic memory, possibly owing to a disruption of binding (Cohen and O'Reilly, 1996; Reinitz et al., 1996; Quinette et al., 2006; Braun et al., 2008; Finke et al., 2013). Although the hippocampus is traditionally associated with episodic memory, recent studies have shown that it is also engaged over short time spans (Ranganath et al., 2005; Piekema et al., 2006; Olsen et al., 2012). More precisely, the hippocampus may receive information from multiple cortical regions and automatically bind it together (Vargha-Khadem et al., 1997; Eichenbaum, 2000; Baddeley et al., 2010; Opitz, 2010; Olsen et al., 2012). Some authors have suggested that the hippocampus is involved in actively maintaining associations with spatial information, but not with other types of information, although this issue has yet to be explored (Mitchell et al., 2000a; Piekema et al., 2006). Finally, others have conjectured that the hippocampus actively forms and consolidates long-term memory traces of associations immediately after their creation and plays a role in the transition from WM to long-term memory rather than in WM *per se* (Piekema et al., 2006; Quinette et al., 2006; Allen et al., 2014).

Concerning frontal involvement, two studies have provided evidence that the medial prefrontal cortex is more active when young adults have to remember a combination of features, rather than individual ones (Mitchell et al., 2000b; Prabhakaran et al., 2000). These frontal areas may underlie the reflective processes that allow for the coordination of strategies to control the coactivation of features and the length of time they remain coactive, in order to permit the short-term maintenance and manipulation of the integrated features or to permit the integration itself (Mitchell et al., 2000a; Prabhakaran et al., 2000; Koechlin and Summerfield, 2007).

Mitchell et al. (2000a) have examined the brain substrates of the age-related decline in effortful binding. They used functional MRI to explore differences in activation between younger and older adults during the recognition of object-location associations. Their findings suggested that an age-related dysfunction of the left anterior hippocampus accounts for the difficulty that older people have with feature binding in WM. The authors also found that while the prefrontal cortex subtended the retrieval of bound features in young adults, this was not the case for older adults, who performed more poorly (Mitchell et al., 2000a). This result is in line with reports of frontal lobe disruption with advancing age in neuroimaging studies (for reviews, see Raz and Rodrigue, 2006; Kalpouzos et al., 2009a) even if other studies suggest that increase in frontal lobes activation during memory tasks may reflect the use of compensatory strategies in response to a structural decline (Persson et al., 2006; Miller et al., 2008). In summary, these results suggest that the integrity of the frontohippocampal network is critical for feature binding.

The present study aimed at exploring the capacity of binding in healthy aging by combining neuropsychological and neuroimaging approaches. We had three main objectives. First,

previous studies had suggested an age-related decline of binding on tasks featuring intervals that were too long to allow for the formation and storage of associations to be dissociated. Our study was therefore designed to explore age-related effects in a feature-binding task with a very short 1 s interval (Quinette et al., 2006), in order to focus on the formation stage. Second, although the disruption of effortful binding is thought to stem from a reduction in processing speed and a decline in executive processes (shifting, inhibition, updating), the respective contributions of these cognitive functions has never been fully assessed. In order to gain a clearer understanding of their contribution to the age-related binding decline, we therefore conducted forward stepwise regression analyses. Finally, neuroimaging findings have suggested that the disruption of a frontohippocampal network could be responsible for the age-related decline in binding (Mitchell et al., 2000a). In our study, where we focused on effortful binding which is more conducive to frontal lobe involvement (since participants had to mentally combine verbal and spatial features), we therefore expected an age-related reduction in frontal lobe metabolism to mainly account for the age-related decline in strategic binding.

MATERIAL AND METHODS

PARTICIPANTS

This protocol was approved by the regional ethics committee (CPP Nord-Ouest III). The participants all gave their written informed consent.

Cognitive data sample

A total of 72 healthy individuals aged 18–84 years (mean age = 45.75 ± 18.83 years) underwent the cognitive assessment. As the participants were homogeneously distributed across the age groups, age was treated as a continuous variable. Descriptive data are reported in **Table 1**. All participants stated that they were in good health in a health questionnaire. They did not report any history of neurological or psychiatric conditions, head trauma, or alcohol and drug abuse. Individuals aged 50 years or above were screened for general cognitive impairment on the Dementia Rating Scale (Mattis, 1976). All had normal performances for their age and education level. Each participant had received at least eight full years of education. Because of changes in the French education system over the years, we assessed education level using a composite index (see Gonneaud et al., 2011) that took into account both the participants' years of schooling and their vocabulary level (assessed with Part B of the Mill Hill test; Deltour, 1993). There was no significant correlation between age and this composite index ($r = 0.07$, $p = 0.55$).

Imaging subsample

Of the 72 participants included in the cognitive sample, 34 individuals aged 20–77 years, all right handed except for three who were ambidextrous, underwent structural T1-weighted MRI and [^{18}F]fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) scans. Descriptive data are reported in **Table 1**. The subsample did not differ from the original sample in terms of age, sex ratio or education level. The T1-, T2- and/or FLAIR-weighted MRI scans were normal for all participants, with no significant white-matter hyperintensities on the T2/FLAIR-weighted images (see Kalpouzos et al., 2009a, for further details). As with the whole group, there was no significant correlation between age and the composite index of education level ($r = -0.11$, $p = 0.53$).

Table 1 | Characteristics of the two samples.

	Whole sample	Imaging subsample
Number	72	34
Women/Men	40/32	19/15
Age (years): mean ± SD	45.75 ± 18.83	46.79 ± 18.82
Age range	18–84	20–77
Mean years of education ± SD	12.47 ± 2.91	12.82 ± 2.73
Mean Mill Hill vocabulary score /44 ± SD	33.97 ± 4.98	35.09 ± 4.36

PROCEDURE

The protocol comprised an assessment of binding in WM, executive functions (shifting, inhibition and updating), manipulation of information in WM and processing speed, divided in two sessions separated by a one-week interval. Binding was assessed during the first session.

MATERIALS

Binding

We assessed the association of multimodal information by means of a WM binding task that had already been used in several studies in our laboratory, and which measures the ability to associate verbal and spatial features (Mitchell et al., 2000a,b; Prabhakaran et al., 2000; Quinette et al., 2006, 2013; Hainselin et al., 2011; see **Figure 1**). The task was presented on a computer using SuperLab Pro software, which also recorded responses. In the learning phase, stimuli consisted of four colored uppercase consonants, displayed for 5 s in the center of a 5 × 4 grid, and four colored crosses placed randomly in the remaining 16 squares. Participants were asked to mentally match each consonant with the location represented by the cross of the same color. After a 1-s retention interval, a black letter was displayed in a specific square in the grid, and participants had 4 s to determine whether the letter was in the same place as it had been matched in the learning phase. The "L" and "D" keys on the keyboard randomly corresponded across participants to "yes" and "no". Individuals were asked to answer as quickly as possible, though giving priority to accuracy. For half the stimuli, the letter was in the right location (target type), and for the other half, the letter was in the wrong place (i.e., a place that was initially matched with another letter, lure type). The task was divided into two sessions of 10 trials, and the score was the number of correct answers (accepted targets and rejected lures) out of 20 trials.

Other cognitive function assessments

In order to investigate whether the effect of age on binding was mediated by an effect of age on other cognitive functions,

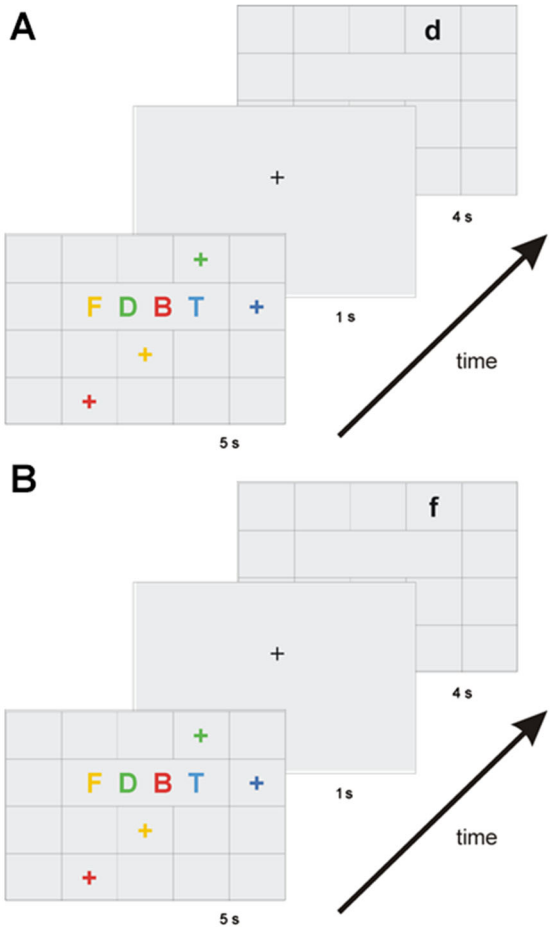

FIGURE 1 | Diagram of the working memory binding task. After the binding processing (matching letter with location according to color), participants had to memorize the integrated information for 1 s. Two types of stimuli were presented: the target type **(A)**, when the letter was in the right location, or the lure type **(B)**, when the letter was in the wrong place.

the neuropsychological assessment included tests of cognitive functions that are thought to play a role in binding. The neuropsychological battery comprised assessments of executive functions (shifting, inhibition, updating), the central executive of WM, and processing speed.

Executive functions. We administered a set-shifting test (Mayr and Kliegl, 2000) in which participants alternated between two different tasks every four trials. They were given 16 words accompanied by a sign that changed every four trials. When this sign was a heart, they were asked to make a living/nonliving judgment for each word. When the sign was a cross, they were asked to decide whether the words represented something bigger or smaller than a soccer ball. The measurement was the switch cost, that is, the difference between the time it took for participants to answer in situations where there was a shift from a task to the other one and in situations where there was none.

Inhibition process was assessed using the Stroop Color and Word Test (Stroop, 1935). Participants had to name colored dots (e.g., blue, red, green) in the first condition; to read out the name of common colors printed in black in the second condition; and to name the color in which the names of colors were printed as quickly as possible (e.g., "red" printed in blue, "green" printed in red, etc.) in the last condition. The inhibition score was the time it took to participants to complete the third condition (i.e., interference score).

The running span task (Quinette et al., 2003; adapted from Morris and Jones, 1990) assessed updating. Participants were orally provided with 16 consonant strings of variable length (4, 6, 8 or 10 letters) without any prior information about their length, and were required to recall the last four items in each string, in the same order as they had been provided. The updating score was the total number of successfully recalled strings.

Central executive of working memory. The central executive of WM was assessed using the backward digit span (Wechsler Adult Intelligence Scale; Wechsler, 1987). The score was the length of the correct sequence containing the greatest number of items.

Processing speed. The BAMS-T (Lahy, 1978) was administered to measure processing speed. Participants were provided with a sheet of paper filled with rows of eight different symbols and asked to cross out every instance of one of the three target symbols printed at the top of the sheet. The processing speed score was the total number of crossings-out per second.

IMAGING ACQUISITION

T1-weighted MRI images, used to coregister the PET images, were acquired on a General Electric 1.5-tesla Sigma Advantage echoplanar imaging device. There were 128 adjacent axial slices parallel to the anteroposterior commissure (AC-PC line), with a slice thickness of 1.5 mm and in-plane resolution of 0.94 × 0.94 mm. A spoiled gradient-echo sequence was used, with a repetition time (TR) of 10.3 ms, an echo time (TE) of 2.1 ms, a field of view (FOV) of 24 × 18 cm, and a matrix of 256 × 192. The standard correction for field inhomogeneities was applied.

The regional distribution of radioactivity was followed using an ECAT Exact HR+ PET scanner with a resolution of 4.6 × 4.2 × 4.2 mm and an axial FOV of 158 mm. Participants were scanned with their eyes closed, in a dark and quiet room (resting state). Their head was immobilized in a headrest following the orbitomeatal line. The radiotracer was injected via a catheter inserted into a vein in the arm. Transmission scans were obtained with a 68 Ge source. At Time 0, 3–5 mCi (111–185 Mbq) of ^{18}F-FDG were injected as a bolus, and a 10-min data acquisition session began 50 min post-injection. Full 3D volume acquisition allowed for the reconstruction of 63 planes, with a voxel size of 2.2 × 2.2 × 2.43 mm.

BEHAVIORAL DATA ANALYSIS

We conducted Pearson's correlations between (i) binding performance and age, to assess the effect of age on binding; (ii) other cognitive scores and age, to determine whether other cognitive functions were sensitive to age; and (iii) binding

scores and other cognitive scores, to determine whether binding performance was linked to other cognitive abilities. We then conducted forward stepwise regression analyses on the binding scores, including all the cognitive scores that correlated with binding and with age, in order to identify the variables that best explained the interindividual variability in binding performance. This model also allowed us to select variables for the subsequent imaging analyses.

NEUROIMAGING DATA ANALYSES

Preprocessing of the images

All imaging data were preprocessed and analyzed using statistical parametric mapping software (SPM5; Wellcome Department of Cognitive Neurology)[1] implemented in Matlab (MathWorks, Sherborn, MA, USA). The T1-weighted MRI images were preprocessed using the voxel-based morphometric procedure (VBM), with the VBM5.1 toolbox, which corresponds to a unified segmentation approach (Ashburner and Friston, 2005). PET images were first corrected for partial volume effects (PVEs) using PMOD software (Quarantelli et al., 2004), for an optimized voxel-based method. This software allowed us to correct for gray-matter (GM) signal loss owing to spill-out onto non-GM tissues, and for GM signal increase caused by spill-in from adjacent white matter. Every reconstructed PET image was coregistered to the corresponding MRI image and spatially normalized to the MNI template by adopting the normalization parameters obtained from the unified segmentation procedure applied to the MRI images. These PET images were resampled to a voxel size of 1 × 1 × 1 mm. The resulting PET images were then divided by their individual vermis ^{18}F-FDG uptake values to control for individual variations in global PET measures, following a procedure already used in our laboratory (for details, see Mevel et al., 2007). A 14-mm isotropic Gaussian filter was applied to the images to smooth them in order to compensate for interindividual differences and maximize the signal-to-noise ratio. Smoothed and scaled PET data were masked in order to keep only GM voxels of interest for further analyses. A statistical threshold of $p(uncorrected) < 0.001$ and cluster extent $k > 150$ voxels was used to achieve a corrected statistical significance of $p < 0.05$ determined by Monte-Carlo simulation (see program AlphaSim by D.Ward).

Negative correlations between ^{18}F-FDG uptake and age (mask)

Negative correlations were conducted across the 34 participants by performing a multiple regression in SPM5 between preprocessed PET images and age. The result of this analysis was used as a mask for the forthcoming correlations analyses between ^{18}F-FDG uptake and binding in order to constrain results within clusters for which age-related decrease in metabolism was observed.

Positive correlations and partial correlations (with cognitive functions partialed out) between ^{18}F-FDG uptake age-related decrease and binding

The methodology was adapted from a previous study conducted in our laboratory (Kalpouzos et al., 2009b). First, correlation analyses were conducted without covariate to identify the regions with age-related decrease in metabolism that was related to the binding scores. Positive correlations were conducted across the 34 participants by performing a multiple regression in SPM5 between preprocessed PET images for which a mask of age-related decrease in metabolism was applied and binding scores. In order to pinpoint more specific binding regions, we then entered the cognitive measures that partially mediated the effect of age on binding (revealed by the above-mentioned regression analysis; Section Behavioral data analysis) as covariates in a new model. If the brain areas that were initially correlated with binding scores ceased to be so, we would conclude that these regions were linked to the cognitive functions we entered as covariates. By contrast, if brain regions remained correlated with the binding scores, we would conclude that these regions were associated with binding *per se*.

RESULTS

BEHAVIORAL RESULTS

For all results, correlations were in the expected direction, with negative correlations between age and scores and positive correlations between age and time indicating a deleterious effect of aging on scores and time, and positive correlations between scores and other scores, and negative correlations between scores and time indicating shared variance for both measurements.

Effect of age on binding and other cognitive functions

A negative correlation between age and binding scores revealed that age had a deleterious effect on binding ($r = -0.68$, $p < 0.001$, see **Figure 2**). It also had a deleterious effect on inhibition ($r = 0.49$, $p < 0.001$), updating ($r = -0.37$, $p < 0.005$), the central executive ($r = -0.36$, $p < 0.005$), and processing speed ($r = -0.46$, $p < 0.001$). There was a marginal correlation between age and shifting ($r = 0.22$, $p = 0.06$).

Cognitive correlates of binding in working memory

Correlations are reported in **Table 2**. Significant correlations were found between binding scores and inhibition ($r = -0.49$, $p < 0.001$), shifting ($r = -0.34$, $p < 0.005$), updating ($r = 0.27$, $p < 0.05$), the central executive ($r = 0.35$, $p < 0.005$) and

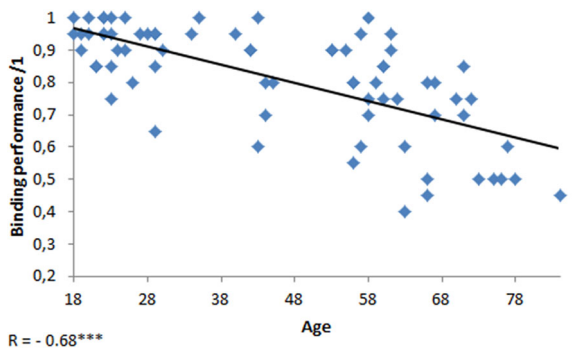

FIGURE 2 | Scatterplot of the performance at the binding task as a function of age. ***$p < 0.001$.

[1]http://www.fil.ion.ucl.ac.uk/spm

Table 2 | Correlations between other cognitive functions.

Cognitive function	Inhibition	Shifting	Updating	Central Executive
Inhibition	–			
Shifting	0.19	–		
Updating	−0.30*	−0.12	–	
Central executive	−0.30*	−0.17*	0.59***	–
Processing speed	−0.33**	−0.42***	0.26	0.24

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

processing speed ($r = 0.55$, $p < 0.001$), with better performances on these tasks associated with better performances on the binding task.

Forward stepwise regression

The results of the forward stepwise regression are reported in **Table 3**. The five variables that correlated with binding performance and with age (shifting, inhibition, updating, central executive and processing speed) were included as potential explanatory variables. This analysis showed that the variance in the processing speed (first step) and inhibition (second step) measures accounted for a significant proportion of the variance in the binding measure (i.e. 40%).

NEUROIMAGING RESULTS

Table 4 shows the brain regions in which ^{18}F-FDG uptake significantly correlated with age (**Table 4A**) and binding (**Table 4B**). Results are illustrated in **Figure 3**.

Negative correlations between ^{18}F-FDG uptake and age

Negative correlations were found between age and FDG uptake mainly in frontal cortex, and extended to temporal and parietal areas (**Table 4A**).

Positive correlations between ^{18}F-FDG uptake and binding

Positive correlations were found between binding performance and FDG uptake in the medial frontal, prefrontal, anterior and middle cingulate cortices on both sides, and in the left insula (**Table 4B**).

Partial correlations between ^{18}F-FDG uptake and binding (with other cognitive functions partialed out)

When inhibition and processing speed were statistically controlled for, no brain area remained correlated with binding performance.

Table 3 | Forward stepwise regression on binding accuracy with complementary cognitive scores and age for the whole sample.

Binding		R^2	Beta	F	p
Step 1		0.30		29.77	***
	Processing speed		0.55		***
Step 2		0.40		23.32	***
	Processing speed		0.43		***
	Inhibition		−0.34		***

***$p < 0.001$.

DISCUSSION

This study sought to explore the effect of age on the ability to bind individual features together, and to unravel the cognitive and cerebral substrates of this effect. We investigated binding using a task where individuals were asked to recognize newly created associations, and which minimized the short-term maintenance of these associations in WM. Older adults performed more poorly than younger individuals on the recognition of bound features, and the decline in binding was found to be mainly explained by an age-related decline in processing speed and executive functioning, particularly in inhibition. In accordance with a previous study conducted by Kalpouzos et al. (2009a), neuroimaging analyses showed an age-related decrease in ^{18}FDG uptake in the superior, medial and inferior frontal, anterior and middle cingulate cortices, as well as in the parietal and temporal areas, bilaterally with left-sided predominance. Among these areas, the metabolism of frontal areas, the left insula and the anterior and middle cingulate cortex on both sides correlated with binding performance. Finally, when inhibition and processing speed were partialed out, no brain area remained correlated with binding accuracy.

BEHAVIORAL RESULTS

In line with the associative-deficit hypothesis (Naveh-Benjamin, 2000) and with previous results (Chalfonte and Johnson, 1996; Mitchell et al., 2000a,b; Plancher et al., 2010), we found that age had a deleterious effect on binding. The older adults' failure to recognize the associations partly arose from a previously demonstrated decline in executive functioning, particularly in inhibition, and processing speed (West and Alain, 2000; Rush et al., 2006; Wolf et al., 2014). These results are not surprising, as a failure of inhibitory processes is one of several hypotheses that have been put forward to explain the age-related decline in WM (Hasher and Zacks, 1988). Older adults have greater difficulty performing tasks with high WM demands, because they have difficulties to inhibit the processing of irrelevant internal and external stimuli. As a consequence, their WM is cluttered with useless material, and fewer resources are available for relevant information. They therefore experience difficulty focusing their attention on a specific resource-demanding task (Stoltzfus et al., 1996; Oberauer, 2005). The idea of a general reduction in processing speed has also been put forward to account for age-related changes in memory, and processing speed has already been identified as a mediator between age and various cognitive functions (Salthouse, 1996). In our study, cognitive slowing may have contributed to the binding decline among the older participants, especially since the presentation of the stimuli was so fast (participants had just 5 s to associate four letters with four spatial localizations in the learning phase, and only 4 s to respond in the recognition phase).

NEUROIMAGING RESULTS

Our results are only partly consistent with the idea propounded in the literature that age-related decline in binding is subtended by a frontohippocampal network (Mitchell et al., 2000a; Prabhakaran et al., 2000). We found a positive correlation

Table 4 | Brain areas in which ^{18}F-FDG uptake correlated with age (A) and binding (B).

MNI coordinates			*t*-value	*k*	Labeling	BA
x	*y*	*z*				
(A) Age						
−12	14	66	8.73	14566	Frontal mid bil Frontal sup bil Precentral bil Frontal sup med bil Postcentral L Supp motor area bil Parietal inf bil Frontal inf bil Temporal pole sup M Parietal sup bil Insula L Postcentral R Cingulate ant bil Cingulate mid L SupraMarginal L	6/8/9/10/13/23/24/47
−44	−44	−40	5.19	300	Cerebellum	
54	24	−2	4.09	252	Frontal inf R Insula R	45/13
(B) Binding						
6	6	28	5.08	357	Cingulate mid bil Cingulate ant bil Supp motor area bil	23/24
−6	42	52	4.71	848	Frontal sup med L Frontal mid L Frontal sup L	6/8
−30	10	−18	4.49	602	Insula L Temporal pole sup L Frontal inf L	13/47
4	66	12	4.10	563	Frontal sup med R Cingulate mid R Cingulate ant R	10/8/9

Note: k = number of voxels within the cluster. Mid = middle. Sup = superior. Med = median. Suppl = supplementary. Inf = inferior. Ant = anterior. L = left. R = right. Bil = bilateral. BA = approximate Brodmann area.

between age-related decrease in frontal lobe metabolism on both sides (Brodmann areas, BAs 6, 8, 10, 13 and 47) and binding accuracy. The exact role of frontal areas is not yet fully understood, but there is evidence that these brain areas are associated with executive control and monitoring of sensory inputs such as those activated along the visual dorsal and ventral paths for the representation of spatial relations (Shimamura, 2010) and allow short-term manipulation of these active representations (Mitchell et al., 2000a) and inhibitory control (Volman et al., 2011). Therefore, age-related decrease in frontal areas metabolism could be responsible for the difficulty that older adults have in encoding and maintaining associations over very short periods and possibly also in adopting efficient strategies to achieve task goals. Furthermore, when we statistically controlled for inhibition processes and processing speed, the correlation between these frontal areas and binding ceased to be significant. These findings indicate that reduced metabolism within the frontal lobes may disrupt inhibition processes and processing speed that may affect older adults' binding ability.

Similarly, regarding the anterior and middle cingulate cortices, firstly we found that their metabolism was correlated with binding performances, and then that this did not remain true when inhibition and processing speed were statistically controlled for, suggesting that the initial correlation was also driven by inhibition and processing speed. Some studies have suggested that the anterior cingulate cortex is recruited during error detection and the resolution of cognitive conflicts between representations (Botvinick et al., 1999), and plays a role in attentional tasks (Torta and Cauda, 2011) and dual-task conditions (D'Esposito et al., 1995). An age-related reduction of anterior cingulate metabolism may have affected older individuals' ability to detect when a letter was associated with a wrong location during the recognition phase. It may also have affected older individuals' ability to encode an object and its location at the same time, a task imposing high attentional demands that is sometimes envisioned as a dual-task condition (Castel and Craik, 2003). Our findings also suggest that reduced metabolism of the left insula was linked to the age-related binding decline. This brain area is involved in higher-order mental processes such as the bottom-up

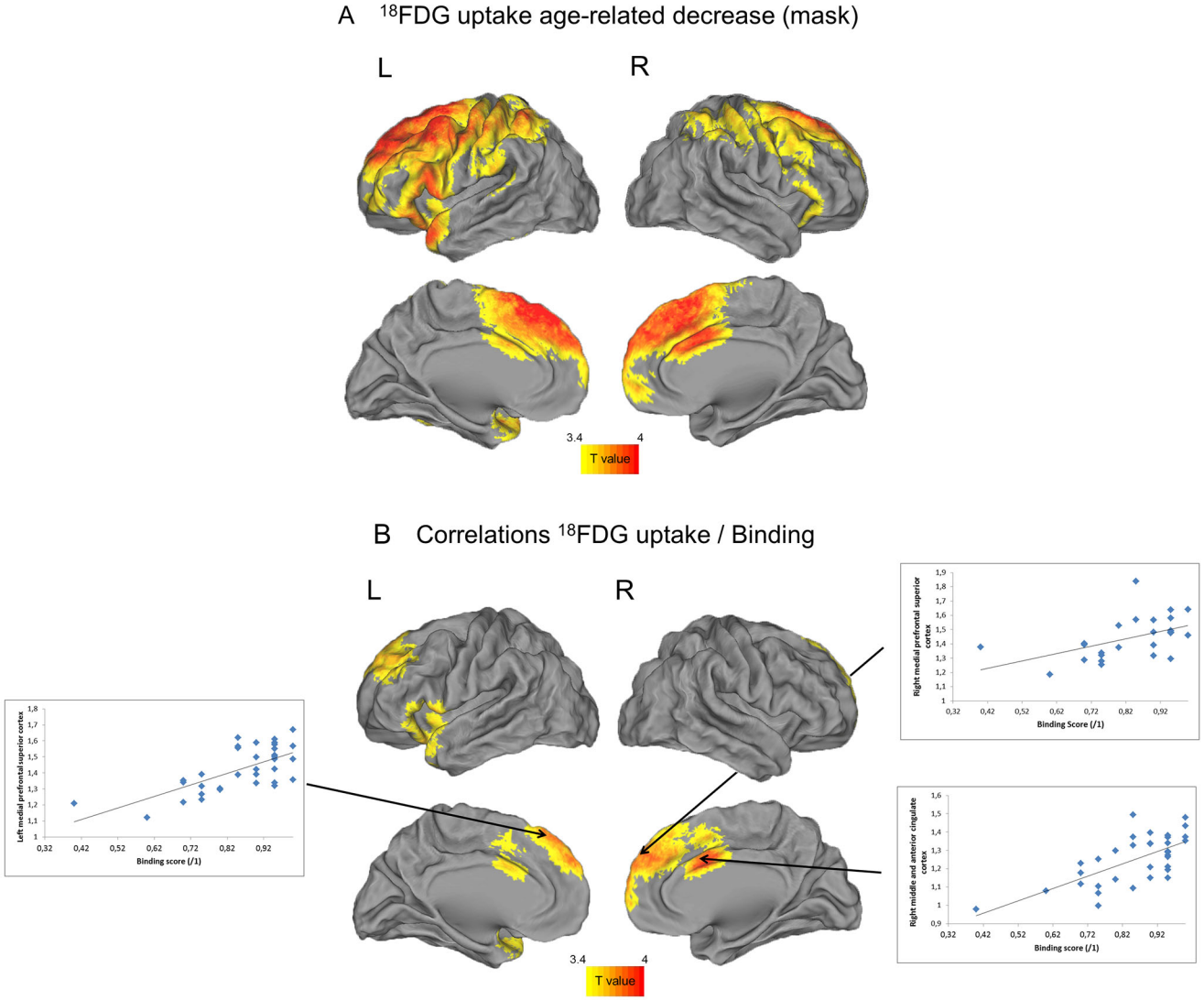

FIGURE 3 | Negative correlations between FDG uptake and age (A) and positive correlations between FDG uptake and binding limited to regions concerned by age-related changes (B). The threshold was significant at uncorrected $p < 0.001$.

detection of stimulus saliency across modalities (Menon and Uddin, 2010). The age-related metabolism decline in the left insula may have disrupted older participants' ability to focus on visuospatial stimuli and hampered the detection of letters presented in different locations in the learning and recognition phases.

Interestingly, both the anterior cingulate cortex and the insula are critical areas of the salience network, whose main function is to identify the most relevant internal and external stimuli in order to guide behavior. The role of this network is to participate in the integration of bottom-up attention switching with top-down control (Menon and Uddin, 2010). This switch in attention resource allocation is expressed in the brain by switching between the default mode network and a task-specific network (Song and Tang, 2008). Thus, a dysfunction of the salience network in aging that has already been reported in a previous study (He et al., 2014) may have affected the older participants' ability to mobilize sufficient attentional resources to focus on performing the task.

As the hippocampus was not included in the mask of age-related decrease in metabolism, which is in line with a previous study (Kalpouzos et al., 2009a), we conducted a supplementary analysis (data not shown) to test the correlations between binding performance and ^{18}F-FDG uptake for the whole brain. We found that hippocampal metabolism was not correlated with binding accuracy, which is in line with a recent study showing no evidence for a critical hippocampal contribution to item-location binding in WM (Allen et al., 2014). This may be down to the characteristics of our binding task, for which the very short (1-s) interval between the encoding and retrieval of associations may not have allowed the hippocampus sufficient time to start

forming long-term memory traces, contrary to what was observed in previous study featuring an 8 s interval (Piekema et al., 2006).

AGING ANALOGY OF MEMORY IN ASD

The relationship between executive functions, WM and binding was previously reported in ASD with other paradigms. In a study by Maister et al. (2013) several relational memory tasks were used, in which participants had to produce either autobiographical memories or recall related words. The authors found that adolescents with ASD had impaired relational memory performances that were correlated with visuo-spatial WM and shifting abilities. The present study refines these observations by highlighting, in healthy subjects the contribution of inhibition and processing speed in binding processes. One might think that the general slowness that characterizes ASD (Williams et al., 2013) also participates to the binding deficit in this pathology. In addition, the impairment of inhibition observed in some patients (de Vries and Geurts, 2014) may major these difficulties. The present study also shed light on neuronal substrates that contribute to these binding deficits. Very few functional studies on WM have been conducted in ASD and they pointed out abnormalities in prefrontal and parietal cortices. We did not report correlations with parietal regions, however we have shown that the frontal lobe, the left insula and the anterior and middle part of the cingulate cortex underpinned binding decline with age. This is a very interesting result considering structural and functional abnormalities of frontal lobe and anterior cingulate cortex in ASD. Studies focused on the attentional networks reported abnormal anterior cingulate cortex activation in ASD (Agam et al., 2010; Fan et al., 2012) that may reflect neural dysfunctions in the executive control of attention. Neuroimaging investigations on WM also reported decreasing activation in prefrontal regions including the anterior cingulate during in a mental rotation task (Silk et al., 2006) and medial prefrontal regions during a one back color matching task with increasing cognitive load (Vogan et al., 2014). In light of this literature, the present data suggest that the binding deficit observed in ASD may result in part from difficulties in top-down control with reduced higher cognitive integration of complex situations.

CONCLUSION

This study provides strong evidence in favor of an age-related binding decline that may partly stem from the age-related slower processing and disruption of executive processes, particularly inhibition. The older adults appeared to be disadvantaged when intentional processing was needed, which is in line with the age-related disruption of the frontal lobes. The neuroimaging analyses argued in favor of this idea and also suggest that an age-related reduction of metabolism in the left insula and in anterior and middle cingulate cortices also subtend binding decline. This pattern of results contributes to reinforce the aging analogy of memory in ASD from both a behavioral and neuronal point of view. First, processing speed is a cognitive function thought to be concerned in ASD and we could expect that it may also participate to the integration deficit. Second, the key role of the frontal lobe, the left insula and the anterior cingulate cortex into the genesis of these deficits in integration highlights the possible contribution of these areas to process complex situations in ASD.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fnhum.2015.00090/abstract

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Memory integration in the autobiographical narratives of individuals with autism

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INTRODUCTION

As part of a unifying theory of autism, Ben Shalom (2009) proposed that while procedural, perceptual and semantic memory functions are intact in Autism Spectrum Disorder (ASD), the more integrative level of episodic memory is impaired. According to Ben Shalom, this reduced integration may be due to the reduced function of the medial prefrontal cortex (mPFC), which may also explain the reduced integration found in motor, sensory-perceptual and emotional processes in ASD. The present review examines this hypothesis, by focusing on evidence regarding autobiographical memory (AM) episodes in ASD—arguably the highest form of memory integration processes.

Most research on memory in ASD thus far has focused on memory for experimentally-presented stimuli (Lind, 2010; Boucher et al., 2012). The present paper builds on this literature to examine the rich evidence that has recently accumulated from in-depth, systematic studies of AM in ASD—memories of personally-related events that are naturalistically accumulated over a person's lifetime. Of note, research on AM is limited in its focus on memories that cannot be as readily verified (but see Bruck et al., 2007), and in its reliance on high-functioning verbal individuals. Nonetheless, studies of AM provide us with an unparalleled perspective on the naturalistic process of memory integration in ASD. Specifically, this review aims to determine how well memory episodes are integrated in ASD; which elements become integrated and which do not; whether the ability to form integrated, episodic memories relates to other cognitive and emotional capacities; and how this pattern of integration changes over time.

Abbreviations: AM, Autobiographical Memory; ASD, Autism Spectrum Disorders; AS, Asperger Syndrome; mPFC, medial Prefrontal Cortex; TD, Typically Developing.

SEMANTIC AND EPISODIC AUTOBIOGRAPHICAL MEMORY (AM)

The declarative memory system comprises semantic and episodic components. Semantic memories are memories of timeless, de-contextualized facts. Episodic memory refers to personal events recollected in the context of a particular time and place, with some reference to oneself as a participant in the episode (Tulving, 2002). Thus, episodic memories involve two functions: the ability to bind different perceptual elements; and, in humans, the ability to perceive of oneself within this context. On a neurobiological level, episodic memory storage and retrieval are thought to involve the interaction of cortical association areas, in which basic sensory information regarding what occurred and where is stored; the hippocampus, which binds these elements into cohesive memories of individual events; and the mPFC, which further contextualizes these events into schemas, such as the self (Preston and Eichenbaum, 2013).

AM refers to memory for information pertaining to the self; and while it is often viewed as overlapping with episodic memory, the two are not synonymous (Gilboa, 2004). Episodic memory is a memory system, while AM is a type of content (Gardiner, 2008). Thus, episodic memory functions can encompass both AM and simple phenomena that do not necessarily represent self-relevant information (e.g., source memory). At the same time, AM in fact comprises of both semantic and episodic knowledge (e.g., semantic knowledge of one's date of birth, alongside an episodic memory of one's last birthday).

In children with ASD, both semantic and episodic AM is reduced (Bruck et al., 2007; Bon et al., 2012; Goddard et al., 2014), though by adulthood, adults with ASD show a spared memory for semantic AM, alongside reduced episodic AM (Klein et al., 1999; Crane and Goddard, 2008). These studies suggest that as semantic AM may grow in ASD, episodic AM impairments are pervasive. These results fit with the general memory profile in ASD, viz., spared semantic memory alongside difficulties with episodic memory, which is found across experimental studies (Boucher and Bowler, 2008). The present review concerns itself primarily with episodic AM in ASD, though semantic memory will be discussed as it relates to the content of autobiographical narratives.

EPISODIC SPECIFICITY AND NARRATIVE INTEGRATION

The most common marker of successful episodic AM integration is its degree of specificity: to what extent is the memory vivid? Memory specificity is considered a marker of hippocampus and mPFC re-engagement during memory retrieval (Piolino et al., 2009). Memories are coded

as "specific" if, in response to a cue, participants provide a narrative that is specific in time and place (e.g., "on my last birthday I went to Yogurtland with friends"); rather than a vague or repetitive occurrence. Using several variants of this task, autobiographical narratives in ASD have consistently been shown to be reduced in specificity, compared with control participants, in every reported study (Goddard et al., 2007, 2014; Crane and Goddard, 2008; Crane et al., 2009, 2010, 2012, 2013; Tanweer et al., 2010; Brezis et al., 2012; Chaput et al., 2013; Maister et al., 2013). In some cases, AM retrieval in individuals with ASD than is also slower and more effortful than for control participants (Goddard et al., 2007; Chaput et al., 2013).

More broadly, the narrative structure of AM in both children and adults with ASD has been found to be reduced in integration. The personal narratives of adults with ASD are less likely to have an organizing high-point and resolution (McCabe et al., 2013); and those of children with ASD are more likely to resemble a list of actions or descriptions than a goal-directed sequence (Goldman, 2008). Furthermore, both children and adults with ASD employ fewer causal connectors and evaluations and less complex syntax in their personal narratives than TD controls (Losh and Capps, 2003, 2006; King et al., 2013; McCabe et al., 2013). Together, these studies point to a general impairment of AM integration in ASD, manifest both in reduced specificity and narrative structure.

MEMORY CONTENT

The richness of autobiographical narrative data allows an examination not just of what is missing from the personal memories of individuals with autism, but also of what they include. Early studies found that both the published and experimentally-induced autobiographical narratives of adults with autism included very concrete, visually-oriented reports (Hurlburt et al., 1994; Frith and Happé, 1999); and this finding was further replicated in a study of children's narratives (Losh and Capps, 2006; but see Boucher, 2007 and Ben Shalom et al., 2010 for a conflicting case study). Indeed, these findings fit with Ben Shalom's (2009) claim that perceptual memory, presumably subserved by a network including the rhinal cortex, is unimpaired in autism.

Further studies of the *content* of personal memories in ASD found striking differences in the topics raised by individuals with ASD and TD controls. For instance, youth with ASD are less likely to mention humans (e.g., family members), and more likely to mention non-humans, than TD youth (Brezis et al., 2012; Chaput et al., 2013). Given that difficulties in social-emotional processing are considered a core symptom of ASD, it is not surprising that individuals with autism have a reduced memory for social and emotional content (Souchay et al., 2013; Brezis et al., 2014). Beyond their reduced mentions of self and others, children and adults with ASD consistently make fewer evaluations regarding their own, or others' mental states (Losh and Capps, 2003, 2006; Brezis et al., 2012; Brown et al., 2012; Bang et al., 2013; King et al., 2013).

The reduced focus on self and others and increased focus on fictional characters in the personal narratives of individuals with autism is echoed in naturalistic, ethnographic studies of autism. During dinnertime conversations, youth with autism are more likely to spontaneously recount a pre-existing narrative they read or viewed, than a personal event they experienced, compared with their TD interlocutors (Solomon, 2004). Furthermore, ASD individuals' personal interests in finance, dinosaurs, and religious narratives, or even their tendency to hoard, can become woven into their identities and sense of self (Nickrenz, 2007; Sirota, 2010; Brezis, 2012; Skirrow et al., 2014). Returning to Ben Shalom's hypothesis, spared semantic memory in individuals with high-functioning ASD may indeed serve them as a compensatory mechanism for episodic AM. Further research is needed to understand the ways in which semantic knowledge becomes integrated into their personal memories and identities.

COGNITIVE CORRELATES OF EPISODIC AM

Different cognitive functions have been hypothesized to affect AM patterns in ASD. Impairments in executive functions in ASD, viz., the ability to bind and integrate information (Bowler et al., 2014), correlate significantly with AM performance (Maister et al., 2013; Goddard et al., 2014). Further, AM ability is related to Theory of Mind (Adler et al., 2010; Crane et al., 2013) and emotional understanding (Losh and Capps, 2003); presumably because the ability to understand others' thoughts and feelings may help one understand that one's own experiences change over time. Emergent findings point to a strong relation between difficulties in AM and future thought in ASD, which may be subserved by a common difficulty in binding and constructing mental events (Lind et al., 2014).

Other basic functions of memory, such as visual, verbal and working memory are not associated with AM (Crane et al., 2013; Goddard et al., 2014). And while reduced AM is considered a symptom of depression, depressed mood is not associated with AM in ASD (Crane et al., 2013). Further, though language ability relates to performance on AM tasks (King et al., 2013), difficulties in AM appear to extend beyond language difficulties (Losh and Capps, 2003; Lind et al., 2014).

The relation between AM and self-understanding is more complex. In line with known atypicalities in self-knowledge and self-awareness in ASD (Lind, 2010; Tanweer et al., 2010), adults with ASD have been found to extract less meaning from their personal memories (Crane et al., 2010), and were less likely to organize their self-related memories around the self (Crane et al., 2009). These findings suggest a failure to use the self as an effective memory organizational system in ASD. Further research should clarify whether reduced self-concept leads to reduced AM or results from it (Lind et al., 2014).

EPISODIC AM FOR RECENT AND REMOTE EVENTS

Examining episodic AM for different periods in participants' lifetimes, studies have found that AM in ASD follows typical patterns of memory deterioration—with more specific memories for recent than remote events—in both adults (Crane and Goddard, 2008; Tanweer et al., 2010) and children (Bruck et al., 2007; Goddard et al., 2014; but see Bon et al., 2012). Interestingly, Crane and Goddard (2008) found that adults with ASD lack the typical increase of memories around adolescence

years (the "reminiscence bump") that is associated with identity-building memories. Further cross-sectional and longitudinal research is needed to replicate and extend these findings.

CONCLUSIONS

According to Tulving (2002), episodic memory is a "late-developing, and early-deteriorating past-oriented memory system, more vulnerable than other memory systems to neuronal dysfunction" (p. 5). Thus, it is perhaps not surprising that in autism, episodic AM is reduced in specificity and structural integration. Nevertheless, an examination of the autobiographical narratives of individuals reveals certain unique characteristics that are shaped by their specific difficulties with social-emotional processing and integration, possibly pointing to a differently configured memory system that may require its own descriptive terminology (Mottron et al., 2008). The narratives of individuals with ASD tend to focus on perceptual or semantic details, favoring pre-structured narratives over lived, emotional experiences. And AM impairments are related to underlying difficulties with integration and emotional understanding, but are not consistently related to other psychological functions, such as depressed mood. As our understanding of AM in ASD deepens, it will be necessary to further delineate the ways in which the memory profile of ASD overlaps and differs from that of other neurological conditions (such as depression, amnesia and other developmental disorders), in order to identify unique and common processes of memory in ASD.

The rich findings regarding AM in ASD call for several additional avenues of research. First, while reduced episodic AM integration suggests atypical engagement of the hippocampus and mPFC during memory processes (Ben Shalom, 2009), and several studies have shown reduced mPFC engagement during self-related processes in ASD (see Uddin, 2011 for a review), no neurobiological study to date has directly examined AM in ASD. Second, it is necessary to further examine the complex relation between AM, self-understanding and identity, both through careful experimental research that disentangles these components, and through further naturalistic studies that seek to determine how they are *integrated*. Finally, more longitudinal research, especially around the "reminiscence bump" in adolescence, is needed in order to track the developmental trajectory of semantic and episodic AM in ASD (Bon et al., 2012). Together, these studies will enable us to develop subtle interventions to strengthen the memory integration of individuals with autism, while maintaining their unique characteristics and supporting their self-identity.

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Visual integration in autism

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Atypical integration is a topic of debate in the autism literature. Some theories suggest that altered perception in autism spectrum disorder (ASD) is due to a failure to integrate information from meaningful context into the final percept, whereas others suggest that integration of low-level features is impaired. Empirical research which forms the basis for these theories has failed to account for higher-level influences not inherent in the stimuli (i.e., instructions and goals) and assess integration at both lower and higher perceptual levels within the same task. Here, we describe how perceived expectations and goals of a task can modulate the processing of low-level visual input via the medial prefrontal cortex (mPFC). We then go on to illustrate how future research might assess the relative contribution of both low and high-level processes using the same paradigm. We conclude by recommending that when results appear conflicting, consideration of the relative strength of low-level input vs. feedback or high-level processes may prove helpful. Importantly, research in this area needs to more broadly consider the various influences on perception, and find better ways to assess the contributions of early and later visual processes.

Keywords: autism, vision, integration, feedback, low-level, high-level, attention, stereopsis

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Sensory abnormalities are observed in a large proportion of people with Autism Spectrum Disorder (ASD; Geschwind, 2009) and many clinical, parental, and personal reports focus on atypically intense attention to, or avoidance of, sensory information (Williams, 1998; Bogdashina, 2003; Grandin, 2006; Ben-Sasson et al., 2009). Although people with an ASD diagnosis exhibit superior performance in some tasks, such as block design and finding embedded figures (Muth et al., 2014), deficits are also shown in simple visual tasks such as orientation or motion detection (Simmons et al., 2009; **Figure 1**). There is considerable disagreement regarding the mechanisms underlying atypical perception, however a common theme is abnormal integration (Dakin et al., 2005; Simmons et al., 2009). When the ASD literature discusses visual integration, it is often within the reference frame of higher-level information derived from the stimulus such as its meaning or surrounding context. For instance, Plaisted et al. (1999) note that individuals with ASD do not exhibit a global interference effect of contextual information in a divided attention Navon-type task (Navon, 1977). However, even when stimuli appear devoid of meaning there may be higher-level influence in the form of personal goals or task expectations. Current perceptual theories of ASD disagree as to whether integration is affected at early (i.e., lower) or later (i.e., higher) levels of visual processing. To date, there has been little success in disentangling these experimentally. This paper will first give a brief overview of the visual pathway and then outline how current theories attempt to explain atypical visual integration in autism. We then discuss important considerations that need to be addressed in this area of research; specifically, how an individual's goals or understanding of a task can exhibit modulatory feedback upon low-level vision through the medial prefrontal cortex (mPFC). Finally, we provide an example of how integration at both lower and higher levels could be assessed independently in the same task.

Visual perception is commonly conceptualized as hierarchical, with inputs arriving in area V1 from the thalamus, and being successively processed in a number of different areas. Neural response properties vary along the visual hierarchy, with latency increases that imply more complex processing when moving from earlier to later areas such as the inferotemporal cortex (Lamme and Roelfsema, 2000). Receptive field sizes also increase, implying convergence of inputs from lower- to higher-level areas (Poggio and Riesenhuber, 1999; Rao and Ballard, 1999).

Low-level integration begins to take place once simple local features, such as the orientation and location of lines and edges, are extracted from primary visual input in areas V1 and V2 (Hubel and Wiesel, 1962). The outputs of these areas, which are comprised of local representations, are then gradually consolidated, binding together different stimulus features to represent a global or overall shape at successive levels of the visual system (Kourtzi et al., 2003; Rousselet et al., 2004; Roe et al., 2012). For instance, in **Figure 1B**, the orientation of each line in both the simple/component and complex shapes would be extracted by early visual filters. These components would be combined at a later stage, within the lateral occipital cortex (Kourtzi and Kanwisher, 2001), to form the overall shapes.

Once simple visual features are consolidated, in feedforward models of vision, their signals are projected to higher levels of the cortex such as the inferotemporal and prefrontal areas, where sensory input is integrated with attention and task demands. Areas such as the orbitofrontal cortex and mPFC are thought to play a central role in the evaluation of potential outcomes (Shalom, 2005; Bar, 2007) by limiting the number of possible representations for a viewed object (Bar et al., 2006), assisting with identification of objects, and categories (Tanaka, 1996). Alternative conceptualizations of the visual system (e.g., Hochstein and Ahissar, 2002) propose that this higher level processing occurs early and projects information downsteam as needed, biasing early visual processing from the start.

In **Figure 1B**, the extraction and integration of component edges is influenced by possible representations of the overall shape (i.e., a house or a rectangle with a triangle on top). If an individual identifies the target for which they are searching as a "house" this will increase and reinforce attention towards the outline of this shape. However, integration of irrelevant distractor features, such as color, may impair the identification of the house.

Integration in ASD

There is consistent evidence of an atypical visual processing style of ASD (Dakin and Frith, 2005; Behrmann et al., 2006; Simmons et al., 2009), commonly manifesting as deficits in global processing (i.e., processing of the whole object or scene) or superior low-level processing. Most current theories of ASD attempt to provide explanations for this atypical integration.

Weak central coherence theory (WCC; Happé and Frith, 2006) proposes that individuals with ASD have a detail-focused cognitive style where they are unable to bind details into more global forms. There is also a bias away from integrating higher-level information such as context. In support, individuals with ASD have been shown to exhibit faster performance in tasks involving embedded figures (Shah and Frith, 1983; Jolliffe and Baron-Cohen, 1997) and block design (Shah and Frith, 1993), where a lack of global feature-binding would be advantageous.

In contrast to WCC, the enhanced perceptual functioning (EPF) hypothesis (Mottron and Burack, 2001) focuses on evidence that low-level perception is enhanced in people with ASD. Mottron et al. (2006) suggest that the integration of "higher-order" information—which is automatic in typically developing/developed (TD) populations—is optional in those with ASD, meaning that the default setting of perception is more locally-oriented. Basic visual functioning may be superior in ASD populations but low-level integration of features may be impaired. This is supported by the literature that has demonstrated that although people with ASD appear to have intact or superior processing of simple dynamic stimuli (Bertone et al., 2005; Pellicano et al., 2005), they exhibit poor performance when required to combine simple visual features such as in texture-defined second-order gratings (Bertone et al., 2005) or motion coherence tasks (Milne and Szczerbinski, 2009; Koldewyn et al., 2011).

These theories conceptualize high-level and low-level processes as separate entities. However, these processes are not so easily dissociable; neurons in the visual cortex receive feedforward information (from the retina), feedback (from higher cortical areas) and have inputs from lateral connections. Research has increasingly focused on examining the interplay between these sources of information using a variety of tasks including figure-ground segregation (Vandenbroucke et al., 2009), degraded face and object recognition (Loth et al., 2010), and contextual modulation caused by collinear facilitation and contour integration (Jachim et al., 2015). All found a difference in modulatory feedback in individuals with autism. The exact nature of this difference in ASD is yet to be determined: it has been proposed to be both enhanced (Vandenbroucke et al., 2009), and reduced (Loth et al., 2010; Jachim et al., 2015).

Hypo-prior theory (HPT) has framed the perceptual atypicalities found in ASD in terms of a failure to incorporate modulatory feedback. HPT proposes that people with ASD may perceive the world differently due to attenuated priors (Pellicano and Burr, 2012). Priors encode biases towards attributes that are most likely, based on previous experience. They can improve the efficiency of neural computations by acting as constraints and reducing noise or error. Reduced priors lead to a decrease in the influence of context and prior knowledge causing superior performance in certain tasks. Like EPF, HPT predicts that people with ASD ought to rely more heavily on low-level sensory information, but does so by implicating reduced feedback. However, high-level information may come in a number of different forms (see Brock, 2012), and in its current form, HPT only considers perceptual sources of high-level information.

Similar to HPT, Lawson et al. (2014), Sinha et al. (2014) and Van de Cruys et al. (2014) propose prediction-based explanations for ASD. Here, the relative influence of prior beliefs (high-level information) compared to sensory evidence (low-level information) is controlled by the precision of predictions made

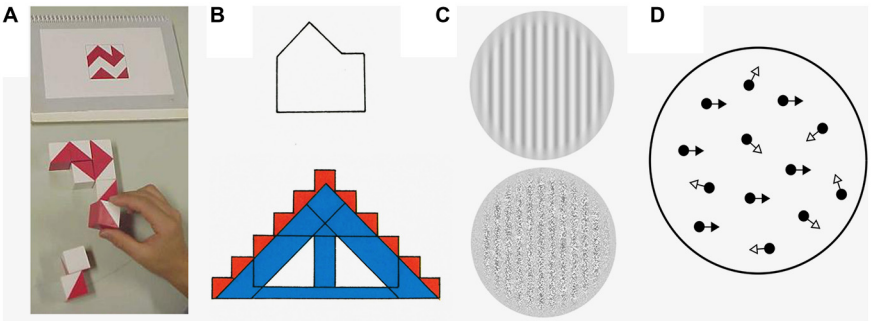

FIGURE 1 | Examples of the stimuli that are used to explore low- and high-level visual integration in autism spectrum disorder (ASD). (A) The block design task (Wechsler, 2011). This task requires line drawings to be broken up into logical units, so that individual blocks can be used to reconstruct the original design. Here the shape above is constructed of the blocks below. **(B)**The embedded figures test (Witkin et al., 1971). Here, the participant is asked to find a simple component shape (above, in the example given) within a complex design (below). There is an increase in performance in both the block design task and the embedded figures test if there is a lack of automatic global processing. **(C)** First and second order gratings. Bertone et al. (2005) asked participants to determine the orientation of two different types of gratings, one which only contained first-order information (upper grating, which is composed of changes in luminance) and the other contained second order information (lower grating, which consists of differences in texture). **(D)** Global motion perception using random-dot kinetograms (RDKs). When presented in a motion sequence, a certain proportion of the dots in an RDK move in the same direction (signal dots; black arrows) whilst the rest move in a random direction (noise dots; white arrows)—the participant is asked to specify the perceived overall direction of the stimuli. Processing both second-order visual stimuli and RDKs involves integrating information from multiple visual channels and should be worse if there are deficits in low-level visual integration.

by higher-level brain areas. Sensory evidence that has not been predicted is termed "prediction error". The precision of these prediction errors is thought to determine the relative weight of high- and low-level information. Perceptual atypicalities in ASD have been proposed to occur both due to poor prediction (Sinha et al., 2014) and an over weighting of prediction errors, leading to missing of patterns and regularities (Van de Cruys et al., 2013, 2014). In **Figure 1B**, for instance, the integration of the larger shape has not been reliably learnt from previous experience. A further alternative explanation proposes that the pattern of impairment is due to increased precision of low-level input, leading to over-reliance on sensory signals (Friston et al., 2013; Lawson et al., 2014). Thus, there is a reduction in the weighting of higher-level information and less suppression of sensory information by prior information. In **Figure 1B**, for people with ASD, there might be reduced suppression of the local features by the larger shape.

In summary, with the exception of EPF, all theories discussed illustrate how a failure to incorporate feedback correctly can result in atypical visual integration. However, most empirical research in this area has considered meaning to be inherent in the stimulus—for instance, a stimulus may be immediately identifiable or similar to stored perceptual representations in memory. However, even when a stimulus appears to be absent of meaning (e.g., abstract lines), visual processing can be affected by the viewer's own goals or their interpretation of task expectations.

The Role of Goals and Expectations in Visual Feedback

An individual's goals and expectations can affect attention, reduce the time taken to respond to stimuli and increase performance (Bravo and Nakayama, 1992). Attention to a particular location, or feature, can be characterized in terms of enhancement of neural responses (gain control) and suppression of neural responses outside the focus of attention (Motter, 1993; Chen et al., 2008). The enhancement of neural responses can be observed throughout the visual cortex (Motter, 1993) and the temporal lobe (Tanaka, 1996; Liu et al., 2009). The magnitude of the attentional effects throughout the visual system depends upon the nature of the task and the configuration of the stimulus (Watanabe et al., 1998; Ito and Gilbert, 1999). Li et al. (2004) trained monkeys to indicate the central point on a line and discriminate misalignment between the same lines. Critically, although identical stimuli were used in both tasks, the patterns of cell activity depended on which task was being performed. That the understanding of a task can vastly change activation patterns resonates with the effects of task instructions on cognitive tests in those with ASD (White, 2013).

Task instructions have been shown to have a differential effect on performance by those with ASD on the Navon task (Plaisted et al., 1999); when individuals were not told which level (i.e., global or local) to search for the target, those with ASD were better than typically developing (TD) children at finding the target at the local level. However, where they were told to search only one level to identify the target, both groups were faster when identifying the larger global letter than the local letter. As previously has been argued (Shalom, 2005; Bzdok et al., 2013), it is specifically under circumstances of ambiguity where those with ASD may perform differently. The mPFC may serve a specific purpose by means of establishing an order of importance (i.e., global) in TD individuals whereas it does not do so in the ASD group. When attention is directed to a single level, individuals with ASD do not perform differently as the possibilities are minimized. When cued to look for a specific

feature, the selectivity of neuronal receptive fields in early visual area V1 changes to a form which approximates the cued feature (McManus et al., 2011). Even at the earliest stages of visual processing, neurons can be dynamically adjusted to be selective for complex geometries from top-down influences. Returning to **Figure 1B**, the failure to find the hidden figure might reflect that the entire shape is bound by a high-level automatic grouping mechanism. Once enough processing has occurred to identify the overall complex shape the filters of the early visual system can adjust to become more selective for these salient features, effectively hiding the embedded figure. It has been observed that the frontal and parietal brain areas (including the mPFC) exhibit reduced activation during the embedded figures task in ASD populations compared to controls (Lee et al., 2007; Damarla et al., 2010; Spencer et al., 2012). Previously, these areas were thought to be involved in suppression of global perceptual bias (so the reduced activation of the ASD group may be interpreted as a sign that the global form of the complex visual figure was processed to a lesser extent by the ASD than control children; Lux et al., 2004; Lee et al., 2007)—however, this can also be interpreted as reduced activation of the feedback pathways.

High-level processing is key to understanding perception and the back projections that are present throughout the visual system are likely to play an important role in the integration of low-level with high-level information. Until recently, research on visual perception in ASD has tended to focus on *either* low-level vision or higher-level influences (Simmons et al., 2009). Since differences in visual processing in individuals with ASD are not isolated to either the higher (global) or low-level (local) domains, perhaps a more parsimonious explanation is that interaction between low- and high-level mechanisms is less developed in this population. Thus, the theories that emphasize the interaction between low- and high-level mechanisms are a welcome development and are consistent with evidence that indicates that brain connectivity is disrupted in ASD (Barttfeld et al., 2011; Wass, 2011; Samson et al., 2012). Enhanced resource allocation in early visual areas, due to a lack of suppression of irrelevant details could explain the heightened performance of those with ASD in low-level visual tasks. However to-date, there is little evidence to discriminate between the specific alternatives (see Skewes et al., 2015; Westerfield et al., 2015, for two relevant studies). One paradigm that may allow differentiation between the contributions of feedforward and feedback processing in visual perception is shape constancy.

Example: Shape Constancy

Shape constancy is the phenomenon where regardless of an object's orientation, the shape of the object is perceived as the same (**Figure 2**). Ropar and Mitchell (2002) asked participants to replicate the retinal projection of a tilted circle. When participants knew the true shape, both ASD and TD participants increased the circularity of their reproduced shape, as predicted by shape constancy. However, in the ASD group this increase was significantly smaller. They concluded that perception in ASD was less influenced by prior knowledge, which can in the present context be interpreted as a reduction in the modulatory feedback. For TD participants, the higher-level information interfered with the task whereas participants with ASD reported veridical perception more easily (see, Liu et al., 2011, for a brain imaging result consistent with this interpretation).

However, shape perception and constancy can be elicited by both low- and high- level visual cues. Low-level cues to slant such as linear perspective (Howard et al., 2014) and binocular disparity (Hibbard et al., 2012) can induce shape constancy, even when the participant does not know the true shape. Ropar and Mitchell (2002) allowed binocular viewing, which may have caused shape constancy from binocular disparity. This leads to a second possible explanation of Ropar and Mitchell's findings; individuals with ASD may be less able to utilize disparity due to an increased prevalence of deficits with convergence or strabismus (Scharre and Creedon, 1992; Milne et al., 2009). The reduction in shape constancy observed in ASD may be explained by an inability to use

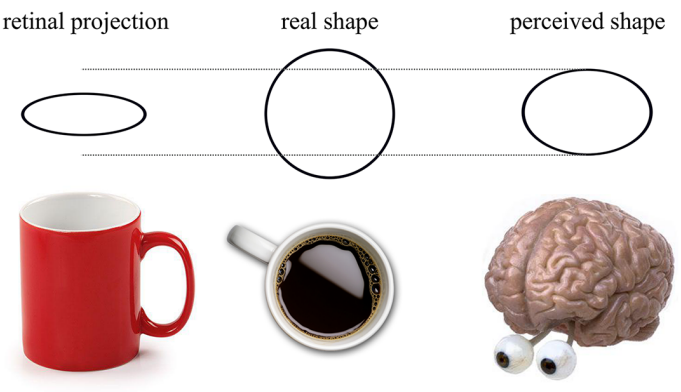

FIGURE 2 | When a cup is viewed obliquely, the retinal projection of the lip of the cup forms an ellipse. Despite the apparent transformation, the viewer knows that the "real shape" of the lip of the cup is circular—this is the phenomenon of shape constancy. When asked to reproduce the retinal projection of the ellipse, shape constancy means that the observer is unable to accurately determine the true retinal projection. Instead, the observer will reproduce what is labeled the "perceived shape", represented in the above image as being between the retinal projection and the real shape.

low-level cues to slant rather than a reduced effect of prior knowledge.

A final possibility is that feedback connections caused prior knowledge of true shape to change perception by adjusting receptive fields. It may be the case that people with ASD *were* influenced by prior knowledge but its modulatory effect was different compared to TD groups. For instance, prior knowledge may cause a decrease in shape constancy elicited by binocular disparity for participants with ASD but actually increase the efficacy of disparity for the TD group.

We aim to highlight the importance of considering perception as an interactive and dynamic process where the integration of low- and high-level sources of information may differ between populations. Research in this domain is often unable to come to a consensus due to conflicting data. Methodological differences may account for these discrepancies. For instance, some existing results appear dependent on participant characteristics such as IQ (Jarrold and Brock, 2004), on task demands (e.g., with the Navon task; Navon, 1977) or on the exact instructions given (Plaisted et al., 1998; Ropar and Mitchell, 1999, 2001). Each of these changes will produce different top-down modulations of low-level mechanisms, relating to different connectivity pathways between frontal and visual regions (for a review, see Martínez-Sanchis, 2014). Within the context of shape constancy, it has been found that results depend on how subjects interpret instructions. Even when they are instructed to replicate the retinal projection, they may believe they are being asked to replicate a shape that matches the actual inclined shape (Howard et al., 2014). Differing interpretation of instructions can change expectancies, modulating the importance and/or salience of different features of the stimulus. This will affect the strength and nature of the low-level processing and modulatory feedback. We therefore recommend that when results are conflicting and appear dependent on participant characteristics, task demands or stimulus features, considering the results in light of possible interplay between low- and high-level processes is helpful.

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Neurobiological foundations of multisensory integration in people with autism spectrum disorders: the role of the medial prefrontal cortex

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This review aims to relate the sensory processing problems in people with autism spectrum disorders (ASD), especially multisensory integration (MSI), to the role of the medial prefrontal cortex (mPFC) by exploring neuroanatomical findings; brain connectivity and Default Network (DN); global or locally directed attention; and temporal multisensory binding. The mPFC is part of the brain's DN, which is deactivated when attention is focused on a particular task and activated on rest when spontaneous cognition emerges. In those with ASD, it is hypoactive and the higher the social impairment the greater the atypical activity. With an immature DN, cross-modal integration is impaired, resulting in a collection of disconnected fragments instead of a coherent global perception. The deficit in MSI may lie in the temporal synchronization of neural networks. The time interval in which the stimulation of one sensory channel could influence another would be higher, preventing integration in the typical shorter time range. Thus, the underconnectivity between distant brain areas would be involved in top-down information processes (relying on global integration of data from different sources) and would enhance low level perception processes such as over focused attention to sensory details.

Keywords: autism spectrum disorders (ASD), multisensory integration, medial prefrontal cortex (mPFC), default network, temporal multisensory binding

INTRODUCTION

In people with autism spectrum disorders (ASD), the existence of aberrant sensory perceptions may be as characteristic and disrupting as the presence of deficits in communication and social cognition (Hilton et al., 2007; O'Connor and Kirk, 2008; Donnellan et al., 2013). In line with the classification established by Miller et al. (2007), the sensory processing disorders (SPD) include disturbances in sensory modulation (SM) and alterations in the integration, organization and discrimination of sensory stimuli. Individuals with these disorders exhibit inappropriate responses to sensory inputs in such a way that the activities of daily life as well as emotional and behavioral patterns are severely affected. We can identify three types of SM disorders (SMD): hyper-responsiveness, hypo-responsiveness and sensory-seeking behavior. The hyper-responsiveness to sensory stimuli implies reactions disproportionately intense, rapid or prolonged. Hypo-responsiveness is unresponsiveness or slowness to respond to specific sensory stimulation. Finally, sensory-seeking behaviors encompass prolonged or intense sensory experiences reflecting craving/fascination with some stimuli.

The majority of people with autism present SMD in various sensory channels (Baranek et al., 2007; Tomchek and Dunn, 2007; Baker et al., 2008; Ben-Sasson et al., 2009; Lane et al., 2014). Regarding visual stimuli, some of them avoid bright lights and prefer the darkness; others are able to stare at intense light stimuli; and there are people who look lengthily at objects and people (Behrmann et al., 2006; Simmons et al., 2009). At vestibular level, many people within the autistic spectrum are hypo-responsive and seek this type of stimulation by spinning and rocking themselves (Lane et al., 2011). With regard to tactile stimulation, in some of these people hyper-responsiveness to certain stimuli (the shower, cutting hair or nails, being touched) could cohabit with hypoalgesia. Lastly, with respect to responsiveness to auditory stimuli, there have been cases of hyper-responsiveness to sounds that are not unpleasant for most people together with hypo-responsiveness to auditory linguistic stimuli (Ludlow et al., 2014).

In general, most information instead of being processed through one sensory modality arrives at the brain from multiple systems and favors a decision process about convergence or segregation of the different sensory inputs. Nevertheless, many people with ASD experience serious difficulties in multisensory integration (MSI), which results in an increment of their behavioral problems and an aggravation of the nuclear symptoms related to communication. Many subcortical regions such as the brainstem (superior colliculus), cerebellum and thalamus participate in this multisensory processing, although the superior temporal sulcus and prefrontal cortex (PFC) are also involved (Ghazanfar and Schroeder, 2006). The classical convergence model considers MSI as a feedforward process of unimodal signals when firing

rate changes occur in neurons receiving convergent inputs from different sensory modalities. However, this approach does not explain sufficiently all aspects of MSI and a "temporal correlation hypothesis" has been proposed to account for a flexible setting for cross-modal interactions. It emphasizes the appearance of highly specific patterns of effective neuronal binding depending on synchronization of neural signals ("neural coherence") (for a review, see Engel et al., 2012). Thus, MSI as a consequence of neural coherence could be associated with the modulatory role of the frontal areas in temporal patterns in cortical multisensory regions. In ASD, as discussed later, the abnormal cross-modal synchronization could be at the bottom of the impairment in MSI.

Different studies dealing with the neurobiological foundations of symptoms in ASD, including SPD, point out the important role played by the PFC. The orbital and medial prefrontal cortex (mPFC) is an area which is comprised of the medial wall (medial frontal gyrus and anterior cingulate cortex) and ventral surface of the frontal lobe. The whole region (including the lateral PFC) is involved in regulating planning, decision-making and solving problems in everyday situations (Executive function). The orbital network receives sensory inputs from different modalities and participates in integrating them. The mPFC network, basically projects viscero-motor outputs through its connections to the brainstem, although it also receives a few sensory inputs. Additionally, both networks are closely connected to the thalamus and the limbic system (amygdala, hippocampus, nucleus accumbens and central striatum). It has been hypothesized that this region contributes to evaluating external events and generating autonomic or somatic changes, which would enable the choice of the best behavioral option depending on the "somatic markers". The mPFC and the anterior cingulate cortex would be involved in the evaluative component and in forming associations between sensory stimuli, responses and outcomes (Ongür and Price, 2000; Ridderinkhof et al., 2004; Bissonette et al., 2013).

The mPFC is also part of the brain's Default Network (DN), which also includes the posterior cingulate, the inferior temporal lobe and the hippocampal formation. This network is deactivated when attention is focused on a particular task and activated on rest when spontaneous cognition emerges ("Internal mentation hypothesis"), although it also seems to play an important role monitoring the environment ("Sentinel hypothesis"). Thus, if this were the case, it would contribute to the formation of integrated internal representations of the environment and the self. According to the sentinel hypothesis, in some cases the DN activity correlates positively with sensory processing tasks. When this system implicated in global attention is hypoactive, as in Balint's syndrome, just one visual object is perceived at a time, which impedes the understanding of the scene as a whole, which is just the experience narrated by several persons with ASD.

Following the hypothesis outlined by Shalom (2009), sensory processing in typically developing persons can occur at three levels: basic level, integrative level and higher-order level and networks including mPFC regulate integrative level. Sensory processing problems, especially MSI, in people with ASD could be related to the integrative role of the mPFC. The purpose of the present review was to explore this topic by exploring four issues: neuroanatomical findings; brain connectivity and DN; global or locally directed attention; and temporal multisensory binding.

NEUROANATOMICAL FINDINGS

Postmortem studies in people with ASD have revealed early postnatal brain overgrowth, especially an overabundance of neurons in the PFC, which correlated with enlarged head circumference in children under 3 years old, this being the most consistent neuroanatomical evidence in autism (Hazlett et al., 2005; Courchesne et al., 2011a,b). Subcortical areas connected to the PFC and related to sensory processing, such as the thalamus and cerebellum, exhibit functional and anatomical alterations too.

Nair et al. (2013) found reduced functional and anatomical connectivity between the thalamus and prefrontal, parieto-occipital, motor and somatosensory cortex in children and adolescents with ASD (9–17 years old). Conversely, there was a relative temporo-thalamic overconnectivity which was greater in the right hemisphere. The fronto-thalamic underconnectivity correlated with the severity of symptoms assessed with the Autism Diagnostic Observation Schedule (Lord et al., 1999). The thalamus is not only a relay station of sensory and motor information, but also seems to filter the flow of information to the cortex. This suggests its possible involvement in sensory symptoms of autism. In fact, several studies have reported reduced thalamic volume and glucose metabolism in persons with ASD (Haznedar et al., 2006; Tamura et al., 2010). Hardan et al. (2008) explored the presence of abnormalities in the thalamus comparing subjects with autism and controls and although no volumetric differences were observed between either group, metabolic differences were found. The group with autism showed lower levels of glutamate and N-acetylaspartate (a functional marker of neuroaxonal tissue), suggesting an imbalance in oxidative stress with consequent neurotoxicity. These metabolic results also correlate with sensory disturbances evaluated by the Sensory Profile Questionnaire (SPQ; Dunn, 1999).

There are strong associations between the cerebellum and the PFC, and abnormalities in both areas have been associated with the severity of symptoms (Carper and Courchesne, 2000; Kumar et al., 2010). Several studies reveal that the size of the cerebellum (cerebellum hemispheres and vermis lobes VI and VII) is significantly minor in the population with ASD when comparing with controls and there is also a reduced number of Purkinje cells (Bailey et al., 1998; Courchesne et al., 1988; Fatemi et al., 2002; Webb et al., 2009). The cerebellum participates in motor planning, which could be understood as the prediction of sensorial consequences of a motor act. This structure compares the predictions with the real consequences and learns to correct deviations. In this prediction, the cerebellar cortex would be in charge of rapid unconscious processes and, additionally, the parietal lobe would be responsible for the slow conscious ones (D'Angelo and Casali, 2013). Studies using animal models have found some empirical evidence of

the existence of two pathways to connect cerebellum and PFC (Rogers et al., 2011). The first circuit involves the dentate nucleus, brainstem (reticulo-tegmental nuclei, pedunculopontine nuclei and ventral tegmental area) and finally the mPFC. The second is from the dentate nucleus via the thalamus (mediodorsal/ventrolateral nuclei).

BRAIN CONNECTIVITY AND THE DEFAULT NETWORK (DN)

The identification of abnormal patterns of neural connectivity has proven to be one of the most promising explanatory approaches that permits one to unify cognitive theories (theory of the mind or central coherence theory), neurobiological findings and a neuropsychological perspective (Hughes, 2007). Neuroimaging methods have evidenced the presence of inter- and intra-hemispheric as well as cortico-subcortical underconnectivity in people with ASD. However, these findings coexist with data supporting just the opposite, i.e., the presence of hyper-connectivity using task-based and resting state functional connectivity (for review, see Vissers et al., 2012; Uddin et al., 2013). Functional connectivity has been studied by means of fMRI exploration of temporary associations between neurophysiological events using three approaches: regression analysis of a particular seed area; correlations analysis of multiple regions and; independent component analysis (ICA). In a systematic review, Uddin et al. (2013) indicate that the developmental perspective could contribute to conciliate these apparently contradictory results. These authors suggest that there is a shift from hyper- to hypo-connectivity in ASD with age, with two possible trajectories across adolescence: a reduced developmental increase or an abnormal pattern of functional connectivity. Coherent with the developmental perspective described above, stronger functional connectivity (ICA and seed-based) has also been found in the DN and other networks (salience, frontotemporal, motor and visual networks), predominantly in prepubertal children with ASD (Di Martino et al., 2011; Lynch et al., 2013; Uddin et al., 2013; Washington et al., 2014). There is also evidence, in adolescents and adults with ASD, of weak connectivity in long distance brain circuits such as reduced connectivity between DN nodes using correlations and ICA (Assaf et al., 2010; von dem Hagen et al., 2013; Tyszka et al., 2014).

The activity of mPFC and the posterior cingulate region, which are the midline portions of DN, correlates with internal mentation (self-referential thinking and theory-of-mind processes) and monitoring the environment for unexpected events. Spontaneous thoughts are absent and theory of mind impaired when mPFC is damaged (Mantini and Vanduffel, 2013). Although this network is intact in people with ASD, it is hypoactive in the mind's resting state, in fact the higher the social impairment the greater the atypical activity during rest (Buckner et al., 2008). With a dysmaturation of the DN in ASD, the neural integration of signals from different sensory systems seems to be impaired, resulting in a collection of disconnected fragments instead of a coherent global perception. Additionally, different studies using evoked potentials have shown that discrimination of sounds of varying complexity (simple tones, complex tones and vowels) and the cortical representation are similar to those of the control in "oddball" sequences when attending to the stimuli. In this kind of task, the standard stimuli should be ignored while the novel stimulus (the "oddball") must be attended to. On the contrary, processing is deficient when attention orienting is involuntary, especially if the stimulus is linguistic (Ceponiene et al., 2003; Dunn et al., 2008).

GLOBAL OR LOCALLY DIRECTED ATTENTION

Weak central coherence and enhanced perceptual functioning theories account for different hypotheses about perceptual processing in ASD people. In the former, it is suggested that there is an impairment in global processing, while in the latter it is proposed that the perception in ASD people is more locally oriented. Several studies using functional connectivity analyses have thrown light on the global and local level processing in people with ASD and their families (Briskman et al., 2001). One of the approaches consists of using local-to-global interference such as counting colored lines on a tridimensional object. Using this task, Liu et al. (2011) found that in the ASD group there was no global interference as revealed by the lower activation in executive brain areas and less synchronization between these regions and the visuospatial areas. When embedded figures tests or similar were used, the activity pattern in children, adolescents and adults with ASD was greater in right posterior regions (cuneus, occipital gyrus and inferior parietal areas). Finally, in visual matrix reasoning tasks (i.e., Raven matrices) greater occipital activation together with less prefrontal activity was observed in comparison with controls. Gadgil et al. (2013) explored differences in local and global level attention between adults with ASD and controls by means of a hierarchical, abstract shape recognition task. In the ASD group there was increased activation in the right PFC during the local condition, and increased activation of right occipital regions and decreased deactivation in mPFC during the global condition. The latter finding was consistent with less deactivation of the DN during global task processing in the ASD group, which could be related to greater distractibility under this attention condition. Additionally, the increased activation in occipital regions correlates with enhanced local level processing.

As has been hypothesized by Shalom (2005, 2009), perceptual problems in ASD could rely on processing in three levels: basic, integrative and logic, the integrative stage possibly being regulated by the mPFC. The visual recognition process implies the activation of both the mPFC and the anterior temporal cortex. The input from early visual areas first activates the mPFC when low spatial frequencies in the image predominate and globally oriented attention is required, then the temporal cortex region is activated. The mPFC selects the correct object representation and reward value assigned to it, and contributes to make the object itself more important than its sensory features when processed in the anterior temporal cortex. As indicated by fMRI studies, the superior temporal cortex is a neural center responsible for a wide range of high and low level MSI processes. Thus, as previously stated, one of the biological foundations of MSI problems could be the structural or functional abnormalities in the mPFC and superior temporal cortex (Stevenson et al., 2011; Mueller et al., 2013). Thus,

relating data from connectivity and perceptual processing studies, the hypothesis of the modulating role of developmental factors is strengthened. The enhanced perceptual processing theory would explain functioning in the first years, while the weak central coherence approach could be more appropriate to clarify functioning later on.

TEMPORAL MULTISENSORY BINDING

The deficit in MSI, therefore, may lie in the temporal synchronization of neural networks, both local and distributed, since the ability to combine information from multiple sensory modalities to form a unified perception depends on the temporal synchrony of sensory stimuli. It has been hypothesized that frontal cortex could modulate temporal patterns in multisensory parietotemporal areas (Engel et al., 2012). Several studies have shown that the integration of low level visual and auditory stimuli is intact (Foss-Feig et al., 2010; Kwakye et al., 2011). There is, therefore, a certain degree of MSI when the audio-visual information is non-linguistic and simple, although there would be disruptions in temporal processing. Neural networks are intact, but atypical time intervals (temporal multisensory dysfunction) are needed to activate them. In the same way that the latency of response to sensory stimulation is longer, the time interval in which the stimulation of one sensory modality could influence another one in a different channel would necessarily be higher. Foss-Feig et al. (2010) evaluated this issue using the illusion "flash-beep". In most subjects when pairing a visual (one flash) and several auditory stimuli (beeps) at the appropriate time interval, the illusion of perceiving two or more flashes was produced. The results of this study showed that this illusion also occurred in the group with autism, although the time window for the association of the two stimuli was larger. Using another kind of sensory tasks, these researchers also found similar results with respect to the existence of a wider temporal window MSI (Kwakye et al., 2011). However, if people with ASD are highly motivated this window could be smaller as has been hypothesized (Lawson, 2013).

Studies using electrophysiological and behavioral indicators (audio-visual reaction time task) of integration of audio-visual stimuli as well as judgment of audio-visual temporal order tasks have revealed deficits in general audiovisual temporal processing, and impairment in behavioral facilitation to multisensory inputs and in effective neural MSI (de Boer-Schellekens et al., 2013a,b; Brandwein et al., 2013; Collignon et al., 2013). These findings in multisensory temporal processing could be associated with the deficits in speech perception observed in people with ASD (Stevenson et al., 2014a,b). In fact, Foxe et al. (2013) found that high-functioning ASD children presented serious problems to integrate seen and heard speech especially as background noise increased. The developmental factor seems to be important since the impairment was ameliorated in adolescence.

SUMMARY

The insufficient connectivity between the mPFC and other areas distant from each other would be involved in top-down information processes relying on global integration of data from different sources (i.e., verbal and body language) and would enhance low level perception processes (bottom-up information) as in over focused attention to sensory details. The reduced deactivation in the mPFC and in the rest of the DN during global task processing together with a wider temporal window in MSI is consistent with the integrative modulatory role of mPFC as has been hypothesized. Researchers, people with ASD and their families have stressed the importance of understanding the degree to which sensory and movement anomalies in people with ASD can contribute to social impairment. In fact, many acts are mistakenly interpreted as non-compliance, reluctance, lack of interest and even aggressiveness when most of them are not volitional and are secondary to the idiosyncratic sensory and movement profile (Donnellan et al., 2013). Nevertheless, further investigation on the neurobiological basis of sensory symptoms and its relationship to other clinical features found in ADS is still needed to improve understanding and quality of life of persons with ASD and their families.

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Older Adolescents and Young Adults With Autism Spectrum Disorder Have Difficulty Chaining Motor Acts When Performing Prehension Movements Compared to Typically Developing Peers

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It is known that motor actions performed by individuals with autism spectrum disorders (ASD) are clumsy and a previous study revealed that children with ASD of around 8 years old showed less smooth movement and dysfunction of appropriate usage of online vision for grip aperture control. The present study investigates whether and how the kinematic properties of reach-to-grasp movements in older adolescents and adults with ASD [mean (±SD) age: 18.3 ± 2.1] differ from those in typically developing (TD) peers [mean (±SD) age: 19.1 ± 2.2]. Revealing the kinematic properties of reach-to-grasp movements in older adolescents and adults with ASD is indispensable in determining the developmental trajectory of this motor behavior in individuals with ASD. While wearing liquid crystal shutter goggles, participants reached for and grasped a cylinder with a diameter of either 4 or 6 cm. Two visual conditions were tested: a full vision (FV) condition (the goggles remained transparent during the movement) and a no vision (NV) condition (the goggles were closed immediately after the movement was initiated). These two visual conditions were either alternated with each trial in a single experimental session (alternated condition) or blocked within the session (blocked condition). We found that the reaching movement smoothness calculated as a normalized jerk score (i.e., index of skilled, coordinated human movements) of ASD participants did not differ significantly from that of TD peers although ASD participants showed smoother reaching in the alternated condition than in the blocked condition. The influence of online vision and its visual condition schedule on grip aperture during the in-flight phase was remarkably similar between the ASD and TD groups. Furthermore, we found that ASD group experienced a significant longer transition period from grasping end (i.e., stable holding

when touching the surface of the object) to uplift initiation than the TD group. The results suggest that (1) deficits in movement smoothness and the use of online vision for motor control are rectified by the time individuals with ASD reach late adolescence and (2) older adolescents and adults with ASD still have difficulties chaining motor acts.

Keywords: reach-to-grasp movements, kinematics, grip aperture adjustment, chaining motor acts, autism spectrum disorders (ASD)

INTRODUCTION

Autism spectrum disorder (ASD) was first identified by Kanner (1943) and Asperger (1944). Although its etiology is not yet fully known, this developmental disorder is characterized by impairments in social interaction, communication, and imagination (Wing and Gould, 1979; Wing, 1981; American Psychiatric Association, 2000). ASD has traditionally been regarded as a social and cognitive disorder (e.g., Frith et al., 1991; Baron-Cohen and Belmonte, 2005; Happé and Frith, 2006; Senju and Johnson, 2009, for reviews). However, researchers have also explored how people with ASD are different from typically developing (TD) peers in terms of sensory processing (see Iarocci and McDonald, 2006; Ben Shalom, 2009; Bhat et al., 2011; Marco et al., 2011, for reviews) and motor behaviors (see Leary and Hill, 1996; Ben Shalom, 2009; Elliott et al., 2010; Fournier et al., 2010; Bhat et al., 2011; von Hofsten and Rosander, 2012; Fabbri-Destro et al., 2013; Gowen and Hamilton, 2013; Whyatt and Craig, 2013; Sacrey et al., 2014; Cook, 2016, for reviews).

The prospect for early detection of motor abnormalities in infants with ASD is still controversial (Teitelbaum et al., 1998; Ozonoff et al., 2008), but movement disturbances in children with ASD have been found in various motor behaviors, including postural balance (e.g., Kohen-Raz et al., 1992; Molloy et al., 2003), gait (e.g., Vilensky et al., 1981), and hand/arm movements (e.g., Schmitz et al., 2003; Haswell et al., 2009). Some researchers have argued that individuals with ASD (including school-age children and adolescents) have a normal ability to execute movements but showed atypical properties in movement preparation and planning (Hughes, 1996; Rinehart et al., 2001). However, this is still controversial.

Among the various hand/arm motor behaviors, the reach-to-grasp movement is fundamental to daily life and, since Jeannerod's (1981, 1984) pioneering studies, has been extensively explored in adults (see Fukui et al., 2006; Castiello and Begliomini, 2008; Filimon, 2010; Grafton, 2010; Rosenbaum et al., 2012; Gaveau et al., 2014; Turella and Lingnau, 2014, for reviews in the past decade). Other studies have investigated infants (e.g., von Hofsten and Ronnqvist, 1988; Newell et al., 1989; Corbetta and Thelen, 1995) and children (e.g., Kuhtz-Buschbeck et al., 1998; Smyth et al., 2004; Zoia et al., 2006).

Mari et al. (2003) were the first to investigate the kinematic properties of the reach-to-grasp movements in children with ASD beyond simply the standardized test batteries (e.g., the movement assessment battery for children, Henderson and Sugden, 1992). The authors found that children with ASD (aged 7–13 years) showed longer movement durations, longer deceleration times, lower peak wrist velocities, and longer times to peak grip aperture (PGA) than age-matched control participants, though they noted no significant difference in PGA between the ASD and age-matched control groups. They further suggested that performance in the ASD group could be differentiated according to IQ, finding that children with lower IQ scores (IQ: 70–79) exhibited abnormal coordination between reach and grasp components in slower motor behavior, while children with average and higher IQ score group (IQ: 80–109) showed normal, or even "superior" motor behavior, compared to age-matched control group. Recently, Campione et al. (2016) investigated younger children (aged 4.3–5.9 years) with ASD and no intellectual disability (full-scale IQ >80), and obtained results that were generally consistent with those of Mari et al. (2003).

Yang et al. (2014) also investigated the kinematic properties of reach-to-grasp movements in children with ASD [mean (SD) age: 7 years 8 months (1 year 4 months)] by manipulating online vision during the movement [i.e., full vision (FV) and no vision (NV) conditions]. The classical finding that PGA in the NV condition was significantly larger than that in the FV condition in adults (e.g., Wing et al., 1986; Jakobson and Goodale, 1991; Fukui and Inui, 2006) is well known and has been partially confirmed in children (Kuhtz-Buschbeck et al., 1998; Smyth et al., 2004; Zoia et al., 2006). Yang et al. (2014) found that the contribution of online vision to grip aperture adjustment was smaller in participants with ASD, indicating a significantly larger PGA (compared to that in the control groups) even when online vision was available during movement (i.e., the FV condition). The authors also recorded normalized jerk scores (NJSs), which indicate an extent of movement smoothness (i.e., index of skilled, coordinated human movements) and found that the movement in ASD group was longer (slower) and less smooth than that in the control group, especially when children were reaching for and grasping a smaller target without online vision (i.e., the NV condition).

Recently, it has been demonstrated that grip aperture control can be modulated by the presentation order of trials of FV and NV conditions in healthy adults (Whitwell et al., 2008; Tang et al., 2014, 2015). Specifically, the difference in PGA between FV and NV conditions is smaller when these trials are intermixed in an experimental session than when they are blocked separately. The authors named this effect "homogenization" and argued that the homogenizing effects are "mediated by movement-specific memories that operate over iterations of the same action" (Tang et al., 2015, p. 62). One of the aims of the current study is to test whether homogenization is typical or atypical in adolescents and adults with ASD.

Reach-to-grasp movements are usually performed with a subsequent motor act, depending on a final goal of the action

(e.g., Marteniuk et al., 1987; Johnson-Frey et al., 2004). Therefore, proper chaining of motor acts as an entire action is essential for appropriate performance. Fabbri-Destro et al. (2009) investigated how ASD children [including early adolescents (mean age: 10.0 ± 2.3)] and TD peers (matched by non-verbal cognitive level) performed tasks requiring them to reach for and grasp a metal object on a plate, and then pick up and place (drop) it into a container on the right side of the plate. Task difficulty was manipulated by the size of the container (i.e., big vs. small). The authors found that, unlike in the TD group, the reach-to-grasp movements in the ASD group were not appropriately modulated by the subsequent motor act [i.e., placing (dropping)]. Therefore, the authors concluded that the children with ASD had difficulties in chaining motor acts as an entire action (see also Cattaneo et al., 2007; Forti et al., 2011).

The above studies regarding the kinematic properties of reach-to-grasp movements in individuals with ASD were focused on pre- and early adolescent children. No study has yet explored how older adolescents and adults with ASD perform simple reach-to-grasp movements, although pointing movements (without grasping) (Glazebrook et al., 2006, 2009) or more complex motor actions, including in social contexts such as passing a tool to another person after holding it (Gonzalez et al., 2013) have been studied in young adults with ASD. When performing pointing movements, Glazebrook et al. (2009) demonstrated that compared to TD peers, young adults with ASD showed (i) longer reaction time regardless of online vision availability and (ii) longer execution time, especially when vision is available during movement. Furthermore, Gonzalez et al. (2013) showed how people with ASD pass a tool to another person, which is quite different from how TD peers pass a tool to another person. In addition to previous kinematic findings regarding simple pointing movements and social motor action, elucidating the kinematic properties of planning and execution processes in reach-to-grasp movements in older adolescents and adults with ASD is indispensable for uncovering the developmental trajectory of this motor behavior in individuals with ASD. Such elucidation could support the development of prospective therapeutic interventions for movement disturbance.

In this study, we used motion capture system to investigate whether and how the kinematic properties of reach-to-grasp movements in older adolescents and adults with ASD differ from those of TD peers. Based on the studies mentioned above, we tested a task requiring individuals to reach to grasp the object and lift it up after holding it based on three functions: (1) movement smoothness, (2) grip aperture control modulated by availability of online vision (i.e., FV or NV during the movement) and its presentation order, and (3) chaining of motor acts (as an entire action). Specifically, in comparison with TD peers, we focused on (1) whether older adolescents and adults with ASD show clumsy movement (i.e., larger NJS), (2) whether people with ASD could use online vision and show a "homogenization" effect in relation to grip aperture control, and (3) whether people with ASD show a deficit in terms of chaining motor acts as an entire action (i.e., longer time difference between the grasp-end time and the time of lifting initiation).

MATERIALS AND METHODS

Participants

The experiment involved 12 individuals with ASD [one female, mean (±SD) age: 18.3 ± 2.1 years] and 12 TD individuals [one female, mean (±SD) age: 19.1 ± 2.2 years] (**Table 1**). All participants were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971) and had normal or corrected-to-normal vision. They were naive regarding the purpose of the experiment and were paid for their participation. Since the task involved minimal verbal demands of the participants, the participant groups were matched with respect to non-verbal IQ (Mosconi et al., 2015; Wang et al., 2015), in addition to age, sex, and handedness. IQ assessments were carried out using a Japanese version (Fujita et al., 2006) of the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997) and all participants' non-verbal IQ scores were higher than 80. The mean verbal IQ in the ASD group was 102.2 (76–134, **Table 1**), so the participants with ASD and the TD participants were able to understand the task instructions correctly and were confirmed to be capable of following those instructions during the experiment.

A Japanese version (Wakabayashi et al., 2004) of the autism–spectrum quotient (AQ) test (Baron-Cohen et al., 2001) confirmed that none of the participants in the TD group had clinically significant levels of autistic traits, since each participant's AQ score was less than the cutoff score (i.e.,

TABLE 1 | Demographic characteristics of participants with ASD and typically developing peers.

		Age	IQ			AQ	ADOS-2 (Module 4)		
			Full	Non-verbal	Verbal		Comm.	SI	Comm. + SI
ASD	MEAN	18.3	100.1	97.7	102.2	27.3	3.4	6.2	9.6
	SD	(2.1)	(13.0)	(10.4)	(16.2)	(8.1)	(1.4)	(2.1)	(2.8)
TD	MEAN	19.1	110.6	102.8	114.8	19.1			
	SD	(2.2)	(12.1)	(10.1)	(15.2)	(4.6)			
		$t(22) = -0.847$	$t(22) = -2.044$	$t(22) = -1.213$	$t(22) = -1.976$	$t(22) = 3.060$			
		$p = 0.406$	$p = 0.053$	$p = 0.238$	$p = 0.061$	$^*p = 0.006$			

$p < 0.05$ (independent-samples t-test for comparison of ASD and TD groups). Comm., communication score (cutoffs: 3/2); SI, social interaction score (cutoffs: 6/4); Comm. + SI, summed score (communication and social interaction) (cutoffs: 10/7). The cutoffs shown above in parentheses denote the minimum scores for diagnosing autism and autism spectrum disorder, respectively.

33 in the Japanese version). All participants with ASD were diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association, 2000) or 5th edition (DSM-V; American Psychiatric Association, 2013) by child psychiatrists. Their diagnoses were also assessed by a Japanese version (Kuroda and Inada, 2015) of Autism Diagnostic Observation Schedule Second Edition Module 4 (ADOS-2 Module 4; Lord et al., 2012). Although one participant in the ASD group was classified as non-spectrum by ADOS-2 (Module 4) criteria, this participant was diagnosed by a child psychiatrist; therefore, the participant was included in the ASD group. The exclusion of this participant did not alter the pattern of significance.

The study was approved by the institutional ethics committee at the National Rehabilitation Center for Persons with Disabilities, and all the participants (and their parents, for participants younger than 20 years old) provided written informed consent according to institutional guidelines conforming to the Declaration of Helsinki.

Apparatus

As shown in **Figure 1**, participants wore liquid-crystal shutter goggles (Takei Scientific Instruments Co., Ltd.) while seated comfortably on a chair in front of a table. The shutter goggles, which were also used in our previous studies (e.g., Fukui and Inui, 2006, 2015), take about 3 ms to become transparent and about 20 ms to become opaque. In the starting position, a pressure-sensitive switch button (diameter: 5 cm) was located in line with the participant's mid-sagittal plane. The center of target object was positioned 30 cm from the center of the switch button. Two wooden cylinders, measuring 4 or 6 cm in diameter and 11 cm in height [weight: 51 g (4 cm), 136 g (6 cm)], were used as targets for the task. Hand movement (monitored by reflective marker attached to the tips of the thumb and index fingers and the dorsodistal aspect of the radial styloid process) was recorded with a three-dimensional motion capture system (NaturalPoint, Inc., Corvallis, OR, United States) at a frequency of 100 Hz (the spatial resolution was less than 0.5 mm). PCs with custom software were used to control the apparatus and record the kinematics.

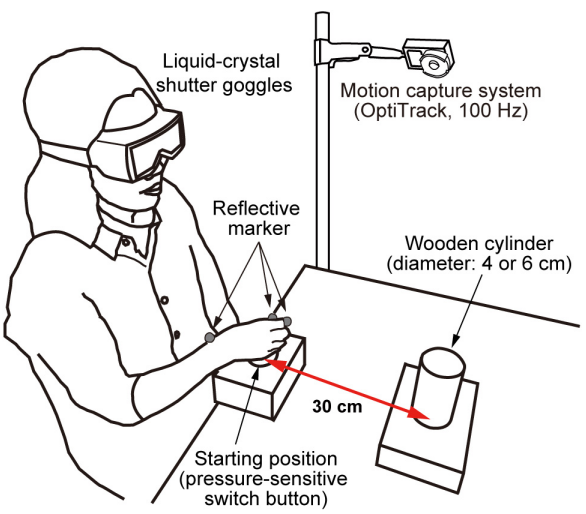

FIGURE 1 | Configuration of the experimental apparatus. Participants wore liquid-crystal shutter goggles and rested their hand on a pressure-sensitive switch button (a starting position). Two wooden cylinders measuring 4 and 6 cm in diameter and 11 cm in height were used as targets in the task. The motion of the reflective markers was recorded by the motion capture system.

Procedure

Each participant was required to place his or her right hand on the starting position before each trial. In this position, the lateral side of the little finger and ulnar palm was touching the surface of the button. Participants were also required to begin each trial with the tips of the thumb and index finger of the right hand touching each other. This pre-trial condition was consistent across every trial of the experiment.

The task in each trial required each participant to reach out to grasp the target object at a comfortable daily life speed and then lift the object about 5 cm. After lifting up the object, the participant put the object back to where it had been and returned his/her hand to the starting position. With respect to grasping (holding) the object, the participants were instructed to approach the object laterally with their fingers and to use the thumb and index finger in such a manner that the line connecting the surface points of each thumb and finger passed through the center of the object's horizontal circle. Use of the other three fingers was allowed to grasp the target object as long as the thumb and index finger were always the main digits used in the grasping action (Fukui and Inui, 2015).

The vision during the task was manipulated using liquid-crystal shutter goggles. The goggles were opaque before each trial, and participants started their movements after the goggles became transparent. This was accompanied by the experimenter's voice cue (the "go" signal). Two visual conditions during the movement were tested: an NV condition, in which the goggles closed immediately after the release of the hand from the start switch, and an FV condition, in which the goggles remained transparent during the entire movement (e.g., Fukui and Inui, 2006, 2015). We investigated the effects of the presentation order of these two visual conditions (i.e., visual context) by considering: (i) a blocked condition (separate experimental sessions of trials in FV and NV conditions) and (ii) an alternating condition (sessions of alternating trials of FV and NV conditions) (Whitwell et al., 2008; Tang et al., 2014, 2015).

The experiment comprised two sessions (blocked and alternating), and the order of these sessions was counterbalanced across participants. Each session comprised four sub-sessions, each with 15 trials. In the blocked condition, either the FV or the NV conditions was repeatedly presented during the first two sub-sessions and the other was presented during the last two sub-sessions. Object size was blocked in an ABBA manner. The presentation orders were also counterbalanced across participants; therefore, in addition to the practice trials (fewer than 10 trials), each participant in the groups completed 120 trials [=15 trials × 2 (visual context: blocked, alternating) × 2 (size: 4 cm, 6 cm) × 2 (vision: FV, NV)] across the entire experiment.

Data Processing and Analysis

The three-dimensional positional data given by Cartesian coordinates from the reflective markers were recorded and filtered offline by a second-order dual-pass Butterworth low-pass filter with a cut-off frequency of 15 Hz. Further offline analysis included computation of wrist velocity, acceleration, and jerk from the filtered position signal. We also calculated grip aperture as the distance between the positions of two reflective markers attached to the thumb and index finger.

Movement onset was defined as the frame in which the tangential velocity first exceeded 50 mm/s, and reach-end time was defined as the frame at which the velocity fell back below this threshold. The typical aperture velocity profile for grasping movements shows positive values throughout the aperture-opening phase until the PGA is achieved; that is followed by negative values as the hand's fingers close down upon the object. Grasp-end time was defined as the point in time when the negative grip aperture velocity crossed the criteria line (setting −20 mm/s) before returning to approximately 0 mm/s as the fingers made contact with the object.

The time of lifting initiation was defined as the point in time when wrist height velocity exceeded 15 mm/s. Finally, reach duration denoted the time between movement onset and reach-end time, and movement duration was defined as the time between movement onset and grasp-end time (i.e., not including the uplift of the object).

The current study focused on (1) smoothness of reaching movement, (2) grip aperture control according to online vision, and (3) smoothness of chaining motor acts (in this case, uplifting the object after grasping) in autistic participants, compared to typical developing peers. To evaluate these functions, we calculated the following values.

Firstly, the NJS, which is unit-free, was calculated as an index of movement smoothness using the equation shown below (Kitazawa et al., 1993; Teulings et al., 1997). Calculating jerk is acceptable when sampling frequency is around 100 Hz (Yan et al., 2000).

$$\mathrm{NJS} = \sqrt{\frac{1}{2}\int j^2(t)\mathrm{d}t \times \frac{\mathrm{RD}^5}{\mathrm{WD}^2}}$$

In the equation, RD, WD, and j denote reach duration, total wrist displacement until reach end, and jerk, respectively. Secondly, the differences of the NJS and PGA between the FV and NV conditions (NJSDiff and PGADiff) were computed to evaluate whether a homogenizing effect induced by visual condition schedule appears in reaching movement smoothness and grip aperture adjustment. Lastly, the difference between the grasp-end time and the time of lifting initiation (DiffGrLf) was calculated as an index of the smoothness of chaining motor acts.

In addition to these above-mentioned values, the values of the transport component (peak wrist velocity, time to peak wrist velocity), the time to PGA, and the reaction time (i.e., the time between the goggles' opening at the start of the trial and the onset of movement) were measured.

Mean values for each dependent variable (except NJSDiff and PGADiff) were entered into a four-way ANOVA with the group (ASD, TD) as a between-participants factor and the visual context (blocked, alternating), object size (4, 6 cm), and visual condition (FV, NV) as within-participant factors. With respect to NJSDiff and PGAdiff, a three-way ANOVA was applied with the group (ASD, TD) as a between-participants factor and the visual context (blocked, alternating), object size (4, 6 cm) as within-participant factors. If we found an interaction, the simple main effect analysis was examined with the Bonferroni correction.

Furthermore, by pooling the data for the TD and ASD groups, a multiple linear regression and associated stepwise variable selection method were applied to analyze the relationships between the five subcategories of AQ scores (i.e., social skill, attention switching, attention to detail, communication, imagination) and each kinematic parameter to determine whether and which subscale scores would predict the performance of each kinematic parameter.

RESULTS

The mean values of kinematic parameters in each experimental condition in the ASD and TD groups were shown in **Table 2** and **Figures 2–4**.

Reaction Time (Table 2)

No significant main effects on factors and no significant interactions were noted ($p > 0.109$).

Movement Duration (Table 2)

Visual condition was found to have a significant main effect [$F(1,22) = 28.344$, $p < 0.001$, partial $\eta^2 = 0.563$], and the interaction between object size and visual condition was also significant [$F(1,22) = 8.122$, $p = 0.009$, partial $\eta^2 = 0.270$]. The simple main effect analysis revealed that the movement duration in the FV condition was significantly shorter than that in the NV condition for both object sizes.

Peak Wrist Velocity (Table 2)

No significant main effects on factors and no interactions were noted ($p > 0.108$).

Time to Peak Wrist Velocity (Table 2)

The interaction between group and object size was significant [$F(1,22) = 5.196$, $p = 0.033$, partial $\eta^2 = 0.191$]. The simple main effect analysis revealed that the time to peak wrist velocity for the 6 cm object was also significantly later than that for the 4 cm object in the ASD group while no significant time difference was found between the 4 and 6 cm objects in the TD group.

Normalized Jerk Score (NJS) and the Difference in NJS Between the FV and NV Conditions (NJSDiff) (Figure 2)

The main effect of visual condition was significant [$F(1,22) = 32.846$, $p < 0.001$, partial $\eta^2 = 599$], indicating that the NJS in the NV condition was significantly larger than that in the FV condition. The results also showed a significant

TABLE 2 | Mean values (SEs) of the kinematic parameters for each experimental condition in the ASD and TD groups.

	Blocked				Alternating			
	4 cm		6 cm		4 cm		6 cm	
	FV	NV	FV	NV	FV	NV	FV	NV
ASD								
Reaction time (ms)	467	514	501	480	503	525	510	500
	(35)	(71)	(49)	(45)	(68)	(68)	(62)	(54)
Movement duration (ms)	1124	1257	1130	1212	1071	1227	1082	1189
	(50)	(96)	(49)	(84)	(56)	(70)	(54)	(62)
Peak wrist velocity (cm/s)	42.1	40.7	40.9	41.6	45.0	42.9	44.6	42.5
	(2.3)	(3.2)	(2.3)	(3.3)	(2.9)	(3.1)	(2.7)	(3.0)
Time to peak wrist velocity (ms)	446	453	461	445	435	422	445	449
	(22)	(31)	(25)	(31)	(22)	(21)	(23)	(24)
Time to peak grip aperture (ms)	742	760	766	750	712	753	732	763
	(36)	(54)	(41)	(53)	(44)	(43)	(42)	(45)
TD								
Reaction time (ms)	403	379	403	386	390	395	399	423
	(34)	(35)	(36)	(32)	(35)	(37)	(35)	(42)
Movement duration (ms)	989	1085	988	1031	963	1104	983	1104
	(54)	(56)	(58)	(58)	(60)	(70)	(59)	(78)
Peak wrist velocity (cm/s)	46.4	47.5	47.7	48	48	46.7	48.7	47.2
	(2.9)	(3.3)	(3.4)	(3.3)	(3.6)	(3.8)	(3.9)	(3.8)
Time to peak wrist velocity (ms)	383	376	385	361	384	390	389	384
	(20)	(24)	(22)	(21)	(25)	(27)	(26)	(24)
Time to peak grip aperture (ms)	677	666	686	667	643	698	667	705
	(46)	(47)	(53)	(45)	(49)	(51)	(51)	(55)

FV and NV denote full vision and NV conditions during reach-to-grasp movements. 4 and 6 cm are the diameters of the target wooden cylinders. The blocked condition consists of separate experimental sessions of trials under FV and NV conditions and alternating condition consists of sessions of alternating trials of FV and NV conditions.

interaction between group and visual context [$F(1,22) = 5.021$, $p = 0.036$, partial $\eta^2 = 0.186$], as well as a main effect of visual context which indicated that the NJS in the blocked condition was significantly larger than that in the alternating condition [$F(1,22) = 5.357$, $p = 0.030$, partial $\eta^2 = 0.196$]. The simple main effect analysis revealed that the mean NJS in the blocked condition was significantly larger than that in the alternating condition in the ASD group, while there was no significant difference between the blocked and alternating conditions in the TD group.

As far as NJSDiff was concerned, neither significant main effects on factors nor interactions were noted ($p > 0.345$).

Peak Grip Aperture (PGA) and the Difference in PGA Between the FV and NV Conditions (PGADiff) (Figure 3)

With respect to PGA, significant main effects of group [$F(1,22) = 6.258$, $p = 0.020$, partial $\eta^2 = 0.222$], object size [$F(1,22) = 279.750$, $p < 0.001$, partial $\eta^2 = 0.927$], and visual condition [$F(1,22) = 120.963$, $p < 0.001$, partial $\eta^2 = 0.846$] were found. The results show a larger PGA for the TD group than the ASD group, as well as a larger PGA for the larger object and the NV condition. Significant interactions between visual context and visual condition [$F(1,22) = 25.094$, $p < 0.001$, partial $\eta^2 = 0.533$], and between size and visual condition [$F(1,22) = 46.464$, $p < 0.001$, partial $\eta^2 = 0.679$] were also found. In particular, the simple main effect analysis found that the PGA in the NV condition was significantly larger when performing the task in the blocked condition than when performing it in the alternating condition, while the PGA in the FV condition was significantly larger when performing the task in the alternating condition.

With respect to PGADiff, significant main effects of visual context [$F(1,22) = 25.094$, $p < 0.001$, partial $\eta^2 = 0.533$] and size [$F(1,22) = 46.464$, $p < 0.001$, partial $\eta^2 = 0.679$] were found, indicating that the value in the blocked condition was significantly larger than that in the alternating condition and that the value for the 4 cm object was significantly larger than that for 6 cm object. No significant main effect of group [$F(1,22) = 0.522$, $p = 0.478$] was noted.

Time to Peak Grip Aperture (Table 2)

A significant interaction between visual context and visual condition was found [$F(1,22) = 10.036$, $p = 0.005$, partial $\eta^2 = 0.313$], indicating a longer time to PGA in the NV condition than in the FV condition when performing the task in the alternating condition. This interaction also denoted that the time to PGA in the alternating condition was significantly earlier than

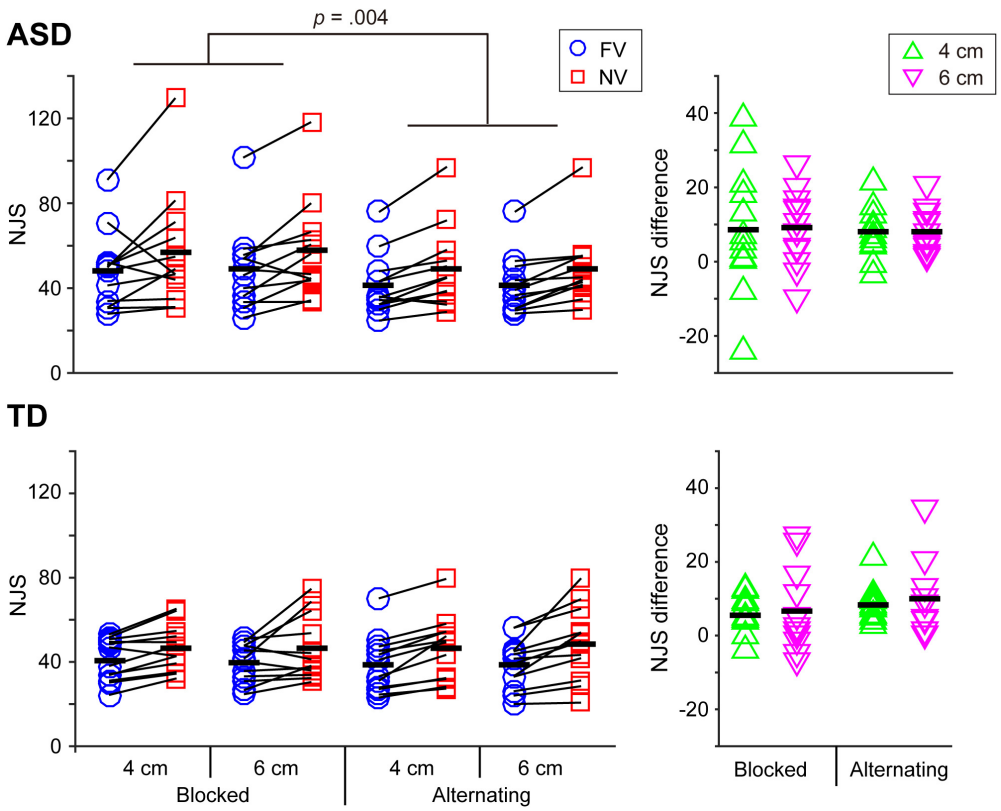

FIGURE 2 | Normalized jerk score (NJS) and the difference in the NJS between the FV and NV conditions in the ASD and TD groups. As for the NJS, a significant interaction between group and visual context was noted and this interaction indicated that the ASD group exhibited a significantly larger value for the blocked condition than for the alternating condition, while the TD group experienced no significant effect of visual context. Black bars indicate mean values in each condition. As for the difference in the NJS, neither significant main effects on factors nor interactions were noted.

that in the blocked condition when performing the task in the FV condition.

Difference Between the Grasp-End Time and the Time of Lifting Initiation (DiffGrLf) (Figure 4)

The results showed a significant main effect of group [$F(1,22) = 6.629$, $p = 0.017$, partial $\eta^2 = 0.232$], indicating that the ASD group took significantly longer time than the TD group to begin to lift up the object after the grasp-end time. A significant main effect of size [$F(1,22) = 5.161$, $p = 0.033$, partial $\eta^2 = 0.190$] was also found, indicating that the value for the 6 cm object was significantly longer than that for the 4 cm object.

Relationship Between Each Kinematic Value and AQ Score

The multiple regression analysis revealed that only the subcategory social skill score was significantly correlated with reaction time ($R^2 = 0.172$, $p = 0.044$), movement duration ($R^2 = 0.416$, $p = 0.043$), time to peak velocity ($R^2 = 214$, $p = 0.023$), and time to PGA ($R^2 = 439$, $p = 0.032$). We also found that only the subcategory attention switch score was significantly correlated with DiffGrLf ($R^2 = 262$, $p = 0.011$). The other kinematic values showed no significant correlation with the subcategory AQ scores.

DISCUSSION

This kinematic study explored whether and how older adolescents and adults with ASD perform reach-to-grasp and uplift movements in comparison to TD peers. Our foci were (1) smoothness of the reaching movement, (2) grip aperture control according to online vision, and (3) smoothness of chaining motor acts.

First, as for the smoothness of the reaching movement, the ASD group showed a significantly larger mean NJS in the blocked schedule than in the alternating schedule, while no significant difference of the mean NJS was shown between these two visual schedule conditions in the TD group. This result indicates that the modulation patterns of reaching movement smoothness according to the visual context itself are different between ASD and TD. Specifically, alternating FV and NV conditions from trial to trial in a session, in contrast to blocking these visual conditions, contributed to reducing the NJS (i.e., increasing reaching movement smoothness) for both FV and NV conditions

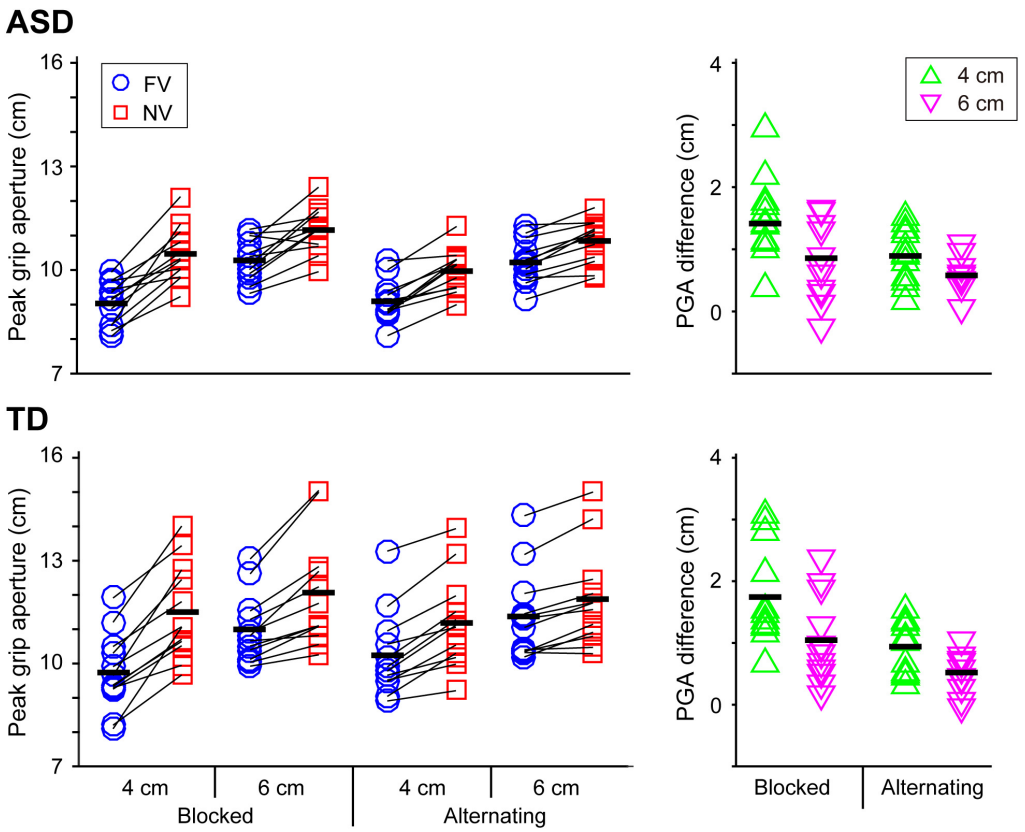

FIGURE 3 | Peak grip aperture (PGA) and the difference in PGA between the FV and NV conditions in the ASD and TD groups. PGA difference between the FV and NV conditions affected by visual context and object size in the ASD group was remarkably similar to those in the TD group. Black bars indicate mean values in each condition.

in the ASD group while visual context had no influence on the NJS in the TD group. At the same time, the main effect of the group (i.e., ASD and TD) on the mean NJS was not significant, suggesting that reaching movement smoothness in the ASD group was comparable to that in the TD group. Furthermore, the homogenizing effect did not operate on the NJS in either the TD or ASD group. This finding strengthens the previous findings by Whitwell et al. (2008), which did not observe the influence of the visual feedback schedule on the transport components they examined.

Second, grip adjustment according to online vision and its context was remarkably similar between ASD and TD peers. Specifically, homogenization in PGA due to visual context (Whitwell et al., 2008; Tang et al., 2014, 2015) occurred in both older adolescents and adults with ASD and their TD peers. This result suggests that sensorimotor memory for grip aperture adjustment was intact (or had been recovered) in the older adolescents and young adults with ASD. Furthermore, in both the TD and ASD groups, the homogenizing effect according to the visual schedule emerged only in grip aperture adjustment (i.e., grasp component), not in reaching movement smoothness (i.e., transport component).

Third, the significantly longer DiffGrLf (i.e., transition period from grasping end to uplift initiation) in the ASD group than in the TD group suggests that ASD participants have difficulties chaining motor acts smoothly and appropriately. It is noteworthy that this significant longer DiffGrLf in ASD group emerged despite no significant difference in reaction time or movement duration between the ASD and TD groups. Namely, the longer transition period from grasping end to uplift initiation in the ASD group cannot be attributed simply to general movement slowness.

As we introduced in the section "Introduction," Yang et al. (2014) showed that movement duration in school-age children with ASD [mean (SD) age: 7 years 8 months (1 year 4 months)] was longer than those of the TD peers when grasping a small target and that reaching movement in the ASD group is less smooth than that of the TD peers. Furthermore, ASD children cannot use online vision to adjust grip aperture while TD peers appropriately adjust their grip aperture according to the availability of online vision. However, the current study did not find significant differences of movement duration and NJS between the ASD and TD groups. Furthermore, the result of the PGA difference indicated that the ability to adjust grip aperture according to visual schedule in older adolescents and adults with ASD is comparable to those in TD peers. Why the TD group showed a significantly larger PGA than the ASD group must be clarified in a future study. Importantly, the experimental situation

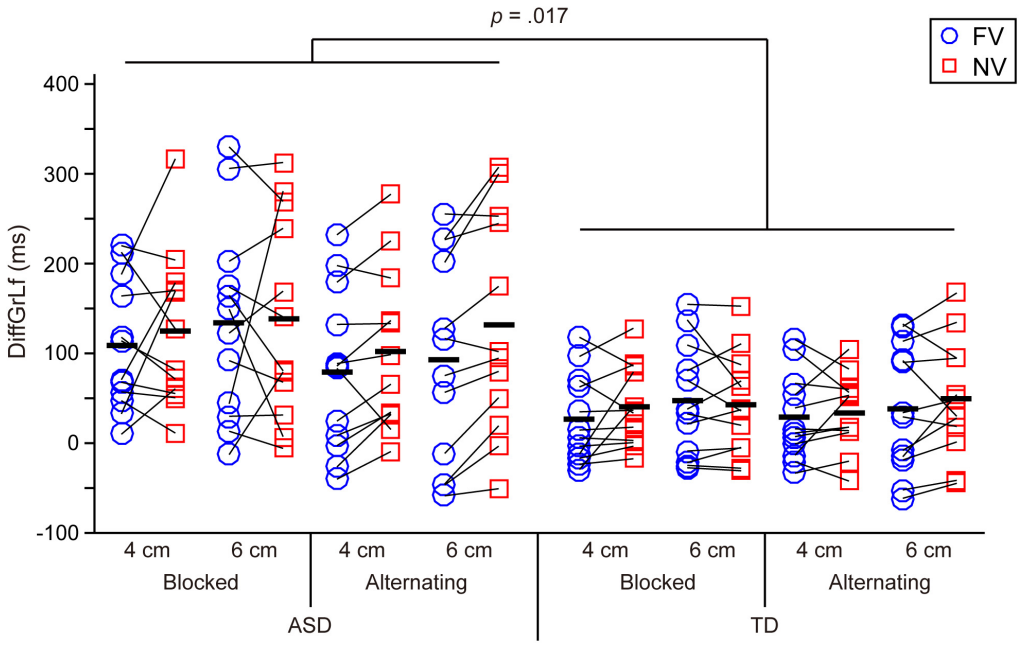

FIGURE 4 | Difference between the grasp-end time and the time of lifting initiation (DiffGrLf) in the ASD and TD groups. Significant main effects of group (i.e., significant longer time in the ASD group than in the TD group) and of object size (i.e., significant longer time for the 6 cm object than for the 4 cm object) were found. Black bars indicate mean values in each condition.

of Yang et al. (2014) was much like our current one where the movement speed of the task was comfortable.

With respect to chaining sequential motor acts, Fabbri-Destro et al. (2009) found that children with ASD [mean (SD) age: 10.0 (±2.3)], in contrast to TD children, could not modulate their first action (i.e., reaching to grasp) according to the task difficulty of the second action (i.e., dropping into a container) and argued that ASD children struggle to chain sequential motor acts as an entire action (see also Cattaneo et al., 2007; Forti et al., 2011). The current study simply required participants to perform an uplifting action instead of manipulating the task difficulty after grasping the target object, and Fabbri-Destro et al. (2009) did not calculate the values comparable to our DiffGrLf (i.e., transition period from grasping end to uplift initiation). Therefore, we could not directly compare our current study with Fabbri-Destro et al. (2009), but our results, which showed significantly longer DiffGrLf in the ASD group than in the TD group, and the results of Fabbri-Destro et al. (2009) both demonstrated that ASD participants have difficulties in chaining motor acts.

By comparing the current results concerning older adolescents and adults to previous studies mentioned above concerning school-age children, we can deduce the following developmental trajectories of prehension movements in ASD: First, impairment of reaching smoothness and grip adjustment in school-age children could be compensated by their developmental processes, and their visuo-motor transformation processes would be comparable to TD peers when they grow older (i.e., become older adolescents). By contrast, organizing their sequential motor acts as an entire action is difficult even for older adolescents and adults.

In addition to comparing ASD and TD participants, we investigated the relation between autistic traits and kinematics by pooling the data on the TD and ASD groups. The transition period from grasping end to uplift initiation (DiffGrLf), which showed a significant difference between the ASD and TD groups, was significantly correlated with the subcategory attention switch. Although we found no significant difference between the ASD and TD groups for the following values (except time to peak wrist velocity for the 6 cm condition), the subcategory social skill score showed a (mild) significant correlation with the temporal components (i.e., reaction time, movement duration, time to peak velocity, time to PGA). Although the reason for this specific subcategory's significant correlations with specific parameters will need to be clarified in future studies, the current results suggest that the AQ subcategory scores could be useful for predicting motor performance for the pooled population of ASD and TD individuals.

The lack of significant differences in parameters between ASD and TD during reach-to-grasp movements (except for time to peak wrist velocity for the 6 cm condition) may be due to the ease of the task in the current experiment, since the target was presented at one fixed location and each target size was blocked in each session. Furthermore, participants were instructed to perform the task at a comfortable daily life speed in the current study (cf. Fukui and Inui, 2006). Of course, the task difficulty would be increased by changing the external and/or internal properties of the target objects (e.g., location, shape, size, etc.) and by increasing the speed of their movement. Such manipulation of task difficulty could result in significant differences in the parameters during reach-to-grasp movements. Furthermore, the

relatively small sample size of the current study is a limitation. However, the current findings show that even in simple and comfortable experimental situations older adolescents and adults with ASD exhibited significantly longer transition periods from grasping end to uplift initiation, indicating difficulties in chaining their sequential motor acts as an entire action. This would be the primary cause of autistic individuals' deficit with regard to understanding others suggested by Fabbri-Destro et al. (2009) and Cattaneo et al. (2007).

Older adolescents and adults with ASD and their TD peers exhibit a similar grip aperture modulation according to online vision and its context in the current experiment, while school-age children cannot perform such a modulation (Yang et al., 2014). That is, like TD peers (Whitwell et al., 2008; Tang et al., 2014, 2015), older adolescents and adults with ASD could appropriately use the predictability of available vision of upcoming trial. Glazebrook et al. (2008) demonstrated that adults with ASD could use advance information, but could not adopt a kind of strategic flexible planning in a manual aiming study. Therefore, what kind of advance (predictive) information could be used (or not used) for individuals with ASD when performing reach-to-grasping movements should be investigated in a future study.

With respect to the effect of visual context on reaching smoothness (NJS), the significant reduction of NJS in the alternating condition compared to the blocked condition was found in the ASD group, while no significant difference in NJS occurred for the TD group. While this latter result for the TD would be due to the ease of the current task (i.e., the floor effect), the increase in reaching smoothness in the alternating condition for the ASD group would support investigations of therapeutic interventions for movement disturbance. For example, it may be better to train motor behaviors across several visual contexts, rather than in fixed visual condition. Although no significant difference in NJS between the ASD and TD groups was found in the current study, future studies using a higher sampling frequency motion capture system in a slightly larger sample size are needed to clarify detailed properties of reaching smoothness.

The current prehension task is simple and performed by one single person. Recently, however, this prehension action was incorporated into a task to investigate the visuomotor processes of joint action carried out concurrently by two people (e.g., Becchio et al., 2008; Sacheli et al., 2013; Curioni et al., 2017). Reasoning about the mind of another person, which is associated with activity in the ventral medial prefrontal cortex (e.g., Castelli et al., 2000; van den Bos et al., 2007), facilitates appropriate joint action. Therefore, both kinematic and neuroimaging studies are required for revealing the mechanism of joint action, and kinematic studies of prehension tasks provide some basis for comparison with kinematic studies of joint action.

In sum, the use of online vision and its context for motor control, which is not fully exploited in school-age children, may be compensated for when individuals with ASD reach late adolescence; however, older adolescents and adults with ASD still have difficulties chaining motor acts.

AUTHOR CONTRIBUTIONS

TF conceived, designed, and performed the experiments, analyzed the data, and wrote the manuscript. SK and KN diagnosed the individuals with ASD. MiS confirmed the diagnoses using the Japanese version of the ADOS. AT, MaS, and HA performed psychological the tests. TF, RF, YN, and MW contributed reagents, materials, and analysis tools. All authors discussed the results and commented on the manuscript.

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frontiers in Human Neuroscience

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Resting-State Time-Varying Analysis Reveals Aberrant Variations of Functional Connectivity in Autism

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Recently, studies based on time-varying functional connectivity have unveiled brain states diversity in some neuropsychiatric disorders, such as schizophrenia and major depressive disorder. However, time-varying functional connectivity analysis of resting-state functional Magnetic Resonance Imaging (fMRI) have been rarely performed on the Autism Spectrum Disorder (ASD). Hence, we performed time-varying connectivity analysis on resting-state fMRI data to investigate brain states mutation in ASD children. ASD showed an imbalance of connectivity state and aberrant ratio of connectivity with different strengths in the whole brain network, and decreased connectivity associated precuneus/posterior cingulate gyrus with medial prefrontal gyrus in default mode network. As compared to typical development children, weak relevance condition (the strength of a large number of connectivities in the state was less than means minus standard deviation of all connection strength) was maintained for a longer time between brain areas of ASD children, and ratios of weak connectivity in brain states varied dramatically in the ASD. In the ASD, the abnormal brain state might be related to repetitive behaviors and stereotypical interests, and macroscopically reflect disruption of gamma-aminobutyric acid at the cellular level. The detection of brain states based on time-varying functional connectivity analysis of resting-state fMRI might be conducive for diagnosis and early intervention of ASD before obvious clinical symptoms.

Keywords: fMRI, autism, time-varying, functional connectivity, brain state, divergence

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1. INTRODUCTION

Autism Spectrum Disorder (ASD) is a lifelong developmental disorder. Children with ASD cannot perform normal social communication, and are characterized by repetitive behaviors and stereotypical interests. Previous studies indicated that impairments in the ASD might reflect deficits in brain network and connectivity (Minshew and Williams, 2007; Vissers et al., 2012; Abbott et al., 2015).

In the neuroimaging analysis, deficits in connectivity have been found to be related to clinical symptoms and behavioral performance in the ASD. Underconnectivity and overconnectivity have been detected in functional connectivity analysis of ASD. In the studies about ASD based on working memory, executive functioning, and response inhibition tasks, the underconnectivity

of frontal-posterior connections supported the theory that malfunction of circuitry with underconnectivity could cause deficits in integration of information in the brain at cognitive level (Just et al., 2004; Koshino et al., 2005; Just et al., 2007; Kana et al., 2007). In the resting-state studies, overconnectivity was found to be associated with ASD symptom severity (Keown et al., 2013). In the network analysis of ASD, underconnectivity disturbed the integration of network and overconnectivity damaged the segregation of network (Abbott et al., 2015). Integration within brain networks and segregation between them played an important role in the functional brain maturation (Dosenbach et al., 2010). And in the development (from childhood to early adulthood) of brain, negative function connectivities associated with right superior temporal cortex were increased (Kelly et al., 2009).

Recently, dynamic network analysis was introduced in studies of functional connectivity to identify brain connectivity states. Dynamic network analysis could reveal functional connectivity variability during a scan period, which might be impossible in the traditional network analysis of fMRI data. Dynamic network analysis has found some time-varying characteristics of brain connectivity based on fMRI data during a scan period (Liu and Duyn, 2013; Allen et al., 2014; Monti et al., 2014; Yu et al., 2015). Relevant studies have indicated that metastable states identified by dynamic networks corresponded to stages of consciousness (Calhoun et al., 2014). In addition, dynamic network analysis promoted knowledge of actual sub-network interactions and separation strategies of brain regions (Allen et al., 2014; Yang et al., 2014). In previous studies, dynamic network analysis showed that connectivity state could be shifted in humans with long-term training and experience, such as taxi drivers (Shen et al., 2016). Childhood and adolescence were key stages of brain maturation, and cognitive function networks showed dynamic reorganization in brain maturation (Uddin et al., 2011). And in the development of adolescence, dynamics of brain state was the basis of the development of executive function (Medaglia et al., 2015). ASD might induce deviation of reorganization process from the normal process, and influence connectivity state. In addition, changes of connectivity state in the ASD were less drastic between the resting-state and the tasking-state as compared to typical development (TD) children (Uddin et al., 2015).

Previous functional connectivity fMRI studies showed that overconnectivity and underconnectivity were the major forms of abnormal connectivity in the ASD. To the best of our knowledge, the relationship between connectivity strength and time-varying functional connectivity states in the ASD based on fMRI has not yet been reported. We hypothesized that ASD could influence time-varying functional connectivity states through affecting distribution of connectivity strength and influence the connectivities related to social function. To investigate the influence of ASD on brain connectivity states, we performed group independent component analysis (GICA) and dynamic network analysis on fMRI data of ASD and TD children. GICA can extract spatial distribution of functional regions in the brain.

TABLE 1 | Demographic information of the participants.

	TD	ASD	*P*-value
N	44	31	-
Age (*Mean* ± *SD*)	12.46 ± 3.1	11.51 ± 2.64	0.1693
Gender	Male	Male	–
Handedness	Right	Right	–
Handedness Score (*Mean* ± *SD*)	62.07 ± 22.82	63.52 ± 23.88	0.7914
FIQ Score (*Mean* ± *SD*)	113.14 ± 12.32	112.52 ± 15.87	0.8495
ADI-R Social Total A (*Mean* ± *SD*)	–	18.77 ± 4.66	–
ADI-R Verbal Total BV (*Mean* ± *SD*)	–	15.26 ± 3.84	–
ADI RRB Total C (*Mean* ± *SD*)	–	5.74 ± 2.61	–
ADI R Onset Total D (*Mean* ± *SD*)	–	2.94 ± 1.34	–
ADOS Module	–	3	–
ADOS Total (*Mean* ± *SD*)	–	11.52 ± 4.41	–
ADOS Communication (*Mean* ± *SD*)	–	3.41 ± 1.74	–
ADOS Social (*Mean* ± *SD*)	–	8.11 ± 3.04	–
ADOS Stereo Behavior (*Mean* ± *SD*)	–	2.67 ± 1.95	–

ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; Subjects evaluated by ADOS module 4 were excluded when we calculated mean and SD of ADOS scores.

2. MATERIALS AND METHODS

2.1. Participants and Functional MRI Data Acquisition

Data of participants were obtained from open accessed dataset collected by NYU Langone Medical Center, a collection site of Autism Brain Image Data Exchange I(ABIDE I) (Di Martino et al., 2014). The site includes 79 (7.1–39.1 years) ASD and 105 TD (6.5–31.8 years) children. The criteria of included subjects are:

(1) male
(2) scores of full intelligence quotient (FIQ, estimated by the fourth subtests of the Wechsler Abbreviated Scale of Intelligence, WASI-IV) above 85
(3) right-handedness
(4) aged 7–18 (not including 18 years old)

TD children were matched with ASD children for age, gender, handedness, FIQ score, and head motion (*P*-values of the rigid 6 using two-sample *t*-test were 0.7654, 0.8762, 0.2053, 0.6026, 0.5831, and 0.6601, respectively). The detailed demographic information of participants is presented in **Table 1**. BOLD fMRI data of each participant were acquired with a whole-brain echo planar imaging (EPI) sequence and interleaved slice acquisition (TR = 2 s, TE = 15 ms, flip angle = 90°, slice thickness = 4 mm, FoV = 240 mm, 180 volumes) on a 3T Allegra scanner. Data collections were approved by local IRB of the site, and all data were anonymized. More detailed information is available at http://fcon_1000.projects.nitrc.org/indi/abide/.

2.2. Data Preprocessing

Resting-state fMRI raw data were preprocessed by Data Processing Assistant for Resting-State fMRI (DPARSF) (Chao-Gan and Yu-Feng, 2010) based on Statistical Parametric

Mapping (SPM8). The procedure of preprocessing included removal of first 10 image volumes, realignment, time-slicing and head motion correction, normalization into Montreal Neurological Institute (MNI) standard space, and spatially smoothened by a full-width at half-maximum of 6 mm. All image volumes were aligned to the first volume for each participant in the realignment. In the head motion correction, head motion parameters were estimated according to Friston 24-Parameter Model (Friston et al., 1996). In the normalization, fMRI data were spatially normalized to the MNI EPI template.

2.3. Independent Component Analysis

Independent component analysis was performed on the preprocessed fMRI data by GIFT v3.0a using Infomax algorithm (Bell and Sejnowski, 1995), and the order of ICA model was 100. Before performing ICA algorithm, fMRI data dimension reduction was performed by Principal Component Analysis (PCA). The reliability of independent components (ICs) was evaluated by repeating the algorithm 25 times in ICASSO (Himberg and Hyvärinen, 2003). According to spatial distribution of ICs in previous studies (Allen et al., 2014), 54 ICs in seven sub-networks were kept for the following analysis. The seven sub-networks were subcortical (SC), auditory (AU), visual (VIS), somatomotor (SM), cognitive control (CC), default mode (DM), and cerebellar (CB) networks (**Figure 1**). The other components were related to movement or physical according to their spatial distributions, so they were not included in this study.

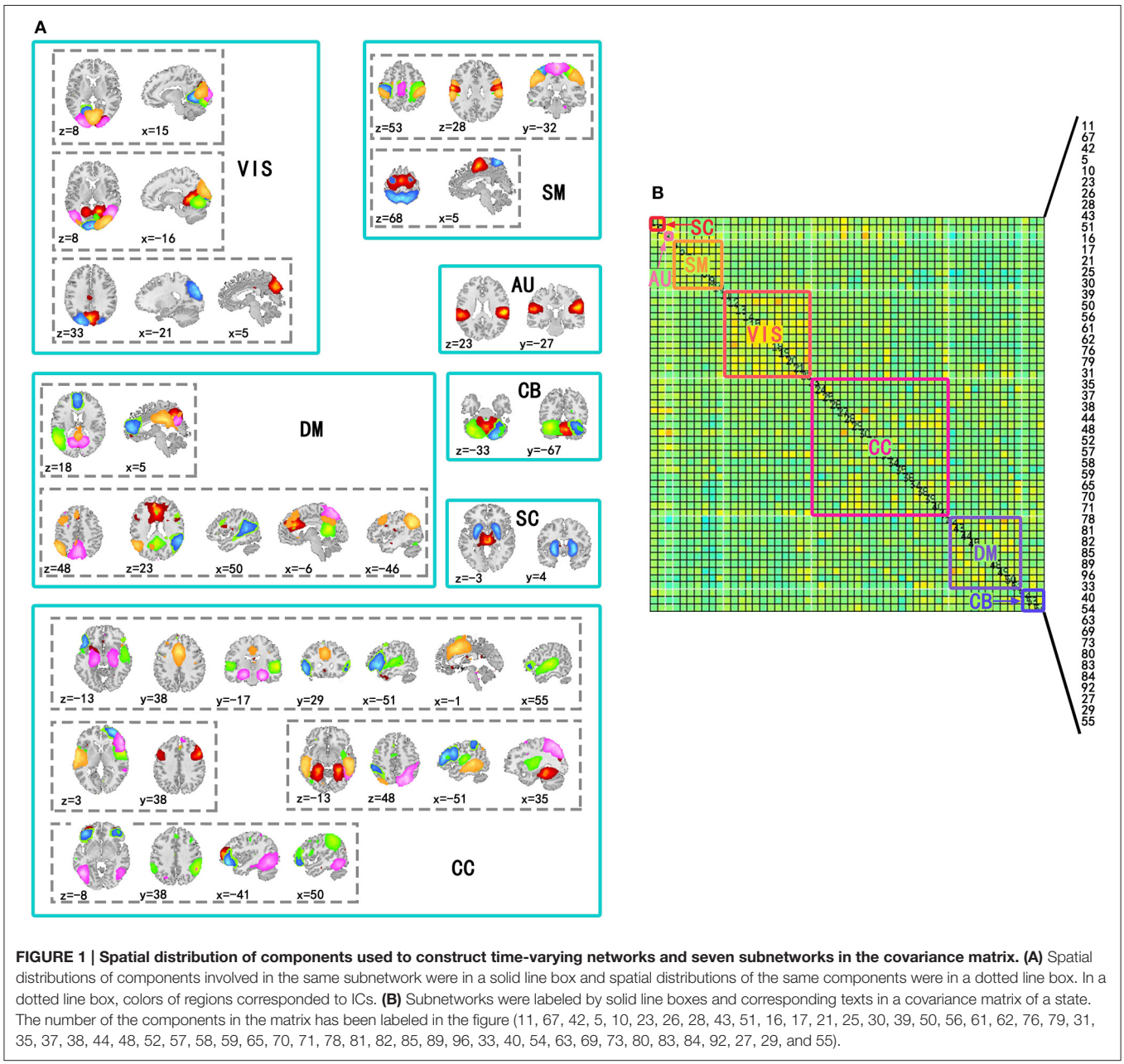

FIGURE 1 | Spatial distribution of components used to construct time-varying networks and seven subnetworks in the covariance matrix. (A) Spatial distributions of components involved in the same subnetwork were in a solid line box and spatial distributions of the same components were in a dotted line box. In a dotted line box, colors of regions corresponded to ICs. **(B)** Subnetworks were labeled by solid line boxes and corresponding texts in a covariance matrix of a state. The number of the components in the matrix has been labeled in the figure (11, 67, 42, 5, 10, 23, 26, 28, 43, 51, 16, 17, 21, 25, 30, 39, 50, 56, 61, 62, 76, 79, 31, 35, 37, 38, 44, 48, 52, 57, 58, 59, 65, 70, 71, 78, 81, 82, 85, 89, 96, 33, 40, 54, 63, 69, 73, 80, 83, 84, 92, 27, 29, and 55).

2.4. Calculation of Time-Varying Connectivity and K-Means Clustering

The selected ICs were defined as regions of interest (ROIs) to construct the networks. Linear, quadratic, and cubic trends of the time courses extracted according to the ROIs were removed, and six realignment parameters were regressed out. Then, the regressed time courses were depicted by 3DDESPIKE to remove the outliers, and filtered with a high cutoff frequency of 0.15 Hz according to the previous study (Allen et al., 2014).

Time-varying functional connectivity was calculated based on segmented time courses in 148 windows created by a tapered window [a rectangle (width = 22 TRs) with a Gaussian (=3 TRs)] sliding in steps of 1 TR. By calculating Pearson's correlation coefficient (functional connectivity) of all possible ROI pairs in the same sliding window, we constructed covariance matrices (54 × 54) of each subject. In addition, we used the graphical LASSO (a shrinkage and selection method for linear regression) to evaluate the log-likelihood of covariance matrices, and regularized matrices after evaluating with L1-norm penalty to control sparsity (Friedman et al., 2008).

To determine the connectivity states, covariance matrices of ASD and TD were clustered by k-means clustering algorithm

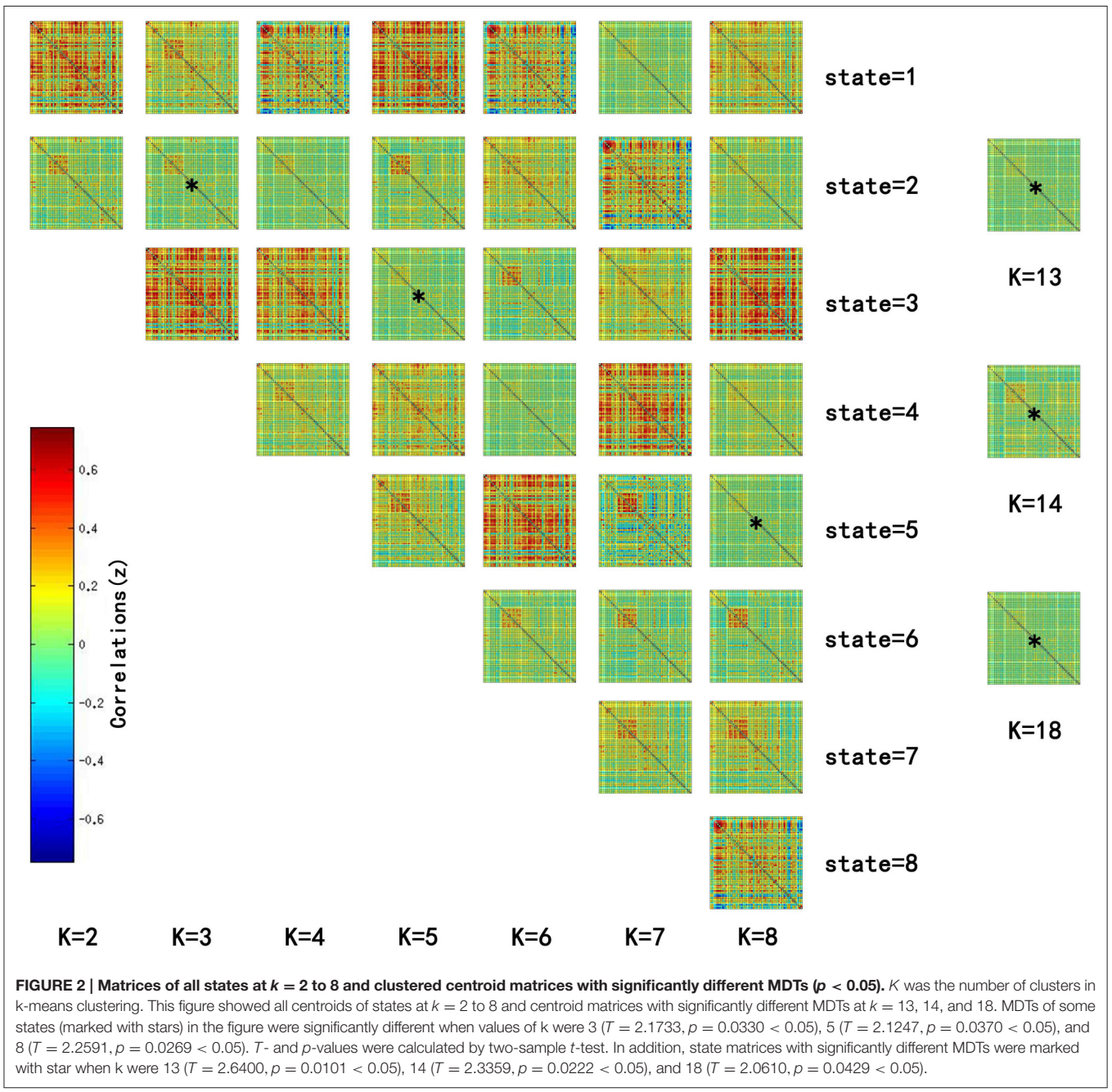

FIGURE 2 | Matrices of all states at $k = 2$ to 8 and clustered centroid matrices with significantly different MDTs ($p < 0.05$). K was the number of clusters in k-means clustering. This figure showed all centroids of states at $k = 2$ to 8 and centroid matrices with significantly different MDTs at $k = 13$, 14, and 18. MDTs of some states (marked with stars) in the figure were significantly different when values of k were 3 ($T = 2.1733, p = 0.0330 < 0.05$), 5 ($T = 2.1247, p = 0.0370 < 0.05$), and 8 ($T = 2.2591, p = 0.0269 < 0.05$). T- and p-values were calculated by two-sample t-test. In addition, state matrices with significantly different MDTs were marked with star when k were 13 ($T = 2.6400, p = 0.0101 < 0.05$), 14 ($T = 2.3359, p = 0.0222 < 0.05$), and 18 ($T = 2.0610, p = 0.0429 < 0.05$).

TABLE 2 | Percentages for three types of connectivity in all clusters of different *k*-values with significantly different MDTs.

Cluster number (k)	Percentage of 1 (weak connectivity)		Percentage of 2		Percentage of 3 (strong connectivity)	
	ASD	NC	ASD	NC	ASD	NC
3	0.5967	0.6687	0.3275	0.2720	0.0757	0.0591
	0.7063	0.6661	0.2598	0.2738	0.0338	0.0600
	0.5059	0.6618	0.3073	0.2782	0.1866	0.0599
5	0.4896	0.6593	0.2876	0.2796	0.2226	0.0610
	0.6784	0.6512	0.2758	0.2809	0.0457	0.0678
	0.7085	0.6704	0.2596	0.2716	0.0318	0.0579
	0.5566	0.6695	0.3424	0.2666	0.1008	0.0638
	0.6196	0.6691	0.3041	0.2795	0.0761	0.0512
8	0.5285	0.6675	0.3368	0.2740	0.1345	0.0584
	0.6573	0.6590	0.2933	0.2764	0.0493	0.0645
	0.4531	0.6531	0.2585	0.2817	0.2883	0.0651
	0.6296	0.6597	0.3180	0.2722	0.0522	0.0680
	0.7198	0.6758	0.2518	0.2698	0.0282	0.0542
	0.7018	0.6500	0.2513	0.2801	0.0468	0.0697
	0.6216	0.6587	0.2970	0.2864	0.0813	0.0547
	0.5290	0.7002	0.3089	0.2605	0.1620	0.0391

Bold percentages were of weak connectivity in clusters with significantly different MDTs at different k-values.

based on Manhattan distance. Clustered centroid matrices were covariance matrices of connectivity states. We used gap, elbow and Calinski Harabasz to estimate the optimal cluster number. However, optimal cluster number of these methods was two and this was improper. So clustering was performed at $k = 2$ to 20, and repeated 150 times per *k*-value. The effectiveness of the states in the ASD and NC was determined upon the span of states in windows number. In this study, reliable state in the ASD and NC covered at least 10 windows; otherwise, state (covered < 10 windows) was unreliable. Mean dwell time (MDT) was calculated at each *k*-value. MDT was the average number of windows that were continuous on the time distribution and classified as the same state, representing the duration of each state.

2.5. Statistical Analysis

Two-sample *t*-test was used to compare the MDTs of ASD and TD children. To detect the differences of connectivity in each connectivity state, subjects with effective state were included in the two-sample *t*-test for the median covariance matrices of each state. In each *k*-value, median covariance matrices were identified by Manhattan distance priority and tested with the two-sample *t*-test, with a threshold ($p < 0.001$) to identify connectivities with differences. Times of different connectivity at each state for all *k*-values were aggregated. Connectivity with frequency of occurrence ≥ 5 times was included in the results.

2.6. Connectivity Strength Discretization

The absolute values of connectivity strength in all covariance matrices for all *k*-values were divided into three levels (1, 2, and 3) by discretization method based on average and standard deviation of TD (0.1828 ± 0.1363) and ASD (0.1698 ± 0.1322) separately. In this study, the connectivity of first level was defined as weak connectivity and last level as strong connectivity. We calculated the percentages for three types of connectivity in all clusters to determine changes in the number of connectivity with different strength in the ASD.

3. RESULTS

Significant differences in the MDTs were found when the *k*-values of k-means clustering were 3, 5, 8, 13, 14, and 18. Functional connectivity of ASD children showed weak connectivity for a longer time as compared to TD children according to the *T*-values. **Figure 2** shows detailed information of the clustered centroid matrices with significantly different MDTs. **Table 2** shows the percentage of three connectivity strength levels at *k*-values with significantly different MDTs. The clusters with maximum ratio of weak connectivity were with significantly different MDTs when *k* was 3, 5, and 8. However, unreliable clusters existed when *k*-values were $>$ 8. **Figure 3** shows means and standard deviations of percentages for three types of connectivity when *k*-values were from 2 to 8. **Figures 3**, **4** indicate less means of weak connectivity in the ASD as compared to TD. **Figure 4** also shows that the fluctuation range of percentages for three types of connectivity in the ASD was greater as compared to TD.

The information of abnormal connectivities is presented in **Table 3**, and the ICs connected by these connectivities are shown in **Figure 5**, **Table 4**. The ICs were distributed in cognitive control (ICs: 35, 37, 48, 52, 57, 71, 78, 82), visual (ICs: 25, 30, 50, 56), and default mode (ICs: 40, 83) networks. These ICs mainly involved

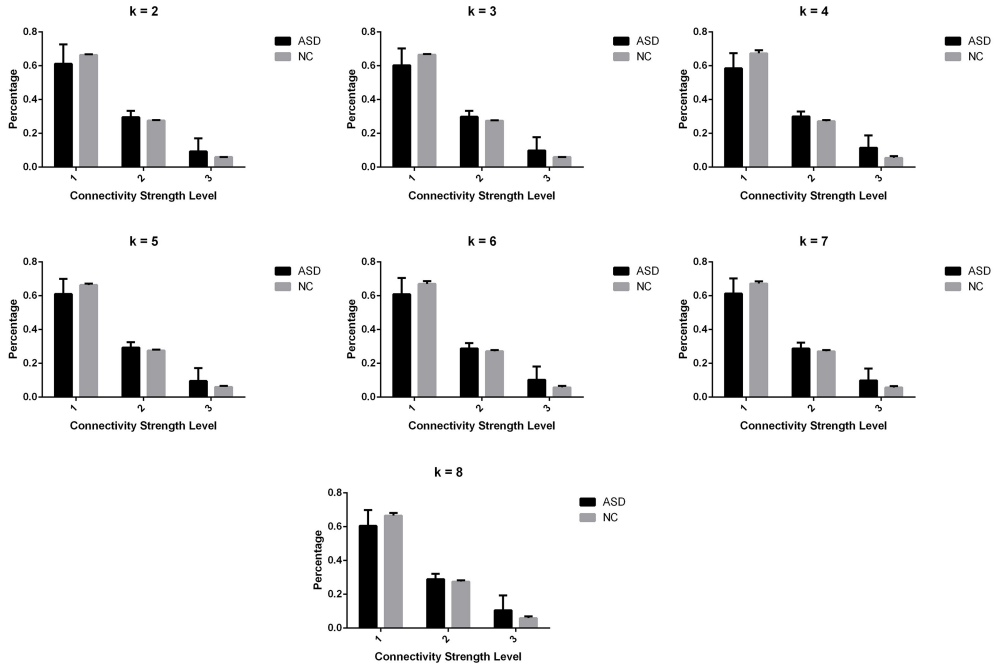

FIGURE 3 | Means and standard deviations of percentages for three types of connectivity at *k*-values from 2 to 8.

TABLE 3 | The abnormal connectivities with ≥ 5 times recurrence in the ASD.

No.	Related components	Frequency of of occurrence	Increase or decrease
1	30, 48	10	Increase
2	37, 57	10	Increase
3	25, 71	6	Increase
4	52, 78	6	Decrease
5	35, 50	5	Decrease
6	40, 83	5	Decrease
7	56, 82	5	Decrease

MOG.L, CUN.L, frontal lobe (ORBinf.L, IFGoperc.R, MFG.R, and SFGmed.L), right temporal lobe (STG.R and ITG.R), ROL.R, FFG.R, CAL.L, INS.R, and PCUN/PCG in spatial distribution.

4. DISCUSSION

The connectivity state in the brain is flexible, which might correspond to diversity of human cognitive functions. Brain connectivity state could change with maturity of the brain, environmental stimulus, and some developmental disorders. And cognitive and behavioral flexibility have been found decreased in the ASD. Also, damages in the connectivities within and between sub-networks (such as default mode, salience, and executive control networks) have been detected in the studies of atypical connectivity patterns and maturation of the ASD (Washington et al., 2014; Abbott et al., 2015).

In the current study, we used time-varying connectivity analysis to detect the impairments of connectivity states in the ASD at resting state. MDTs of brain states with weaker connectivity were abnormal in the ASD (**Figure 2**). Also, ratios of connectivity with different strengths changed more drastically in the ASD (**Figures 3**, **4**). Drastic changes of connectivity strength might mask task-evoked connectivity changes, and make the brain states undifferentiated (Rubenstein and Merzenich, 2003; Uddin et al., 2015).

In our study, ASD showed more divergent connectivity strength of brain state than TD (**Table 2**, **Figure 2**). In the brain, cognitive function depended on connections of specific brain areas. For example, social cognition was related to the prefrontal cortex, the precuneus/posterior cingulate, the hippocampus, the anterior temporal lobes, the posterior superior temporal sulcus and temporo-parietal junction, the fusiform gyrus, the left inferior frontal gyrus, and the anterior insula (Gotts et al., 2012). Hence, some task-evoked functional connectivities were consistent. Based on the consistency, cognitive function state of the brain could be distinguished by whole-brain connectivity patterns (Shirer et al., 2012). Under the same cognitive function, brain states of ASD might diverge from TD due to the disturbed convergence of functional connectivity in the ASD. Also, atypical connectivity patterns of response inhibition were found in previous studies (Kana et al., 2007; Daly et al., 2014).

The abnormal connectivity states may be macroscopical reflection of the excitatory/inhibitory imbalance at the cellular level (Thatcher et al., 2009; Coghlan et al., 2012). In the ASD,

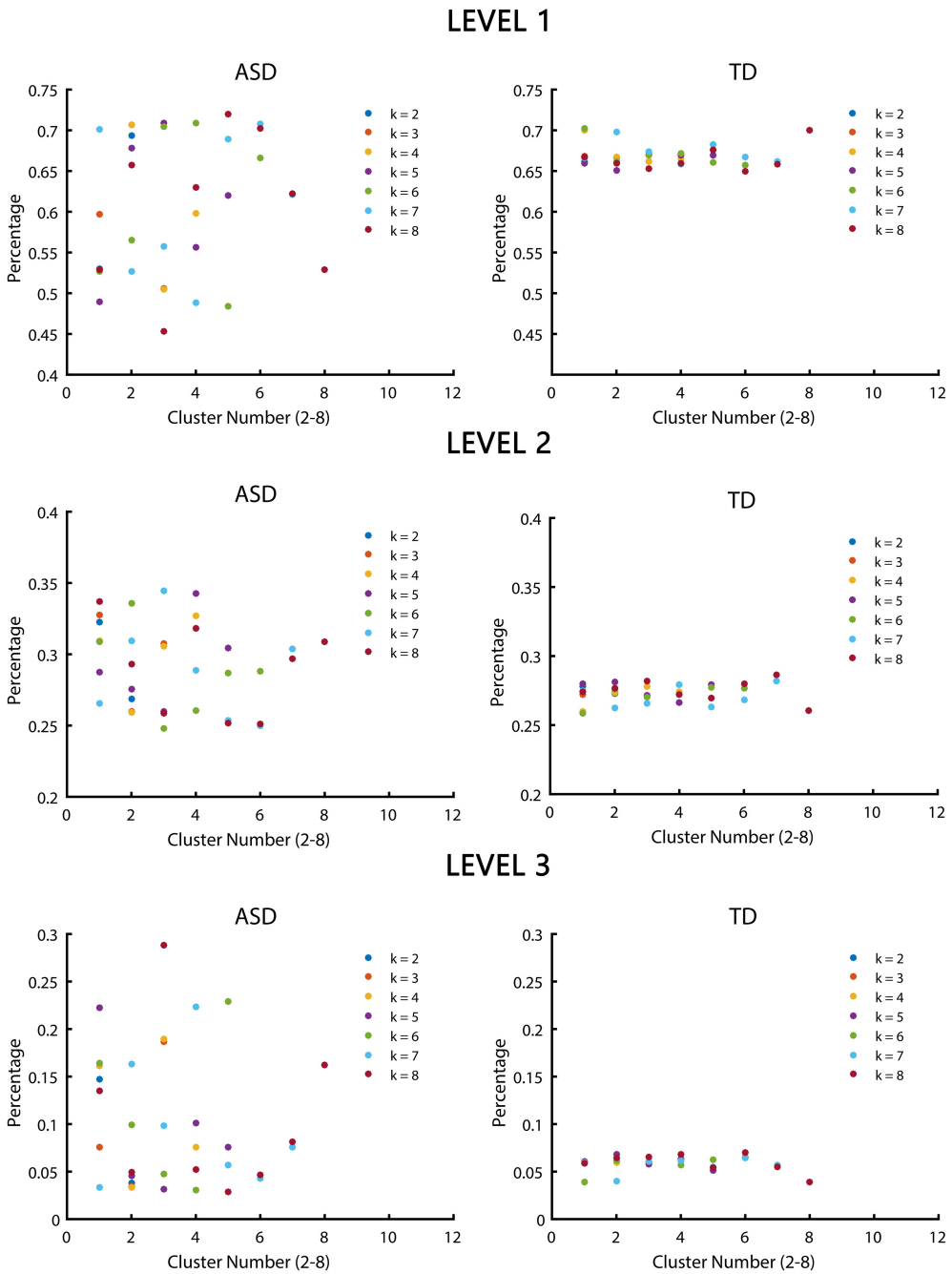

FIGURE 4 | Scatter diagrams of percentages for three types of connectivity at *k*-values from 2 to 8. *K* was the number of clusters in the clustering process. Level 1, level 2, and level 3 represented three types of connectivity.

stereotypical behavior was found to be related to abnormal gamma-aminobutyric acid (GABA) signaling (Chao et al., 2010). A previous study reported that increased inhibition or decreased excitation at the cellular level might be noise for brain spontaneous activity measured by fMRI, and interfere with neural synchronization of brain in the ASD (Dinstein et al., 2011). The disrupted excitatory/inhibitory balance in the nerve cells might result in disruption of the connectivity on the macro scale, because functional connectivity is a measure of the synchronization between discrete brain regions (Dinstein et al., 2011). In addition, increased connectivity between subcortical and cortical cortices from fMRI studies have been observed as well as decreased ratio of GABA to creatinine in the cerebellum and the primary sensory and motor cortices in the ASD (Gaetz et al., 2014; Rojas et al., 2014; Cerliani et al., 2015). The locations of abnormal connectivity and disrupted

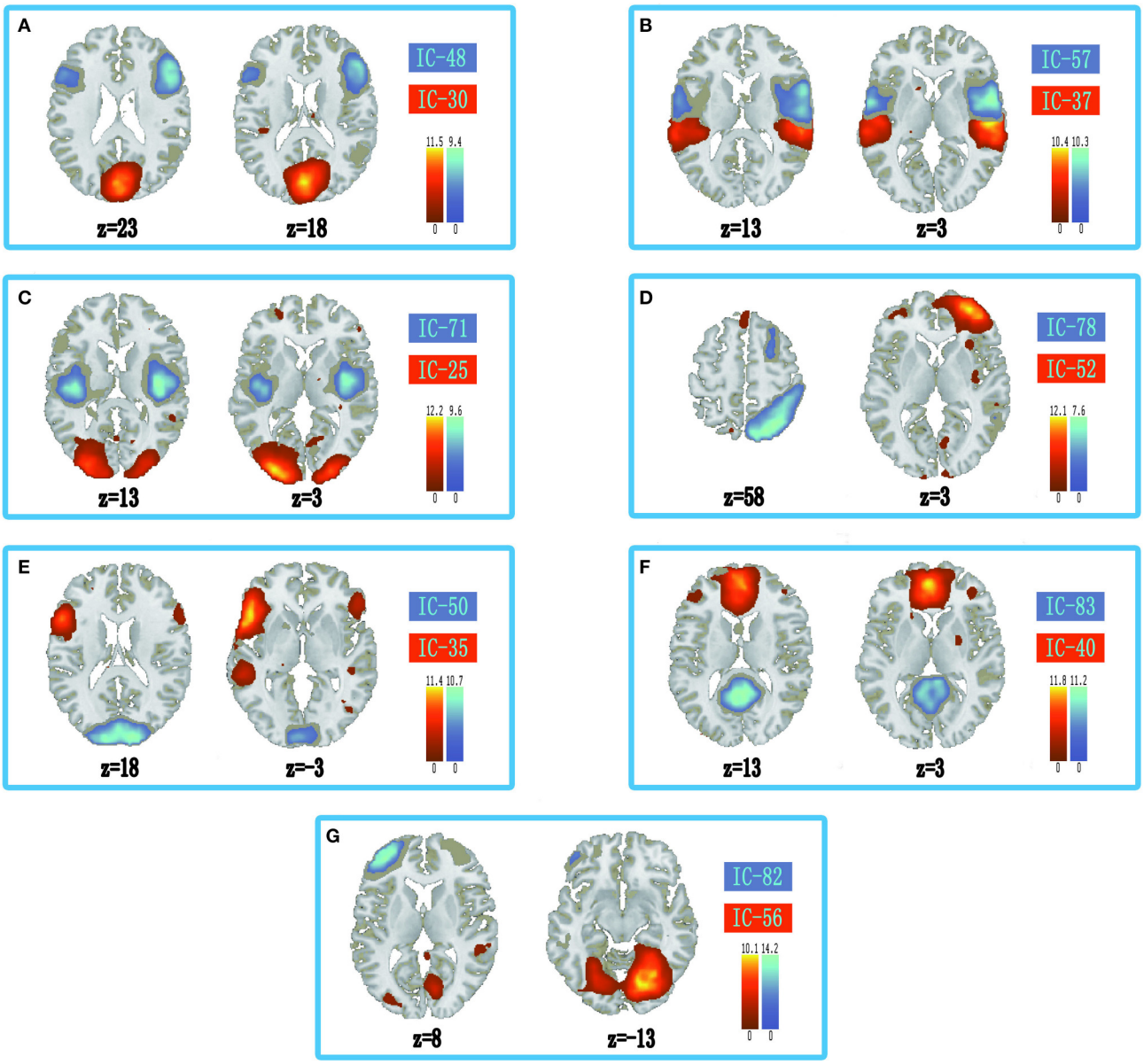

FIGURE 5 | Spatial distribution of independent components linked by abnormal connectivities. The connectivity between independent components in each panel occurred more than five times. **(A)** Red-left cuneus (IC 30), blue-right inferior frontal gyrus: orbital part (IC 48); **(B)** Red-right superior temporal gyrus (IC 37), blue-right rolandic operculum (IC 57); **(C)** Red-left middle occipital gyrus (IC 25), blue-right insula (IC 71); **(D)** Red-right middle frontal gyrus (IC-52), blue-right inferior temporal gyrus (IC 78); **(E)** Red-inferior frontal gyrus: orbital part (IC 35), blue-left calcarine sulcus (IC 50); **(F)** Red-left superior middle frontal gyrus (IC 40), blue-precuneus/posterior cingulate gyrus (IC 83); **(G)** Red-right fusiform gyrus (IC 56), blue-left middle frontal gyrus (IC 82).

GABA signaling were consistent, which might indicate that the abnormal brain activities resulted from aberrant GABA signaling in the ASD. Aberrant connectivity status in fMRI might play an important role in the diagnosis of ASD without obvious clinical symptoms.

In the ASD, several cognitive circuits in the brain were aberrant, such as circuits related to visual control, working memory, inhibitory control, emotion processing, face recognition, etc. Some aberrant connectivities in the ASD were connected to social brain, which were the discrete brain regions dominating social cognition (Frith and Frith, 2007; Gotts et al., 2012). In our results, ASD showed decreased connectivity between posterior and frontal regions in DMN (PCUN/PCG and SFGmed.L, **Figure 5F**). The decreased connectivity was also associated with social deficits, and hampered the ability to maintain a conversation, make eye contact, and perform the pragmatics of language (Assaf et al., 2010; von dem Hagen et al., 2013). In addition, abnormal connectivities in the ASD

TABLE 4 | Peak values distribution of the independent component spatial maps.

Independent Component	Peak MNI coordinate			Peak intensity (*z*-score)	Brain regions
	X	*Y*	*Z*		
25	−27	−96	3	11.3693	Left middle occipital gyrus (MOG.L)
30	0	−81	15	10.9039	Left cuneus (CUN.L)
35	−48	21	−6	11.0173	Left inferior frontal gyrus, orbital part (ORBinf.L)
37	54	−21	3	9.7456	Right superior temporal gyrus (STG.R)
40	−3	54	3	11.3276	Left superior frontal gyrus, medial (SFGmed.L)
48	54	21	33	8.7204	Right inferior frontal gyrus, opercular part (IFGoperc.R)
50	0	−99	6	10.4117	Left calcarine fissure and surrounding cortex (CAL.L)
52	33	57	3	11.2562	Right middle frontal gyrus (MFG.R)
56	18	−78	−9	9.7335	Right fusiform gyrus (FFG.R)
57	57	3	3	9.5117	Right rolandic operculum (ROL.R)
71	39	−6	6	9.1991	Right insula (INS.R)
78	21	−72	54	7.2923	Right inferior temporal gyrus (ITG.R)
82	−36	51	9	13.4001	Left middle frontal gyrus (MFG.L)
83	−3	−63	15	10.8304	Precuneus / Posterior cingulate gyrus (PCUN/PCG)

were also found in and between cognitive control (ORBinf.L, IFGoperc.R, INS.R, MFG, STG.R, ITG.R, and ROL.R) and visual networks (left middle occipital gyrus, left cuneus, left calcarine sulcus, and right fusiform gyrus) in our results. The anterior cingulate cortex, ventrolateral prefrontal cortex, dorsolateral prefrontal cortex, and parietal cortex were associated with cognitive control (Solomon et al., 2014). In the human brain, V1 of visual cortex lies in calcarine sulcus, and motion area of visual cortex is located in the inferior temporal sulcus (Orban et al., 2004). Fusiform gyrus was a key region in face recognition and other social functions (Haxby et al., 2000; Liu et al., 2015). Moreover, CUN was related to control of visual attention and refreshing information in working memory (Makino et al., 2004; Roth and Courtney, 2007; Souliéres et al., 2009). Our results showed decreased connectivity related to visual network in the ASD (**Figures 5A,C,E,G**). In addition, several studies indicated that frontal lobe and right anterior insula played an important role in inhibitory control (Cai et al., 2014; Daly et al., 2014; Shafritz et al., 2015). Our results showed significantly abnormal connectivities linked to medial prefrontal cortex (MPFC) and superior temporal gyrus in the ASD (**Figures 5B,D**), which might be related to aberrant activation levels in these brain regions and abnormally implicit emotion processing in the ASD (Kana et al., 2016). These results showed that abnormally activated brain regions induced by tasks might be aberrant at resting-state, which might display targeted behavior modification in the ASD before clinical symptoms.

The disruption of excitation and inhibition balance at connectivity or circuit level might contribute to clinical symptoms in the ASD. Time-varying connectivity analysis in resting-state fMRI can identify the influence of excitation and inhibition balance on whole brain connectivity state, and abnormal connectivity at resting-state in the ASD. However, underlying pathological mechanisms of ASD relied on the study of neurotransmitters in neurons, and relationship between abnormal connectivity and cognitive function might hinder tasking-state neuroimaging and electrophysiological study. In addition, the volume or scan time of samples was relatively small in this study. Prolonging the scan time could capture more accurate metastable states and data dependence of the method affected the universal application of the conclusion. Our study might reflect some characteristics of time-varying functional state in the ASD and the differences of connectivity states in dynamic network analysis between ASD and TD groups might suggest the imbalance between excitation and inhibition.

AUTHOR CONTRIBUTIONS

ZY, BH, and YX conceived and designed the experiments. ZY, YX, and XC organized and analyzed the raw data. ZY, YX, and GL participated in the statistical analysis and interpretation of data. ZY and YX wrote the article, and BH, FZ, and WZ revised the manuscript.

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OPINION
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Thinking in three dimensions: a different point of view for understanding autism

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Keywords: autism, ASD, prefrontal cortex, sensorimotor, integration, TOM, regulation

Autism spectrum disorder (ASD) is a complex phenomenon. This neurodevelopmental condition is characterized by a hallmark of impairments in social interaction, communication, and restricted activity. Neurocognitive studies in the last three decades provide important insights regarding the pathological development, and the complexity of the ASD condition (Frith, 1989; Belmonte et al., 2004; Baron-Cohen, 2006; Happe and Frith, 2006; Markram and Markram, 2010; Philip et al., 2012; Schore, 2013; Tang et al., 2014; Hahamy et al., 2015).

In this opinion, I discuss the *frontal integration model of ASD* (Ben Shalom, 2009), as a simplified model for understanding autism. I begin by a brief sketch of Ben Shalom's model. Then, I make links between Ben Shalom's model and central neurocognitive theories. I suggest that these novel links mutually elaborate both Ben Shalom's original account as well as these theories. This elaboration offers a three-dimension model that is consistent with frameworks that address neuropsychoanalytic developments in autism, such as developmental deficits in forging a unitary sense-of-self (Schore, 2013).

According to the *frontal integration model of ASD* (Ben Shalom, 2009), neurocognitive processing can be divided into three-levels: (1) a *basic-level* involving primary cognitive, emotional, and sensorimotor processing. For example, a loud unexpected sound that is perceived in primary auditory-sensory systems might trigger physiological emotional-responses, such as, fear (fast heart beats, etc.). (2) an *integrative-level*, that combines the output of all primary processes from the basic-level, and forms a global-coherent meaning, experience, or behavior. For example, the mental representation of the various primary elements that constitute the fear emotional response results in a conscious feeling of being afraid. (3) a *logical-level*, which forms abstract logical rules (if-then rules) from the basic-level. For example, "if I have fast heart beats and cold sweat, then I might be afraid." This three level architecture is applied to four general psychological domains: emotion, memory, sensation-perception, motor.

Ben Shalom (2009) argues that some core ASD abnormalities are the result of deficits in medial-prefrontal cortex. These deficits are manifested in impairments in level-2 *integrative*-processes, which are essential for abilities, such as theory of mind (TOM), emotional-regulation and motor-planning. Moreover, this model suggests that intact level-3 *logical*-processes, can access level-1 basic-processes, and compensate for the deficits in level-2 *integrative*-processes. This type of compensation may assist ASD individuals in understanding and coping with the world around them. For example, an ASD individual with deficits in level-2 integrative-processes may fail feeling typical empathy toward a sad person. However, the ASD individual may rely on intact level-3 processes in order to recognize the emotional state, by forming a logical if-then rule, such as "if a person is crying, then he might be sad." Nevertheless, this compensatory logical mechanism cannot fully cover for the core deficits in level-2 integrative processes. For example, in the absence of integrative-intuitive abilities, such as TOM, compensatory rule-based thinking and behavior often appears rigid and unflexible, accompanied with problems in understanding nuances of

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complex social situations. Consider an ASD individual that tries to apply the rule: "if someone said something that made others laugh then it is a joke, and I should laugh too." While in this situation this ASD individual might laugh, he may not understand why the joke was funny, or may be somewhat confused if some people appear to be crying because they wipe tears from their eyes.

Several existing theories of ASD can be linked to key elements in Ben Shalom's (2009) model. First, the idea that ASD abnormalities relate to deficits in *integrative*-processes, aligns with the *central-coherence theory* (Frith, 1989; Happe and Booth, 2008). According to this theory, ASD individuals display weak central-coherence, that is, a reduction in integrative-processes that pull together large amounts of information into coherent wholes. This theory rests on early concepts of the Gestalt movement, which claimed that perceptual organization is the result of a top-down configuration of the whole, rather than a bottom-up sum of its parts. That is, "*the whole is greater than the sum of its parts*" (Aristotle). The weak central-coherence theory is supported by numerous studies showing that ASD individuals present better *local*-processing than *global*-processing. That is, greater ability to segment the whole design into its component parts, but impaired ability to perceive an integrated-coherent whole (i.e., not seeing the forest for the trees).

Ben Shalom's (2009) idea of impaired integrative-processes is not only consistent with the central-coherence theory, but it can also enrich it, by suggesting that weak central coherence is not limited to perceptual organization, but rather it can also be seen in three other psychological domains: *emotion* (e.g., deficits in forming integrative-conscious feelings to self or other), *memory* (e.g., deficits in the integrative-processes that constitute episodic memory, such as the ability to mentally travel back in time during recollection), and *motor* (e.g., deficits in integrating basic information from several modalities required for motor planning).

Second, Ben Shalom's premise of deficits in level-2 *integrative*-processes together with compensatory level-3 *logical*-processes is also congruent with the *empathizing-systemizing (E-S) theory* (Baron-Cohen, 2006). According to this account, ASD individuals show deficits in *empathizing* (i.e., hypo-empathizing), and an intact or superior ability in *systemizing* (i.e., hyper-systemizing). The term *empathizing* encompasses a range of terms, including TOM, and empathy (Baron-Cohen, 2004, 2006). Specifically, ASD deficits in empathizing, often linked to the medial-prefrontal cortex (Baron-Cohen and Belmonte, 2005), are consistent with Ben Shalom's ideas of medial-prefrontal cortex deficits in level-2 *integrative*-processes. Moreover, the E-S theory suggests that deficits in empathizing may range in severity (Baron-Cohen, 2006), and as such it extends Ben Shalom's model that concentrates on a general dysfunctionality.

Furthermore, the ASD *systemizing* idea suggested by the E-S theory (Baron-Cohen, 2006), aligns with Ben Shalom's idea of *logical* rule-based thinking (level-3). According to this idea, *systemizing* involves the formation of rules that are based on examining whether repeated application of a particular operation to a certain input, leads to a similar output. This theory posits that the human brain's ability to systemize can vary along eight different levels, from *hypo-systemizing* (low or non-ability to formulate rules), to *hyper-systemizing* (high ability to analyze and formulate rules).

Hyper-systemizing at the highest level may represent an outstanding unique ability, such as phenomenal ability to calculate numbers, or to analyze and compose music—i.e., *savant*-abilities. It has been also suggested, that *savant*-abilities operate by directly accessing low-level, less-processed information that exists in all human brains, but is not normally available to conscious awareness (Snyder, 2009). This idea supports Ben Shalom's suggestion regarding level-3 logical-processes that can compensate for deficits in level-2 integrative-processes, by accessing level-1 basic-processes.

Ben Shalom's idea that rule-based processing may interact with basic-processing, is consistent with the E-S theory that relates *hyper-systemizing* to an increased basic sensory sensitivity (Baron-Cohen, 2006). In this sense, the E-S theory expands Ben Shalom's model by suggesting that ASD abnormalities are not exclusively related to level-2, and can also be seen in level-1 *basic*-processes. These level-1 deficits may present different types of abnormalities, such as sensory *hyper-sensitivity* (e.g., covering ears against loud, unexpected sounds) and *hypo-sensitivity* (e.g., failure to react to pain) (Kern et al., 2007; Miller et al., 2007; Ben-Sasson et al., 2009; Lane et al., 2010; Lloyd et al., 2013).

Third, level-1 deficits in ASD are consistent with the *intense world theory* (Markram and Markram, 2010). According to this theory, hyper-functioning, that is, high-local connectivity within neural assemblies (Belmonte et al., 2004), may lead to excessive flow of information from *sensory* areas to *higher integration* areas, causing overload that can lead to intense experiences, and fragmented understanding of the world (Markram and Markram, 2010).

The integration between Ben Shalom's (2009) model and the aforementioned central neurocognitive theories, suggests that ASD abnormalities can be related to each level of Ben Shalom's model (1-basic, 2-integrative, 3-logical), and each level can be seen as a broad *dimension* that holds multiple types of processes that can vary in their functionalities. Furthermore, different potential deficits *within* each dimension, deficits *between* interacting dimensions as well as compensation between dimensions, demonstrate the complexity of the autism spectrum condition. For example, within the *basic-dimension* a differential profile of sensorimotor deficits can include hyper/hypo-sensitivity in auditory, visual, tactile, smell, somatic, and vestibular processes. These differential basic-dimension deficits may interact with different types of global-integration process deficits in the *integrative-dimension*, and with different types of compensatory high-cognitive processes in the *logical-dimension* (e.g., high ability to formulate rules).

This *hierarchical* three-dimensional model also aligns with neuropsychoanalysis frameworks that address the developmental pathology of social-emotional skills in autism. According to the *regulation theory*, the bi-directional mother-infant emotional-communication serves as a mutual psychobiological emotion-regulation process that is the basis of all later social-emotional skills (Schore, 2013). These mother-infant mutual interpersonal emotion-regulation processes begin with early

unconscious emotional communications that are based on primary *sensorimotor* processes (e.g., visual-facial, auditory-prosodic, tactile-gestural). Later in development, these *basic* interpersonal regulatory processes become more holistically *integrated*, enabling the emergence of intrapersonal self-regulation and a coherent sense-of-self (Schore, 2013; Schore and Schore, 2014).

The regulation theory suggests that the infant's social-emotional development is manifested in a *hierarchical* development of interconnected *right-brain-limbic* areas. For example, in the basic-dimension, the right *amygdala*, which is functional at birth, is responsible for various rudimentary elements of emotional-communication, such as production/recognition and arousal-regulation. Importantly, the right amygdala, which is characterized as "a hub of a network" (Markowitsch and Staniloiu, 2011), forms novel connections with multiple integrative self-regulatory regions including the right *anterior-cingulate*, and the right *orbitofrontal cortex*. These regions are responsible for *integrative*-intuitive assessment of complex social situations (Schore, 2013).

The regulation theory posits that basic mother-infant emotional-communication can either facilitate or inhibit the maturation of the infant's self-regulatory processes and social-emotional skills (Schore, 2013). In this sense, deficits in the infant's *basic-dimension*, such as hyper-aroused amygdala (Schumann et al., 2009), and hyper/hypo-sensitivity in primary sensorimotor processes (Ben-Sasson et al., 2009; Lane et al., 2010; Lloyd et al., 2013), may relate to an intense dysregulated emotional state (Markram and Markram, 2010), in which mother-infant sensorimotor emotional-communication is disrupted. These disruptions result in deficits in the infant's integrative dimension development. Deficits between these interacting dimensions, may explain the autistic infant's dissociative withdrawal from the intense emotional world around him (Markram and Markram, 2010; Schore, 2013), and the autistic's need for sameness of environment and activities.

According to the three-dimensional model, repetitive activities may relate to different deficits and compensatory processes within and between dimensions. This illustrates the idea that Ben Shalom's model is non-deterministic, allowing different etiologies to similar symptoms. For example, echolalia (i.e., repetition of phrases, words or parts of words), may serve a self-regulatory function (Prizant and Duchan, 1981), by helping ASD children gain control over their experience when there is intense sensory-emotional arousal in the *basic-dimension*. At the same time, echolalia may also relate to compensatory processes in the *logical-dimension*, because repetitions are needed to formulate logical-rules, or serve as a way of communication (Prizant and Duchan, 1981), as if saying "I heard what you said, and I'm still processing it."

Thinking in these three-dimensions offers a simplified model that may help in understanding autism across different theoretical frameworks and therapeutic techniques. For example, addressing the *basic-dimension* and assessing primary sensorimotor processes are most important when assisting the infant or the child to regulate (or work around) his emotional-sensorimotor experience. These intense emotional-sensorimotor experiences may relate to bodily terrors in the autistic psychic experience, such as "liquefying/burning/freezing," and "losing part of the body," when experiencing physical separation from the caregivers (Tustin, 1972, 1986). Early intervention, that facilitate mother-infant social-emotional communication, and mental connections between emotions, feelings, thoughts, sensations and behavior, may facilitate neural connections (Sullivan et al., 2014). Moreover, assessing the *logical-dimension*, and nurturing rule-based abilities that can compensate for impairments in the integrative-dimension, may help ASD individual to cope better in their surroundings and even excel in their fields of interest.

This opinion invites researchers and clinicians to further elaborate this three-dimensional model. Addressing distinct profiles of deficits *within* and *between* dimensions may help to assess and assist the developmental course of ASD individuals.

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Development of thalamocortical connections between the mediodorsal thalamus and the prefrontal cortex and its implication in cognition

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The mediodorsal thalamus (MD) represents a fundamental subcortical relay to the prefrontal cortex (PFC), and is thought to be highly implicated in modulation of cognitive performance. Additionally, it undergoes highly conserved developmental stages, which, when dysregulated, can have detrimental consequences. Embryonically, the MD experiences a tremendous surge in neurogenesis and differentiation, and disruption of this process may underlie the pathology in certain neurodevelopmental disorders. However, during the postnatal period, a vast amount of cell loss in the MD occurs. These together may represent an extended critical period for postnatal development, in which disturbances in the normal growth or reduction of the MD afferents to the PFC, can result in PFC-dependent cognitive, affective, or psychotic abnormalities. In this review, we explore the current knowledge supporting this hypothesis of a protracted critical period, and propose how developmental changes in the MD contribute to successful prefrontal cortical development and function. Specifically, we elaborate on the unique properties of MD-PFC connections compared with other thalamocortical afferents in sensory cortices, examine how MD-PFC innervation modulates synaptic transmission in the local prefrontal circuitry, and speculate on what occurs during postnatal development, particularly within the early neonatal stage, as well as juvenile and adolescent periods. Finally, we discuss the questions that remain and propose future experiments in order to provide perspective and novel insights into the cause of neuropsychiatric disorders associated with MD-PFC development.

Keywords: mediodorsal nucleus of thalamus, prefrontal cortex, development, cognitive function, psychiatric disorders

INTRODUCTION

The prefrontal cortex (PFC) was originally defined as the projection area of the mediodorsal (MD) thalamus (Rose and Woolsey, 1948), and this was further confirmed with anatomical studies in rodent (Guldin et al., 1981; Groenewegen, 1988; Uylings et al., 2003) and primate brains (Goldman-Rakic and Porrino, 1985; Giguere and Goldman-Rakic, 1988). With its critical roles in cognitive processes, such as working memory, attention, and cognitive flexibility, illumination of the subcortical regulation of the PFC is fundamental to further understanding these abilities. More than a half-century since the initial observation of the MD's extensive reciprocal innervation of the PFC, numerous studies have focused on understanding the role of the MD network in cognitive function (see reviews, Kuroda et al., 1998; Ongür and Price, 2000; Constantinidis and Procyk, 2004; Watanabe and Funahashi, 2012; Baxter, 2013; Funahashi, 2013; Mitchell and Chakraborty, 2013). However, the functional relevance of the MD-PFC circuitry has remained somewhat elusive, specifically how developmental changes in the MD contribute to prefrontal cortical development and function.

A recent study reported an excess of neurons in the human newborn MD compared with that of the adult, suggesting a potential role for extended developmental processes to regulate cell survival in this region (Abitz et al., 2007). In rodents, during the first postnatal week, MD afferent arrival precedes PFC lamination, and thus has been hypothesized to be instrumental to proper differentiation, synaptic organization, and circuit formation in the early neonatal stage (Van Eden, 1986). Yet, behavioral data suggest that MD input is most critical in late postnatal development, such as juvenile and adolescent periods, in which disturbance of MD activity can have deleterious consequences for the execution of PFC-dependent functions like working memory (Vicedomini et al., 1982). This raises the interesting question of whether there is a time window in which MD input is most influential for PFC development. Further, it calls for a more detailed exploration of how MD activity is able to shape the maturation of the PFC circuitry during postnatal development.

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA, gamma-aminobutyric acid; MD, mediodorsal nucleus of thalamus; NMDA, N-methyl-D-aspartate; PFC, prefrontal cortex.

It is widely believed that cortical development is experience and activity dependent. Thus, with the MD providing the majority of excitatory innervation to the PFC, determining how MD activity and afferent fibers affect the development of executive functioning is of considerable importance. The advent of advanced experimental techniques that allow for precise dissection of whether and how a nodal dysfunction in a cognitive circuit affects the development of certain mental attributes represents an extremely exciting time for inquiry in this field. With this in mind, we will return to the seminal anatomical and lesion data that suggest an expanded window for the MD to regulate PFC maturation. Using this as a guide, we will suggest potential mechanisms through which the MD may affect PFC development. Then, after discussing briefly what is known about the MD's involvement in cognition in adulthood, we will propose experiments and discuss future directions in the realm of understanding the MD thalamus and its role in the development of successful PFC-associated cognition.

MD-PFC DEVELOPMENT

Using tract-tracing techniques, early studies indicate that in rodents, MD fibers have arrived in the PFC by birth. These fibers can be found densely coursing through the deeper cortical levels, which will develop prior to the superficial layers. However, what is most intriguing is the sizable projection present in the upper cortical plate, what will later become layer III (Van Eden, 1986). This is in contrast to the developmental trajectory in primary sensory cortices, where thalamocortical innervation occurs days later around postnatal day 4 (P4; Wise and Jones, 1978). The majority of MD innervation of the PFC takes place in layer III (Leonard, 1969; Krettek and Price, 1977). Given that MD projection arrival predates the development of its site of termination, it has been suggested that this innervation may shape the future dendritic architectures of layer III PFC neurons, more so than other thalamocortical afferents in primary sensory cortices (van Eden et al., 1990). The density of this MD projection will continue to increase until it peaks at P10, once cortical differentiation of layer III occurs. However, in the early juvenile stage, at P13, a profound reduction in innervation has been reported through retrograde tract-tracing experiments in mice (Rios and Villalobos, 2004). After P16, the mean average shows a slight increase until P60, after which afferent density remains relatively stable (Rios and Villalobos, 2004).

Notably, changes in the quantity of MD fibers appear to mirror and precede volumetric alterations in the PFC, further suggesting that the MD plays a critical regulatory role over prefrontal cortical development (Van Eden and Uylings, 1985; Van Eden, 1986; Rios and Villalobos, 2004). Following just days behind the arrival and subsequent increase in the density of MD afferent terminals, the PFC undergoes a vast increase in volume (see **Figure 1**), which peaks on average at P24 and P30, for medial and orbital PFC, respectively. Then a decrease occurs in juvenile PFC volume that follows an earlier decrease in the density of MD thalamocortical innervation (Van Eden and Uylings, 1985; Rios and Villalobos, 2004). Data suggest that this reduction in volume may be a reflection of a loss of dendritic complexity and spine density in PFC pyramidal neurons (Marmolejo et al., 2012). This could stem from a refinement of the proper synaptic contacts between the MD and PFC and axonal pruning in the PFC local circuitry, resulting in a net reduction in PFC volume. However, in humans, a profound reduction in MD neuronal number is observed over development. Specifically, the total quantity of neurons in the entire MD was an average of 41% lower in the adult vs. the newborn brain (Abitz et al., 2007). This is the first demonstration of a higher amount of neurons in the neonatal MD compared with the adult, although whether this is also the case for the rodent or primate brain is unclear. Nonetheless, the development of PFC circuitry seemingly under regulation of the MD, proceeds through specific developmental stages or critical windows. This is an intriguing possibility, but requires further experimentation in support of this claim. For example, whether this pattern is seen similarly across species, as well as demonstration of whether experimental reductions in MD afferent density can disrupt these PFC fluctuations would need to be explored. Whether PFC development is dictated through reductions in MD cell density, afferent innervation, or both, the ultimate mature phenotype of either structure is not attained until early adulthood.

Early evidence from animal studies suggests that primary sensory and motor cortices reach developmental maturity prior to regions of association or higher-order cortex such as the PFC (Guillery, 2005). Utilizing measures such as regional blood flow and glucose metabolism, researchers have demonstrated that similarly in humans, the frontal regions show a delayed maturation in comparison with sensorimotor areas (Chiron et al., 1992; Chugani, 1998). Thalamocortical synaptic connectivity in the PFC continues to increase into the late teens (Alkonyi et al., 2011), while myelination, a marker of mature axons, has been suggested to not be complete until the fourth decade of life (Yaklovev and Lecours, 1967). While all regions seem to proceed through distinct phases, including an overproduction of spines and a subsequent reduction, this process is elongated in the PFC. Additionally, the magnitude of this overproduction is exaggerated in the PFC with a tremendous excess in spine number, as well as a slower rate of pruning (Elston et al., 2009). This significant delay is critical because it creates a protracted window for neuronal activity from other brain regions, such as the MD, to mold the development of the PFC (Kolb et al., 2012). It may even allow for greater levels of metaplasticity (a form of activity-dependent changes in neural functions that modulate subsequent synaptic plasticity) than regions with shorter developmental windows (e.g., primary sensory cortices). Through allowing for such a high level of overproduction, there is an enormous potential for experience and environmental influences to affect how the PFC will mature. However, this creates a double-edged sword, given that the PFC needs this plasticity to allow for maximal development of higher order cognitive functions, but it also leaves this brain region in a delicate position to be more easily compromised by various insults, such as stress. This highlights an important window from birth to early adulthood, wherein developmental insults may dysregulate the proper pattern of reciprocal innervation between the MD and PFC.

Accordingly, disturbances localized at both nodes along this pathway have been demonstrated to be present in different

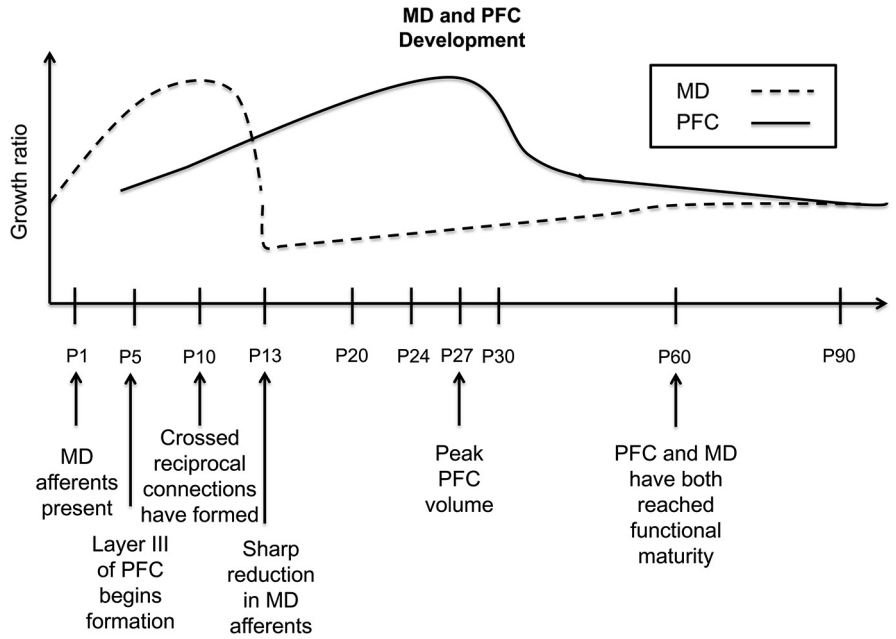

FIGURE 1 | Timeline of the developmental trajectory of MD afferent density and PFC volume in the rodent PFC. Dashed black line—MD afferent density to the PFC, solid black line—PFC volume. MD afferent arrival precedes the differentiation and lamination of layer III; the density of this projection increases through P10, then decreases sharply at P13, and stabilizes by P60. PFC volume begins increasing at P5, reaching its peak around P27, dropping rapidly around P30, and then decreasing gradually until P90. Given that the PFC volumetric changes follow closely behind the density dynamics of inputs from the MD, this may suggest a regulatory relationship of MD innervation on PFC development. This summary graph is based on the previous publications (Van Eden and Uylings, 1985; Van Eden, 1986; Rios and Villalobos, 2004).

psychiatric disorders of potential developmental origin, such as schizophrenia, autism, and depression. Yet, how the MD-PFC connections are affected in the disease state remains to be determined. For example, MD thalamic volume or cell number (Pakkenberg, 1990; Popken et al., 2000; Young et al., 2000) and activity dysregulation (Andrews et al., 2006; Minzenberg et al., 2009) have been implicated in schizophrenia neuropathology. Thus, it has been speculated that decreases in MD activity could result in a loss of synaptic drive to the PFC early in development, leading to a decrease in PFC synaptic density (Minzenberg and Carter, 2012). This hypoinnervation may also underlie the gray matter reductions that have been observed in schizophrenic patients in adulthood (Zipursky et al., 1992; Schlaepfer et al., 1994). Conversely, the reverse situation could be hypothesized, where there is an overactive thalamocortical drive to the PFC, leading to a failure of normal developmental synaptic pruning, as has been demonstrated recently to take place in autism (Tang et al., 2014), i.e., a hyperconnectivity in the PFC (Belmonte et al., 2004). Concurrently, research points to a correlation between thalamus and total brain volume that is preserved in healthy controls and children with autism (Hardan et al., 2008), but lost in samples that incorporate adults with the disease (Tsatsanis et al., 2003; Hardan et al., 2006). However, interpretation of these findings becomes difficult in light of imaging data demonstrating a hypoactivation of the thalamus that occurs in autism spectrum disorders (Buchsbaum et al., 1992; Baron-Cohen et al., 1999). Although the nature of the thalamic disruption in autism is unclear, there seems to be a dysregulation of the normal reciprocal synaptic relationship between the thalamus in the cortex that occurs during development (Fair et al., 2010; Righi et al., 2014). If MD afferent quantity is strictly coordinating PFC synaptic density, hypothetically, thalamic abnormalities could disrupt the normal developmental reduction in synapse number resulting in an over-pruning or under-pruning and compromising PFC function (see **Figure 2**). Thus, it is critical to illuminate what specific alterations in MD-PFC connections occur in the disease condition to better elucidate how these changes contribute to PFC-dependent behavioral deficits.

MD-PFC CONNECTIVITY

The rodent MD is delineated into four major regions, central, medial, lateral, and paralamellar (Krettek and Price, 1977), but can be more broadly grouped into the central/medial and lateral regions (Van Eden, 1986). Similarly, in primates, there is a medial magnocellular portion (MDmc), a lateral parvocellular subdivision (MDpc), but also a lateral multiformis and densocellular portion (Goldman-Rakic and Porrino, 1985; Giguere and Goldman-Rakic, 1988; Barbas et al., 1991). The MDmc targets areas more medially situated in the PFC, such as the ventral and medial PFC, while the MDpc innervates the dorsolateral and dorsomedial areas (Giguere and Goldman-Rakic, 1988; Barbas et al., 1991). As mentioned, these afferents innervate primarily

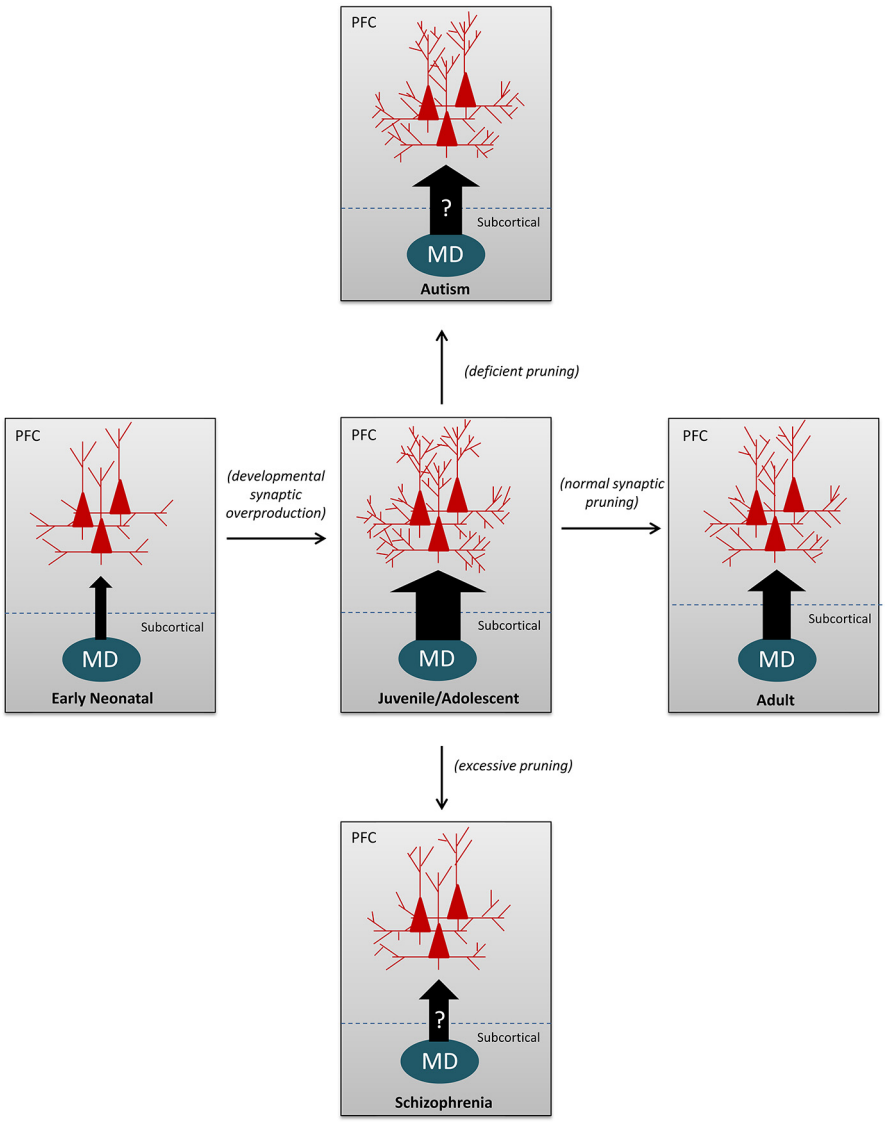

FIGURE 2 | Schematic illustrations to depict the MD-PFC afferents and synaptic pruning under both normal and abnormal developmental conditions. The arrow sizes represent the relative numbers/densities of MD-PFC afferent fibers; whereas the number of dendritic branches in the PFC pyramidal neurons reflect changes in synaptic density and dendritic complexity. During normal development, both thalamocortical afferent fibers and dendritic branches of pyramidal neurons in the PFC are underdeveloped in the early neonate, over-produced during the juvenile and adolescent periods, and then reduced to normal levels in adulthood by eliminating the excess presynaptic axonal arbors (thalamocortical fibers) and/or postsynaptic dendrites. In contrast, as speculated, decreases in MD activity could result in a loss of synaptic drive to the PFC early in development, leading to a decrease in synaptic density, as is observed in patients with schizophrenia. Conversely, a presumably overactive thalamocortical drive to the PFC, could lead to a failure of the normal developmental synaptic pruning, resulting in increased spine density or hyperconnectivity, as demonstrated in autism.

layer III, but also sparsely layer I (in rodents) and layer IV (in primates), while reciprocal connections originate from layer VI and V (Krettek and Price, 1977; Van Eden, 1986; Giguere and Goldman-Rakic, 1988; Groenewegen, 1988). Interestingly, in rodents, the destinations of these different MD areas show distinct developmental patterns, further strengthening the possibility of MD activity regulating the maturation of its target region. The medial MD innervates the prelimbic, dorsal and ventral agranular insular cortex, and these regions show a peak in volumetric density six days prior to the dorsal anterior cingulate cortex (dACC) and medial precentral cortex, areas innervated by the lateral MD (Van Eden, 1986). PFC axons intended for the MD form reciprocal connections between P4 and P10, prior to the peak and later decrease in PFC volume (Van Eden, 1986). This reciprocal innervation is mediated by glutamatergic neurotransmission between the two regions (Pirot et al., 1994; Sherman, 2014).

MD projections synapse directly onto apical dendrites of pyramidal neurons in the PFC (Kuroda et al., 1995; Négyessy et al., 1998). This would imply that coincident with functional

synaptic activity, there is the capacity for glutamate release to cause α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) facilitated depolarization of PFC neurons. Given that cortical development is believed to be activity-dependent (Katz and Shatz, 1996; Catalano et al., 1997), it is likely that the MD's glutamatergic innervation has functional consequences for the maturation of PFC neurotransmission, and this will be elaborated upon in the following sections. Through neuronal processes such as activity-dependent upregulation of the expression of certain neurotrophins like brain derived neurotrophic factor (BDNF; Lu, 2003), as well as NMDA-mediated facilitation of calcium influx and subsequent intracellular signaling cascades (Marmolejo et al., 2012), the MD is in a position to exert a critical regulatory role over plasticity and maturation in the PFC.

EFFECTS OF MD-PFC AFFERENTS ON EXCITATORY NEUROTRANSMISSION IN THE PFC

Synapse development, fine-tuning, and maintenance are heavily reliant on early developmental activity (Goodman and Shatz, 1993). NMDA receptor (NMDAR) function in the PFC, which is pivotal in these processes, is widely recognized as operating importantly in cognitive abilities (Wang et al., 2008, 2013), as well as being linked to cognitive dysfunction in schizophrenia (Snyder and Gao, 2013). During development, NMDARs undergo a developmental shift where the decay time of NMDAR-evoked excitatory currents shortens (Sheng et al., 1994; Flint et al., 1997). Underlying this decrease in NMDAR current decay time is a shift in subunit expression, particularly a switch between the NR2B and NR2A subunit (Monyer et al., 1994). Further, this shift is activity-dependent and is correlated with associative learning. Thus, disruption of early activity prevents this normal maturation (Carmignoto and Vicini, 1992) and learning capability (Dumas, 2005). Given this evidence, it is possible that MD glutamatergic innervation of the PFC helps to facilitate the activation and maturation of NMDARs in the PFC, and thus is critical in plasticity and synapse refinement underlying learning and memory processes.

Data from sensory cortices suggest that a loss of excitatory input would impair the developmental progression of excitatory synapse refinement (Catalano et al., 1997; Quinlan et al., 1999). However, NMDAR development in the PFC appears to be unique and specialized, differing from other cortical areas. Specifically, the PFC lacks a significant NR2B to NR2A subunit switch during development, with the adult level of NR2B-containing NMDARs significantly higher than that of the primary visual cortex (Wang et al., 2008). Thus, the implications for MD disruption on excitatory neurotransmission in the PFC are likely complex and distinct from what occurs in other cortical areas. The effects of a lesion or reduced activity in the MD on PFC NMDAR maturation have yet to be studied, and this certainly represents a vital inquiry to be explored. At present, it remains unclear how MD-PFC afferents shape PFC circuit formation and maintain the excitatory/inhibitory (E/I) balance during development.

EFFECTS OF MD-PFC AFFERENTS ON INHIBITORY NEUROTRANSMISSION IN THE PFC

Gamma-aminobutyric acid (GABA)-ergic neurotransmission follows a developmental trajectory in which GABA release from immature neurons onto a post-synaptic cell results in an excitatory depolarization of neurons during the first postnatal week (Ben-Ari et al., 1989; Staley et al., 1995; Owens et al., 1996; Dammerman et al., 2000). This excitation is a product of the distribution of the chloride (Cl-) pumps, Na-K-Cl cotransporter (NKCC1) and potassium-chloride transporter member 5 (aka: KCC2), that pump negatively charged Cl- into and out of the cell respectively. Early in development there is an upregulation of the expression of KCC2, causing a substantial increase in Cl- extrusion from the cell (Lu et al., 1999; Rivera et al., 1999). Thus, when GABA binds $GABA_A$ receptors, Cl- rushes into the cell, causing hyperpolarization. It has been suggested that the fast inhibitory synaptic neurotransmission facilitated by the release of GABA, specifically from fast-spiking inhibitory interneurons, may help generate oscillations in groups of neurons that underlie certain types of cognitive performance, such as working memory and attention (Gonzalez-Burgos and Lewis, 2008). Indeed, that would make proper regulation of this shift of GABA's reversal potential (E_{GABA}) in the PFC from a depolarized to a hyperpolarized potential, critical for proper development of cognitive abilities.

A crucial role for GABA neurotransmission in facilitating neurodevelopment has been emerging in the developmental literature (Barker et al., 1998; Owens and Kriegstein, 2002). Functional $GABA_A$ receptors are present embryonically (Métin et al., 2000) and it has been demonstrated that these receptors have a higher affinity for GABA and are less vulnerable to early desensitization relative to their adult counterparts (Owens et al., 1999). Further, in the developing cortex, GABAergic synapses constitute almost half of all synaptic junctions (De Felipe et al., 1997). This allows for spontaneous GABA release perinatally to have profound physiological effects on neurons expressing GABA receptors, and also to act as a potent signaling molecule in neuronal development (Wolff et al., 1978). Moreover, it suggests that afferent drive of GABAergic neurons in the PFC may play a significant role in shaping the prolonged development of the PFC. Yet, this assumption remains to be directly examined.

MD projections target both glutamatergic pyramidal neurons and GABAergic interneurons in the PFC (Kuroda et al., 2004; Negyessy and Goldman-Rakic, 2005; Rotaru et al., 2005). This has implications when considering facilitation of GABAergic activity in the mature PFC, but also has important consequences for investigating the neurodevelopment of prefrontal inhibitory circuitry. Data suggests that GABA release in the early developing cortex is able to facilitate the transition of cellular responses to GABA from depolarizing to hyperpolarizing (Ganguly et al., 2001). Although this is mainly hypothesized to be an action potential-independent process (Ganguly et al., 2001), depolarization of GABAergic interneurons by thalamocortical afferents may increase the likelihood of this spontaneous release. Although controversial (Leinekugel et al., 1995; Ben-Ari et al., 1997), AMPA receptor-mediated excitation has been shown to play a role in the facilitation of GABA-induced depolarization.

Thus, the MD could provide a portion of the excitatory drive to GABA interneurons, helping developmentally regulate the maturation of GABAergic neurotransmission in the PFC. Coincidentally, the increase in spontaneous GABAergic currents corresponds with the significant increase in MD innervation of the PFC, and peaks when this afferent input is at its greatest height (Van Eden, 1986; Ben-Ari et al., 1989). This is purely speculative, however, and further experimentation, including repetition of these experiments in PFC neurons *in vivo* and *ex vivo* throughout development, would be necessary to support this hypothesis. If the MD is indeed facilitating this GABA shift, this would have profound consequences for functional connectivity in the PFC, and cognitive abilities that rely heavily on GABA-driven network activity, as well as the E/I balance in the PFC circuitry.

LESIONS AND THEIR IMPLICATIONS FOR MD-PFC DEVELOPMENT

The MD has been implicated in a number of neuropathological diseases, such as schizophrenia, autism, and depression. When you consider MD disruption in the context of the late maturity of the PFC, it has fundamental ontogenic implications. To explore these questions, a number of researchers have employed an array of lesion methods at various points in development and have studied the effects on PFC-dependent functions.

Strengthening the claim that the MD regulates PFC function in adulthood is the plethora of data indicating that lesions of the MD result in deficits in PFC-dependent abilities. For example, MD lesions impair performance in various tasks that measure working memory and executive function, such as the T-maze, radial maze, and set-shifting (Winocur, 1985; Stokes and Best, 1988; Hunt and Aggleton, 1991; Block et al., 2007). However, for many of these cognitive tasks, there are negative data suggesting just the opposite: the MD functions minimally in the execution of these abilities (Beracochea et al., 1989; Neave et al., 1993). These contradictory results could partially be attributed to the variety of the methods used for employing these lesions in early studies. However, the development of more sophisticated lesioning methodology has painted a clearer picture of MD function in the recent decades.

Data regarding subregion specificity of deficits is less robust in rodents, given that the majority of studies employ bilateral lesions of the structure in its entirety. However, in primates the relatively well-delineated boundaries of the MD have allowed for localized lesions and demonstration of specific patterns of deficits. For example, excitotoxic and neurotoxic lesions of the MDmc result in deficits in reinforcer devaluation and scene learning, skills that depend on an intact orbital frontal cortex, the recipient of MDmc fibers (Mitchell et al., 2007a,b). The dlPFC is implicated heavily in working memory processes, and accordingly, lesions involving the lateral MD cause impairments in spatial delayed alternation and delay-response tasks. Additionally, lateral MD neurons seem to represent cue, delay, and response related information necessary for performing a delayed-response task (Tanibuchi and Goldman-Rakic, 2003). Data such as this led to the dogma that the MD is simply relaying information from its extensive afferent network for use by the PFC for execution of cognitive tasks.

Obfuscating this simple congruity of major MD sub-region to its primary cortical target, however, is data indicating that medial MD lesions also cause deficits in delayed non-match to sample tasks, a measure of working memory. In addition, deficits seen following lesions seem to apply more heavily to the integration of newly learned rules or information necessary for completion of tasks, and not re-application of previously learned rules or strategies, which are affected by compromising the function of the corresponding MD projection regions. For example, MDm lesions do not impair retention of pre-operatively learned scenes in a scene learning task, but animals show significant deficits when learning novel scenes (Mitchell et al., 2008; Mitchell and Gaffan, 2008). A similar pattern may exist with strategy implementation as well (Mitchell et al., 2007a). Parallels are also seen in humans with diencephalic damage; patients with lesions which are restricted to the thalamus show fewer instances of retrograde amnesia (Baxter, 2013). This suggests, that the MD generally may play a stronger role in integration and processing of novel information for use by the PFC, challenging the long-standing hypothesis of its function as a passive relay. This topic has been discussed thoroughly in many recent excellent reviews (Baxter, 2013; Funahashi, 2013; Mitchell and Chakraborty, 2013).

An emerging thread in early research, that has been left somewhat dormant in the recent years is exploring differential outcomes of lesions of both the PFC and MD at varying developmental timepoints. Conclusions from this pioneering work suggest that age at time of lesion is critical, and has important implications for cortical reorganization as well as functional recovery (Kolb and Gibb, 2007). Based on the timeline of MD-PFC development, it is not difficult to hypothesize that morphological changes and the extent of functional alterations would be an age-dependent phenomenon.

EFFECTS OF LESIONS OF THE PFC ACROSS DEVELOPMENT ON MD-PFC CONNECTIONS

Early studies suggested that frontal lesions in adult rodents resulted in substantial cognitive impairment, while animals with damage inflicted in early postnatal development had a much greater propensity for functional recovery (Kolb and Nonneman, 1978; Nonneman and Corwin, 1981). Correspondingly in primates, juvenile and adolescent lesions, specifically of the dlPFC, result in a profound impairment in delayed alternation performance (Goldman and Galkin, 1978), a behavior which is spared in prenatally lesioned animals. However, in an elegant series of experiments carried out by Kolb and colleagues, researchers demonstrated that there is a critical period that occurs during the second postnatal week in rats, within which the brain has a tremendous capability for recovery of connectivity and function following lesions. In contrast, prior to and following this time window, animals show profound impairment of PFC dependent abilities (Kolb and Gibb, 1990; Kolb et al., 1996, 1998). In concert, it was demonstrated following frontal lesions during this critical period in both rats and primates, coincident with functional recovery, there was a lack of retrograde degeneration observed in the MD (Goldman and Galkin, 1978; Kolb and Nonneman, 1978). In fact, van Eden et al. reported that in neonatally lesioned animals, MD neuronal cell density was significantly increased. However, after lesions in adults, when animals present with cognitive impairments, a significant

degeneration of MD thalamic neurons has been observed (Kolb et al., 1974; Goldman and Galkin, 1978). This finding led to the hypothesis that the MD may be underlying sparing of PFC-dependent function observed in younger animals (Kolb and Nonneman, 1978). However, others were unable to demonstrate a reorganization of thalamocortical fibers following neonatal prefrontal lesions (de Brabander et al., 1991; Kolb et al., 1994).

Still, this does not rule out the ability of the MD to regulate PFC development and facilitate functional recovery following PFC lesions. The lack of MD neuronal loss following frontal damage that occurs in younger animals, the period in which functional recovery is the most substantial, lends credence to this claim (Goldman and Galkin, 1978; Kolb and Nonneman, 1978; Nonneman and Corwin, 1981). A failure to reorganize projections does not imply that the remaining MD projections do not play a role in sustaining cognitive function. Accordingly, an increase in dendritic complexity in other projection areas has been observed, which may function in rendering PFC-lesioned animals indistinguishable from controls in cognitive tasks (Kolb et al., 1994).

EFFECTS OF LESIONS OF THE MD ACROSS DEVELOPMENT ON MD-PFC CONNECTIONS

Unlike the PFC, early neonatal lesions (P1) of the MD produce negligible deficits in working memory (van Eden et al., 1994). The timing of this lesion prior to the substantial increase in the density of this projection (Van Eden, 1986) may allow for an ample compensation from other thalamic inputs, but this is purely speculative. Similar to PFC lesions occurring in the second postnatal week, however, MD disruption at P8–P10 also results in normal performance in spatial alternation behavior (Vicedomini et al., 1982). Interestingly though, despite the lack of working memory deficits in adulthood, early developmental disruption of the MD at P4 leads to a significant reduction in both the amount of dendrites and dendritic spines in the PFC (Marmolejo et al., 2012). This finding suggests that there may be subtler alterations in PFC synaptic connectivity, which may manifest itself in impairments in more cognitively taxing PFC-dependent tasks such as attentional set-shifting or the five-choice serial reaction task. Nonetheless, interruption of MD function at later points, from the juvenile stage onward results in profound deficits in spatial alternation behavior, and a wealth of other behavioral tasks, suggesting the later stages of PFC maturation rely heavily on the MD's excitatory innervation (Vicedomini et al., 1982).

FUTURE DIRECTIONS AND INSIGHTS

The rise of the use of cutting edge techniques represents an exciting point in the exploration of the role the MD plays in PFC development. With the advent of optogenetics allowing for temporal control of cellular populations with millisecond precision (Boyden et al., 2005), this allows researchers to answer important questions about how the MD is functioning in certain PFC-dependent abilities in an acute manner. For example, this may endow researchers to answer with more certainty the depth of the MD's role in regulating important cognitive functions in adulthood, for which the data thus far has not been entirely consistent. A particular interest is the use of Designer Receptors Exclusively Activated by Designer Drugs (DREADDs; Armbruster et al., 2007; Alexander et al., 2009) for probing PFC circuit function. This novel technology allows for pharmacogenetic down-regulation of specific populations of cells, such as those in the MD. It utilizes ligand-driven activation of receptors, with a drug that can exert its pharmacological action for hours, without the need of continuous light or electrical stimulation. This provides an advantage when exploring the effects of subchronic inhibition in distinct developmental periods. Interestingly, a recent elegant study reported that inhibition of the MD with DREADDs in adult rats can disrupt thalamocortical connectivity and PFC-dependent cognition (Parnaudeau et al., 2013). Following this approach, researchers can begin to explore the major questions raised by this review. Primarily, is MD activity necessary for normal PFC development in the early neonatal period, as anatomical data might suggest? Outputs could include behavior, electrophysiology, as well as biochemical assays. How does MD inhibition in early development affect executive functioning in adulthood? Researchers could also explore the consequences of MD inhibition for single cell activity in the PFC using whole-cell recordings, or groups of neurons while performing cognitive tasks using *in vivo* recordings. This would allow for the precise correlation of neuronal firing patterns with varying levels of cognitive performance, potentially highlighting targets for rescue of cognitive ability. At a more global level, oscillations and synchrony could be monitored to answer whether early MD dysregulation results in changes in frontal synchrony coincident with behavioral impairment in adulthood. Finally, with each of these avenues is an opportunity for the systematic exploration of the underlying pathological mechanisms associated with these changes in function and physiological activity. Thus, an investigation of changes in certain enzymes and receptor distribution, such as those related to excitatory and inhibitory synaptic transmission and plasticity using biochemical assays would be warranted as well. It is critical to explore how MD inhibition affects the maturation of particular receptors and their subtype components in the PFC local circuitry, such as AMPARs, NMDARs or GABARs, all of which are linked to successful PFC-dependent cognitive function. Through this exploration, we can provide important insights into the role of the MD in development of the PFC and related cognitive abilities, and provide novel approaches and targets for the treatment of neurodevelopmental disorders with which MD dysfunction is associated.

In summary, the MD represents a fundamental subcortical relay to the PFC, and is highly implicated in modulation of PFC-dependent cognitive and executive abilities. Further, more recent research challenges the dogma of its role as a passive relay, suggesting it has an important function in the integration of newly learned information for use by the PFC. If this is correct, this underscores the importance of this brain region as a cognitive center, lessening the likelihood of early MD dysregulation being without consequence for PFC maturation. As mentioned, we hypothesize that MD afferent activity may be important in regulation of PFC development earlier than previous data has indicated. Afferent fibers are present prior to thalamocortical

afferents in sensory cortices while reductions in cell number and afferent density have been reported to occur into the juvenile stage and adolescence (Van Eden, 1986; Abitz et al., 2007). This may represent an extended critical period for postnatal development, in which disturbances in the normal growth or decrease of MD afferents can result in PFC-dependent cognitive, affective, or psychotic abnormalities. Therefore, it is imperative for us to further explore how developmental changes in the MD contribute to successful prefrontal cortical development and function. Specifically, it is important to better elucidate the unique properties of MD-PFC connections compared with other thalamocortical afferents in sensory cortices, and to examine how MD-PFC innervation affects synaptic transmission and E/I balance in the local prefrontal circuitry. Finally, we must explore the functional importance of MD-PFC connections in psychiatric disorders such as autism, depression, attention deficit hyperactivity disorder, and schizophrenia. It is our belief that answering these questions will not only enhance our understanding of the MD and PFC function in normal cognition, but also provide perspectives into the cause and pathophysiological processes of neuropsychiatric disorders linked with MD-PFC development.

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Understanding visual consciousness in autism spectrum disorders

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The paper focuses on the question of what the (visual) perceptual differences are between individuals with autism spectrum disorders (ASD) and typically developing (TD) individuals. We argue against the view that autistic subjects have a deficiency in the most basic form of perceptual consciousness—namely, phenomenal consciousness. Instead, we maintain, the perceptual atypicality of individuals with autism is of a more conceptual and cognitive sort—their perceptual experiences share crucial aspects with TD individuals. Our starting point is Ben Shalom's (2005, 2009) three-level processing framework for explaining atypicality in several domains of processing among autistics, which we compare with two other tripartite models of perception—Jackendoff's (1987) and Prinz's (2000, 2005a, 2007) Intermediate Level Hypothesis and Lamme's (2004, 2006, 2010) neural account of consciousness. According to these models, whereas the second level of processing is concerned with viewer-centered visual representations of basic visual properties and incorporates some early forms of integration, the third level is more cognitive and conceptual. We argue that the data suggest that the atypicality in autism is restricted mainly to the third level. More specifically, second-level integration, which is the mark of phenomenal consciousness, is typical, yet third-level integration of perceptual objects and concepts is atypical. Thus, the basic experiences of individuals with autism are likely to be similar to typical subjects' experiences; the main difference lies in the sort of cognitive access the subjects have to their experiences. We conclude by discussing implications of the suggested analysis of experience in autism for conceptions of phenomenal consciousness.

Keywords: autism spectrum disorders, phenomenal consciousness, access consciousness, perceptual integration, categorization

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What are the (visual) perceptual differences between individuals with autism spectrum disorders (ASD) and typically developing (TD) individuals? Do autistic subjects have a deficiency in what is called in standard philosophical jargon "phenomenal consciousness"—the most basic form of perceptual consciousness? Or is it that the perceptual difference between individuals with ASD and TD individuals is of a more conceptual and cognitive sort, whereas the most basic perceptual experiences of individuals belonging to these two groups are similar? Ben Shalom (2005, 2009) suggests a three-level processing framework to explain atypicality in several domains of processing among individuals with ASD, which is highly relevant to these questions. She argues that individuals with

autism and TD individuals do differ in their basic perceptual experiences. In what follows we will discuss the (visual) perceptual differences between individuals with ASD and TD individuals, taking Ben Shalom's tripartite model of perception as a starting point, and present our own view on the issues at hand. We will argue that the evidence tells against the view that autistic subjects have a deficiency in basic perceptual consciousness and support the hypothesis that the perceptual difference between autistics and TD individuals is of a more conceptual and cognitive sort.

In the first section we examine the three-level distinction of perceptual processing proposed by Ben Shalom, by comparing it with two other tripartite models of perceptual processing—Jackendoff's and Prinz' Intermediate Level Hypothesis (Jackendoff, 1987; Prinz, 2000, 2005a, 2007) and Lamme's (2004, 2006, 2010) neural account of consciousness—while emphasizing the role of integration in each model. In the second section we introduce the debate regarding the possible dissociation between two types of consciousness: phenomenal consciousness (or experience) and access consciousness. We discuss each model's stance with regard to this debate. In the third section, we argue that the evidence suggests that in autism second-level integration, which is the mark of phenomenality, is typical, yet third-level integration of perceptual objects and concepts is atypical. In the fourth section we further clarify that argument, and show, further, that it supports the view that individuals with ASD and TD individuals do not differ in their basic experiences, but rather have different cognitive access to those experiences. We conclude by discussing implications of the suggested analysis of experience in autism for conceptions of phenomenal consciousness.

Levels of Perceptual Processing: Examination of Ben Shalom's Model

Tripartite Models of Perceptual Processing

There are several tripartite models of perceptual processing in the literature on perceptual consciousness. Here, we discuss similarities and differences between three such conceptualizations. The first is Ben Shalom's (2005, 2009) framework, used in her analysis of perceptual atypicality in ASD. The other two models are Jackendoff's and Prinz' Intermediate-Level Hypothesis (henceforth, ILH; Jackendoff, 1987; Prinz, 2000, 2005a, 2007), and Lamme's (2004, 2006, 2010) neural account of perceptual consciousness, both of which pertain to the explanation of perceptual experience.

According to Ben Shalom (2005, 2009), processing in different psychological domains takes place at three general levels of processing: basic, integrative and logical. Specifically, in the perceptual domain, conscious object recognition is suggested to involve processing in three levels: (1) a level of basic processing, which does not include a conscious experience of the percept; (2) an integrative level based on perceptual objects, which includes experience; and (3) a logical higher-order level of processing. Ben Shalom suggests that the phenomenon of perceptual object fragmentation among individuals with ASD is the result of atypicality at the integrative level, due to lack of prioritization of the whole integrated object at the expense of object features. The reduced salience of the integrated object can be overcome by effortful logical processing of perception at the third level.

The ILH, proposed by Jackendoff (1987) and elaborated on recently by Prinz (2000, 2005a, 2007), claims that visual processing takes place at three stages that vary in their abstraction, and that conscious visual experience arises at the intermediate level. Similarly to Ben Shalom's model, the theory can be applied to several domains, and here we focus on perception. In the visual modality, the ILH is inspired by Marr's (1982) theory of visual processing. The low-level is "the primal sketch level", which is organized retinotopically, and is responsible for encoding blobs, bars and edges. This level is highly detailed, but does not include a coherent representation of an object. The intermediate-level is "the 2.5D sketch level", which is responsible for the creation of a coherent representation of the object from the specific viewpoint of the observer. The high-level—the "3D model level"—contains a viewpoint-invariant representation that lacks specific details, allowing for the assignment of the object to an abstract category. According to both Prinz and Jackendoff, the high level is ideal for object recognition. That is, the perceptual hierarchy starts from the registration of specific local features, proceeds to the combination of these features into coherent objects (e.g., feature binding) and ends with the processing of abstract properties of the object. Based on introspective and empirical arguments, Jackendoff and Prinz claim that only intermediate-level representations match the content of perceptual consciousness: representations of coherent bound-together objects, including their features represented from a specific point of view.

Lamme (2004, 2006, 2010) distinguishes among three levels of perceptual processing, based on neural processing characteristics: (1) a low level of fast feedforward sweeps; (2) a level of superficial recurrent processing that is limited to visual areas; and (3) a level of deep recurrent processing, in which recurrent processing becomes widespread. At the first level, feedforward sweeps flow serially throughout the visual stream, enabling feature extraction.[1] At the second level—the superficial recurrent processing level—each area to which the feedforward sweeps reaches begins sending feedback to lower levels in local groups, thus enabling perceptual integration of different aspects of objects and scenes into a coherent percept. Similarly to ILH's conception of the intermediate-level, the superficial recurrent processing level is characterized as similar to Marr's 2.5 sketch (Lamme, 2004) and as neural

[1]Lamme has recently divided this level into two distinct levels—superficial feedforward sweeps, which are limited to visual areas, and deep feedforward sweeps, which reach the prefrontal cortex (Lamme, 2010). This distinction leads him to claim that consciousness and attention are orthogonal. This issue is less relevant to our present discussion, and therefore we will focus on the original and simpler version of his distinction.

activity that gives rise to perceptual experience. The third level—the deep recurrent processing level—involves attentional selection of a limited number of local recurrent processes, and manifests in the amplification of these processes to widespread co-activation of visual and frontoparietal regions. Widespread recurrent processing allows accessibility of attended objects to other processes. This stage corresponds to the global workspace conception (Dehaene and Naccache, 2001; Baars, 2005; Dehaene et al., 2006) and to working memory (WM). It should be noted that Lamme's model is highly consistent with other recent accounts of simultaneous bottom-up and top-down processing (e.g., Hochstein and Ahissar, 2002; Bar et al., 2006), which influenced Ben Shalom's model as well (Ben Shalom, 2005, 2009).

The Importance of Integration for Experience

It is noticeable that the three models outlined above share some common ground. Overall, the three models seem to share the same conceptualization of perceptual processing. In all cases, processing begins with extraction of individual features, proceeds with integration of features into coherent objects and ends with abstraction and reasoning. Moreover, all three seem to agree that the content of experience is achieved at the second level of the hierarchy. Both Lamme and Jackendoff and Prinz explicitly argue for this claim and we will shortly outline their considerations in its favor. Ben Shalom does not explicitly present the reasons for her claim that experience should be ascribed at the integrative level. However, her analysis seems to imply that the integration of features into a coherent object is necessary for the emergence of experience.

The main goal of ILH is to claim that the 2.5 sketch level is the locale of the content of experience (Prinz, 2007), i.e., that the content of experience is constituted by second-level representations. According to Jackendoff (1987), the locale of the content of conscious experience can be derived from introspection: the content of our experience is neither as specific as low-level representations nor as abstract as high-level representations, but is rather revealed to us as a coherent bound-together object, including its features represented from a specific point of view. A similar point is vividly made by Treisman (2003): when trying to imagine a triangle, we picture a very specific one, with a certain shape (e.g., a right angle triangle), size, length of sides, orientation, color and location in space, so that all these features are bound together in a particular way. Beyond the argument from introspection, Prinz (2000, 2005a, 2007) argues that detailed viewpoint-specific representations are necessary for deliberate behavioral responses, and that patterns of neuropsychological damage after lesions in areas related to each level support this conclusion as well. However, it should be noted that according to Prinz (2011a), as part of his AIR theory (attended intermediate-level representations theory), the mere processing of representations in the intermediate level is not sufficient for consciousness—only stimuli whose representations are modulated by attention and made accessible to WM are experienced. That is, although the second level is the locale of the *content* of experience, not every second-level representation is experienced.

Lamme (2010) has not only argued in favor of localizing the content of experience at the second level, but also in favor of localizing experience itself at this level. He has argued that representations processed at the second level are phenomenally conscious as part of his neural argument, an argument that bears on the debate that we shall soon present. The neural argument is based on several assumptions. First, Lamme assumes that first-level representations are not experienced. This seems to be agreed on by all models, and consistent with introspection. The second assumption, which is also reasonable and uncontentious, is that third-level representations are conscious, since they are accessible for use in reasoning and behavioral control through WM or the global workspace (i.e., available for report, reasoning and the production of intentional behavior). The third assumption, which is the most important to our current discussion, is that neural processing at the second level is more similar to the third level than to the first, since it underlies properties necessary for consciousness, notably integration and plasticity. Recurrent processing, whether deep or superficial, allows interactions between areas, so that processing in areas that are located higher in the feedforward hierarchy affect and modify processing in lower areas of the hierarchy. This enables aspects of integration such as feature binding and grouping, which, as argued above, are key properties of experience. As Lamme emphasizes, second level activity produces high Φ, which according to Tononi (2007) denotes the amount of integrated information generated by a system when switching from one processing state to another. In Tononi's words, "subjective experience *is* integrated information" (2007, p.297; emphasis in the original), and generation of high Φ is the criteria for conscious systems. Recurrent processing also gives rise to plasticity and learning, by satisfying Hebb's rule. Because the second level is more similar to the third level than to the first, Lamme concludes that second level representations are experienced as well. That is, according to Lamme the second level is not only the locale of the *content* of experience, but also the locale of experience *itself*: second-level representations are experienced in virtue of being processed at this level.

Although all three models agree that integration takes place at the second level, and that integration is essential for experience, they seem to disagree on the type of integration achieved at this level. According to Ben Shalom, integration at the second level is not only perceptual, but also includes precise categorization. For example, when perceiving a white plate, the integrative level is in charge of making the representation of the integrated object "plate" more prominent than the representations of its separate features, "white" and "round". Due to abnormal integration, for people with ASD the representation of the object (e.g., "plate") is not amplified (Ben Shalom, 2005).

In contrast, ILH suggests that precise categorization occurs only at the third level Prinz (2005a, 2007). The second level contains a 2.5D sketch of the world, and thus integration is interpreted as binding of features into a coherent object from a specific point of view. ILH argues that the third level is

the one most suitable for object recognition, since the 3D model of the world contains abstract and viewpoint-invariant representations. As part of his defense on concept empiricism, Prinz has argued that concepts are mental representation of categories in WM (or that can be in WM), that are based on the identification of perceived objects (Prinz, 2002, 2005b, 2012; see also Barsalou, 1987, 2005). Concepts are constructed from representations in long-term memory that are based on third-level representation rather than on second-level representations. This entails that a representation of an object must be formed prior to categorization, at least in a tentative manner. Although this issue is debated in the philosophical literature, Prinz's (2007, 2011a) stance is that high-level perceptual representations (such as concepts or categories, e.g., being a chair) are not part of the content of our experience: even-though third-level representations of concepts can be activated in WM, they are not experienced (but see, e.g., Siegel, 2010, for a contrary view). Prinz (2011b) supports this claim with an example of patients with semantic dementia, who cannot recognize objects and use conceptual knowledge but nonetheless have typical object perception phenomenology (e.g., match images). Thus, ILH would argue that when perceiving a white plate, the features "white" and "round" are bound together at the intermediate level, forming a combined representation of the conjunction "white and round", whereas the category "plate" is assigned to the object at the third level, after the creation of a 3D viewpoint-invariant representation. It should be noted that this process is not strictly bottom-up, and top-down information can affect categorization as well as experience. For example, context can affect the concept representation that will be used in WM in a certain situation (Prinz, 2002, 2011b). However, in the absence of contextual information, a default representation of the concept will be active in WM. In addition, concepts can alter second-level representations in a top-down process.

In Lamme's model, categorization is achieved gradually, with different degrees of categorization occurring at different levels. Although Lamme (2010) regards his second level as similar to Marr's 2.5D sketch (2004), he also argues that conscious percepts are characterized by integration of features and categories, which enables feature-invariant processing and differentiation of the object from other categories (e.g., not a house), a description that better matches the 3D sketch. Lamme has suggested that there is a higher type of integration at the third level. For example, an identification of the stimulus as a face (rather than a still object) is achieved prior to recognition of the identity of the face (Lamme, 2010). Therefore, he may regard basic categorization (e.g., faces vs. still objects) as occurring at the second level and specific categorization (e.g., recognition of the type of still object as a plate) as achieved at the third level.

Lamme's notion of degrees of categorization is in line with other accounts of categorization. According to the Two-State Interactive (2SI) account of visual object recognition proposed by Schendan and colleagues (Schendan and Kutas, 2007; Schendan and Stern, 2008), initial classification is achieved during fast feedforward processing, but precise categorization occurs later on, during co-activation and combined feedforward and feedback interactions between ventral-path areas and areas in the prefrontal cortex and medial temporal lobe. In this later stage, bottom-up and top-down information is integrated. Although there are some discrepancies between Lamme's account and the 2SI account, they share the idea, which is important to our purposes, that precise categorization occurs at the third level. This idea is also consistent with Bar et al.'s (2006) evidence for early categorization of classes of objects according to low spatial frequencies, later used for top-down facilitation of object recognition through narrowing down of interpretation options (similar ideas are portrayed in the reverse hierarchy theory, see Hochstein and Ahissar, 2002). However, Bar's model would predict earlier categorization during rapid feedback modulation (Bar, 2003; Bar et al., 2006; Schendan and Stern, 2008). Additionally, the 2SI theory fits well with Prinz' suggestion that context can affect categorization in a top-down manner. Thus, there are reasons for thinking that for complex objects, there are two main stages of categorization: (1) extraction of a general category based on context and its integration with feature binding information at the second level; and (2) precise categorization resulting in explicit object identification at the third level.

In sum, taken together, we suggest that object integration takes place at the second level, and that precise categorization should be considered as part of third-level processing. We agree with the three models that feature integration takes place at the second level, so that a representation of a coherent object from a specific point of view is achieved at this intermediate level. In addition, this representation of a coherent object is integrated with a general category through an initial classification processes. However, integration of objects with their precise category takes place at the third level, which contains viewpoint-invariant representations of objects with their identification.

Phenomenal Consciousness, Access Consciousness and Perceptual Integration

Two Notions of Consciousness—The Overflow Debate

There are two central notions of consciousness that are relevant to perceptual consciousness: phenomenal consciousness and access consciousness. Phenomenal consciousness is the experience one undergoes when, e.g., perceiving the world (Block, 2002). Hereafter, "phenomenal consciousness" and "perceptual experience" (or simply "experience") will be used interchangeably. Phenomenally conscious states involve subjective experiential aspects, so that there is something "it is like" to undergo them. As was emphasized in the previous section, perceptual integration is a key aspect of experience. Access consciousness (or cognitive access) is obtained when a representation can be used freely in reasoning, decision making, report and rational control of action, in virtue of being accessible to WM or to the global workspace

(e.g., Dehaene and Naccache, 2001; Baars, 2005; Block, 2008).

Clearly, these are two different concepts of consciousness: the one thoroughly phenomenal and the other thoroughly functional (Block, 2002). However, the fact that the concepts are different does not entail that the phenomena are different. There is a debate regarding whether phenomenal consciousness and access consciousness are two aspects of the same phenomena or whether they are dissociable. According to one view, access consciousness is necessary for phenomenal consciousness (e.g., Dehaene and Naccache, 2001). That is, only representations that are accessible to the capacity-limited WM (3–4 items, see, e.g., Luck and Vogel, 1997) are experienced. This view may seem intuitive, since it reflects a folk psychological tendency of subjects to withhold attributions of consciousness to themselves in cases in which they cannot report, or deliberately act upon, perceptual stimuli. According to the opposite stance, cognitive access is not necessary for phenomenal consciousness—i.e., there are phenomenally conscious states that are inaccessible and thus cannot be reported (Block, 2002, 2007, 2008; Lamme, 2010).

The question whether cognitive access is necessary for phenomenal consciousness is essentially related to another issue regarding the nature of experience: is our experience rich or sparse? Introspection seems to reveal rich perceptual experiences of a world full of colors, shapes and many details. However, phenomena such as change blindness and inattentional blindness appear to suggest otherwise: when viewing a visual scene, subjects fail to notice a change or an appearance of a new salient object, such as a gorilla among basketball players (Block, 2008; Smithies, 2011). Does this mean that we suffer from a radical illusion, so that although it seems to us that our experience is rich, it is in fact sparse? Those who claim that cognitive access is necessary for phenomenality would be inclined to answer that our experience is sparse, as we can only experience up to 3–4 items (in accordance with WM capacity limits), or at most up to 4 detailed representations and several other fragmented or generic representations (Block, 2011). This conclusion is hard to swallow, given that phenomenal consciousness is defined as what it is like for the subject to be in a conscious state, and subjects claim that they experience (in detail) more than they can report.

In an influential paper, Block (2007, 2008) argued that phenomenal consciousness and access consciousness rely on two different memory mechanisms with different capacities. Block agrees that access consciousness relies on WM and is thus limited to 3–4 items. However, he suggests that underlying phenomenal consciousness is a different mechanism—perceptual memory—which has a larger capacity. In one of the key moves of his overflow argument, Block appeals to the work of Landman et al. (2003), which demonstrates that when a retro-cue that indicates a specific item appears after the offset of a presentation of a memory array in a Sperling-like change detection task, subjects are able to detect changes in six to seven items, exceeding the limits of WM capacity. This effect is attributed to storage of detailed representations in a temporary memory mechanism with larger capacity than the capacity of WM—fragile short-term memory (Sligte et al., 2008; Block, 2011; Pinto et al., 2013). According to Block, this storage consists of phenomenally conscious representations, whereas the few representations that are subsequently selected to enter WM are also cognitively accessed. Thus, the capacity of the mechanism underlying phenomenal consciousness "overflows" the capacity of the mechanism underlying access consciousness. Block concludes that since phenomenal consciousness and access consciousness rely on different mechanisms with different capacities and properties, they are separate and dissociable. Opponents of his view claim that although there are some representations that are not accessed in WM, these are not phenomenally conscious (e.g., Cohen and Dennett, 2011).

In the context of the overflow debate, it may be helpful to revisit the assumption that the second level is the locale of the *content* of experience. As already mentioned, all three models presented in the previous section (as well as some others, e.g., Block's 2008) seem to agree on this assumption. Yet, it should be noted that it is not universally accepted (e.g., Kouider et al., 2010; Cohen and Dennett, 2011). The question what renders a state phenomenally conscious and the question what sorts of contents are phenomenally conscious are considered by many (if not most) philosophers to be separate questions. Nevertheless, the dissociation view has some commitments *vis a vis* the latter question—clearly, it presupposes that the contents of second-level representations are of a sort that can be made phenomenally conscious. As is demonstrated by Prinz's (2011a) AIR theory, that view may still require further modulation of such representations (that does not amount to their being encoded in WM) in order for them to be phenomenally conscious. Also, it is worth noting that the dissociation view is compatible with the idea that further third-level processing may affect, and specifically add to, the contents of experience—it need not insist that those contents are *exhausted* by the contents of second-level representations. In line with the three models, and as proponents of the dissociation view, we hereafter assume that the contents of second-level representations are of a sort that can be made phenomenally conscious, and further, as proponents of ILH, we adhere to the stronger assumption that the contents of experiences are exhaustively determined by representations of this sort (which can nevertheless be influenced top-down by processing at the third level).

The Tripartite Models in Relation to the Overflow Debate

Let us consider the relations between the different stances towards the overflow debate and the three models of perceptual processing outlined in Section Levels of perceptual processing: Examination of Ben Shalom's model. Although not all advocates of these models explicitly allude to that debate, they would agree that access consciousness resides at the third level, because the mechanism underlying this level in all models is WM. They would further agree on the notion that the content of experience (phenomenal consciousness) arises at the intermediate level. Yet, it seems that they would

disagree over whether to ascribe phenomenal consciousness to second-level representations or to third-level representations. Specifically, they give different predictions as to whether representations that (due to, e.g., attentional selection limitations) are processed only up to the second level and do not enter the third level (i.e., WM), are phenomenally conscious. Lamme is one of the prominent advocates of the dissociation between phenomenal consciousness and access consciousness. Prinz' AIR theory stands somewhere in between the two stances. Ben Shalom does not explicitly address the question.

Lamme (2004, 2006, 2010) provides further support for the dissociation between phenomenal consciousness and cognitive access through his neural argument (which was outlined above). According to this argument, recall, there is a fundamental difference in processing between the first and the second levels, since recurrent processing enables integration, learning and plasticity, whereas feedforward sweeps do not. On the other hand, there is no fundamental neural difference between the second and third levels: both allow the key feature of integration through recurrent processing. Lamme provides evidence that processing at the second level is characterized by the important properties we attribute to experience: feature integration, perceptual competition and susceptibility to illusion (Lamme, 2010). The difference between the two levels lies in the extent of recurrent processing, with superficial recurrent processing at the second level and widespread recurrent processing at the third. The spread of activity at the third level enables connections between modules in the global workspace (Dehaene and Naccache, 2001; Lamme, 2010) and thus reportability. However, the *nature* of neural activity is equivalent in the two stages. Therefore, since the only categorical difference is in reportability, there is no reason to ascribe consciousness to the third level but not to the second level.

Contrary to Lamme, Prinz (2011a) argues in his AIR theory (which expands on ILH) that in order for a second-level representation to become conscious, it should be modulated by attention and thus become accessible to WM. Yet, according to Prinz, phenomenality does not require actual access to, or encoding in, WM. Furthermore, representations *in WM* are third-level representations, and as such, according to the ILH component of AIR, they are of a different sort than phenomenally conscious representations: it is second-level representations, rather than third-level ones, that are representations of coherent bound-together objects, including their features represented from a specific point of view. In this sense, then, phenomenal consciousness does overflow the content of WM.

Access and Phenomenal Consciousness in Autism Spectrum Disorders

The Relevance of the Overflow Debate for Understanding Consciousness in Autism

Ben Shalom (2005, 2009) suggests that individuals with ASD and TD individuals differ in perceptual integration at the second level. According to her account, people with autism do not have the same basic experiences—the same phenomenally conscious states—as other people do. As we have argued above, integration is considered a key aspect of phenomenal consciousness, and thus lack of typical integration in autism would seem to imply different phenomenology.

Notwithstanding, the debate regarding whether phenomenal consciousness and access consciousness are dissociable has implications for the understanding of experience in autism. If access consciousness is necessary for phenomenal consciousness, then, given that people with ASD have lesser access to integrative information, the conclusion that phenomenal consciousness is atypical in autism is inevitable. However, if cognitive access and phenomenal consciousness are dissociable, then another possibility emerges: it is possible that the apparent atypicality in integration among individuals with ASD stems from atypical accessibility, rather than atypical experience. That is, it is possible that integration at the second level is similar among people with and without ASD, but the difference lies in integrative information at the third level. Specifically, we suggest that individuals with ASD have typical phenomenal experiences of objects, yet access those experiences differently: although viewpoint-specific representations of perceptual objects are achieved at the second level among both autistics and non-autistics, viewpoint-invariant representations and precise categorization at the third-level are accessible to a lesser extent among individuals with autism (be it due to less accessibility of these representations or lack of automatic formation of such representations). Here, we suggest a framework in which a core characterization of ASD lies in atypicality at the stage in which perceptual representations of objects (formed at the second level) are integrated with precise categories, yet the experiences of individuals with ASD and those of TD individuals are similar.

Key is the need for a clearer specification of the type of atypical integration in ASD. There is little doubt that the most basic sort of integration, namely feature binding, is achieved in ASD (e.g., Plaisted et al., 1998; see Section Evidence for typical second-level integration in autism). Yet, this leaves room for two possible notions of atypicality: insufficient emphasis of the representation of binding (e.g., the conjunction "white and round") or lack of precise categorization (e.g., "plate"; Ben Shalom, 2005). Both notions are consistent with the possibility that integration at the second level among individuals with ASD is typical, and that the abnormality stems from inaccessibility of integrated representations. According to the first possibility, lack of emphasis of the binding information, manifested in lower activation of binding information, results in the representations' failing to be selected and mobilized to the third level. With regard to the second possibility, if the locale of higher categorization is considered to be at the third (rather than the second) level (as is the case, e.g., according to ILH and 2SI, and as we suggested in Section The importance of integration for experience), then atypicality lies in difficulty to assign the object to the appropriate category at the third level, due to lesser accessibility of viewpoint-invariant representations of objects. Ben Shalom's suggestion that lack of integration in ASD is

compensated by effortful use of third-level resources is consistent with this interpretation.

In the following section, we review findings regarding integration and object categorization among people with ASD and provide evidence indicating typical second-level representation and atypical third-level representations in autism. We suggest that the second option of atypical integration in autism is most suitable for explaining the data, i.e., that atypicality in integration in autism consists in lack of precise categorization. Hereafter, our examination of the nature of representations among individuals with and without autism relies mostly on Prinz' characterization of representations at different levels of processing, and our examination of neural activity among autistics and non-autistics relies mostly on Lamme's framework.

Evidence for Typical Second-Level Integration in Autism

As mentioned, there is little doubt that individuals with ASD achieve feature binding, and thus possess representations of coherent objects. First, people with ASD detect conjunctions of features in the visual search paradigm even faster and more accurately than TD individuals (Plaisted et al., 1998; O'Riordan and Plaisted, 2001; O'Riordan et al., 2001; O'riordan, 2004). In the conjunction condition of the visual search, targets and distractors contain different combinations of similar features, and thus performance on this task would be impossible without feature binding. Furthermore, TD individuals and individuals with ASD perform similarly on discrimination tasks that require color and shape conjunctions (Plaisted et al., 2003). In the discrimination and the visual search tasks, subjects with ASD do not have a conjunction cost: they perform similarly when asked to detect a target according to either a feature or a combination of features (Plaisted et al., 1998, 2003). In addition, children with ASD outperform TD children in mental rotation tasks as well (Falter et al., 2008), which require representations of objects as wholes. Finally, individuals with ASD seem to form "event files" (Zmigrod et al., 2013)—integrated representations of associations between objects and behavioral responses. Event file formation is indicated by an implicit measure of repetition cost—a performance deficit that is evident after incomplete repetitions of stimulus-feature or stimulus-response combinations, as compared to complete repetition or alternation. All these findings indicate that feature binding, and thus the formation of representations of objects, is intact in autism. Moreover, such data refute the possibility that binding information is not accessible to individuals with ASD. On the contrary, it suggests that people with autism have an even better access to representations of this type.

We should note that according to O'Riordan and Plaisted (2001; O'riordan, 2004), the superiority of autistics in visual search does not stem from better feature integration, but rather from an enhanced ability to discriminate between similar items (e.g., targets and distractors). In support of this claim, they found that when performing triple conjunctions conditions (i.e., the target is identified using three features) compared to conjunctions of two features, and when features were highly similar in featural dimensions, subjects with ASD had less cost compared to TD participants.

Susceptibility to visual illusions is another manifestation of a sort of integration that is considered an aspect of phenomenal consciousness (Lamme, 2010). Visual illusions have a remarkably strong impact on experience: TD individuals report experiencing them even when they know how these illusions affect perception (e.g., Bruno and Franz, 2009). Susceptibility to illusions should take place at the second level of processing (Lamme, 2010), and it requires the presence of a representation of an integrated object. Ropar and Mitchell (1999) examined susceptibility to visual illusions such as the Titchener circles and the Muller-Lyer figures, among subjects with ASD. They used two measures in order to assess both explicit and implicit susceptibility to illusions. Explicit susceptibility was assessed using verbal judgment of the stimuli (e.g., subjects were asked "are these two circles different sizes or the same size?" with regard to a Titchener circles stimulus). In the implicit measure, participants were asked to adjust the lengths of lines or size of circles rather than judge them explicitly. Subjects with ASD and TD subjects did not differ in their performance in both versions of the task. Garner and Hamilton (2001) reported susceptibility to visual illusions among subjects with autism as well. We should note that Happé (1996) failed to find susceptibility to illusions among subjects with ASD. However, Happé's results may have been influenced by other factors (see Ropar and Mitchell for criticism of Happé's methodology). Thus, most evidence indicates that individuals with ASD are susceptible to visual illusions similarly to TD people, and may also access the experience of these illusions.

In addition, autistics seem to have typical use of contextual information. López and Leekam (2003) found that participants with and without ASD identified objects presented after a contextually-appropriate scene (e.g., a kettle presented after a presentation of a kitchen scene) faster and more accurately than objects presented after a contextually-inappropriate scene (e.g., a football presented after a presentation of a kitchen scene). That is, object identification was similarly facilitated by the appropriate context in both TD individuals and individuals with ASD. These findings indicate typical use of context in object recognition, a process that according to Bar (2004) occurs early in the hierarchy and that Ben Shalom includes at the second level. It should be noted that López and Leekam's results revealed that subjects with ASD made more errors in naming objects, regardless of whether the previous scene provided appropriate context or not, a finding that we suggest may point toward a third-level deficit in precise categorization, rather than atypicality in second-level integration.

In sum, central properties of perceptual integration that, according to the evidence presented, characterize second-order representations—feature integration, susceptibility to visual illusions and use of context in aiding object recognition—seem to be similar among TD and ASD individuals; and to the best of our knowledge, there is no evidence suggesting atypicalities in second-level representations in ASD. We conclude that it is

plausible that perceptual integration characteristic of the second level is not atypical among people with ASD.

Evidence for Atypical Third-Level Integration in Autism

Studies such as those reviewed in the previous section have led to modifications of the weak central coherence theory (Frith and Happé, 1994). Originally, the theory postulated that there is a core failure in global processing in autism that leads to a reduced ability to integrate component features of a figure into a coherent whole. Later, Happé and Frith (2006) revised the theory, and put more emphasis on superior local processing as reflecting a cognitive style. Plaisted (2001) suggests a competing hypothesis, the reduced generalization theory, according to which there is reduced processing of similarities between objects in autism, and yet processing of differentiating or unique features is intact. This theory postulates that individuals with autism should show lower categorization abilities, which we suggest in the present section is to be attributed to an atypicality in third-level processing, rather than to an anomalous integration at the second level. The reduced generalization and the weak central coherence theories are consistent with both conceptions of atypicality in integration we have suggested—insufficient emphasis of the representation of binding information or a deficiency in precise categorization. However, since the tasks reviewed above indicate high accessibility of representations of binding, the second possibility is more plausible. In this section we examine the second conception of atypicality, i.e., the one on which there is a deficit in higher categorization among individuals with autism. We provide evidence for atypicality in third-level processing among autistics, manifesting in divergence in properties of third-level representations and neural activity.

Evidence for Viewpoint Variant Third-Level Representations in Autism

We have argued that representations of coherent objects matching second-level representations seem to be typical among individuals with ASD. However, we found that there are some indications of atypicality in tasks that require third-level processing. Specifically, we suggest that there is some evidence for atypical formation of viewpoint-invariant object representations at the third level (as it is conceptualized by ILH) among individuals with autism—such representations are not as easily and automatically formed in ASD.

Ropar and Mitchell (2002) examined shape constancy in autism. They showed participants images of ellipses in three conditions, and then asked them to recreate the shape they saw on a different screen. In the prior knowledge condition, the shape was presented alone in a darkened display without any perspective cues, and participants were told that the shape is a slanted circle. In the prior knowledge and perspective cues condition, the shape was presented in an illuminated display containing perspective cues and participants were told the shape presented is a slanted circle. In the control condition, the shape presented was a non-slanted ellipse, presented without any perspective cues. All participants recreated the shape as more circular in the prior knowledge and prior knowledge and perspective cues conditions compared to the control condition. TD participants and participants with ASD differed only in the prior knowledge condition: participants in the ASD group exaggerated circularity less than TD participant, and recreated a shape that more closely resembles the original one. This task examines WM representations of objects, because participants had to recreate the shapes based on their memory. In ILH terms, it seems that individuals with ASD had more difficulty creating a viewpoint-invariant representation of the circle when they were provided with prior knowledge regarding the identity of the shape, thus relying more on the representation of the perceptual object created at the second level (an ellipse), which is dependent on viewpoint. On the other hand, TD individuals relied on a viewpoint-invariant representation (a circle) in accordance with prior knowledge. When perspective cues were provided, individuals with ASD perceived the object as more circular, similarly to TD individuals. In this case, since cues were apparent, representations at the second and third levels should be more similar.

Mottron et al. (1999) found that individuals with autism were better than TD individuals in reproducing impossible 3D figures. Subjects with ASD copied the figures faster than TD participants. In addition, while TD subjects copied impossible figures considerably slower than possible figures, there was a smaller cost of impossibility among subjects with ASD. These findings have recently been replicated (Sheppard et al., 2009). Copying involves the construction and maintenance of a representation of the object in visual WM (Guérin et al., 1999), and thus performance relies on third-level representations. Mottron et al. explain their results as emerging from a difficulty relating elements of a figure among individuals with ASD, perhaps due to limited capacity to hold parts of objects in WM simultaneously. We suggest that, similarly to our interpretation of Ropar and Mitchell's (2002) results, third-level representation among individuals with ASD are more similar to second-level representations, in that they are viewpoint specific, rather than viewpoint invariant. First, this task requires maintaining the shape in WM while copying and thus reflects representations held in WM. In addition, the impossibility of the figure should manifest mainly at the third level of the hierarchy: at the second level, the drawing should be represented as it is seen (from the viewpoint of the observer), yet the fact that impossible figures violate 3D rules obstructs formation of a viewpoint-invariant representation at the third level. The superiority of individuals with ASD may thus reflect differences in third-level representations.

Liu et al. (2011) found that in an explicit possibility task, in which participants were asked to judge whether figures are impossible or not, participants with and without ASD had comparable performance and similar patterns of brain activation. During this task, both TD subjects and subjects with ASD recruited more frontoparietal areas compared to a second task, in which the same stimuli were used but participants were not required to judge the possibility of the

figures. However, in the second task participants with ASD showed less interference from impossible figures, as well as less activation in medial-frontal areas and less connectivity between medial-frontal and posterior-visuospatial areas compared to TD participants. Liu et al. explain their results as indicating a greater need to suppress the global configuration of the figure in the TD group, as indicated by higher activation in frontal areas related to high-level executive functions (such as medial and superior frontal regions). These results may indicate that third-level representations in the form of viewpoint-invariant representations of objects can be achieved among individuals with ASD, but these are not achieved automatically. That is, whereas representation among TD individuals become viewpoint-invariant automatically once they are processed at the third level, among individuals with ASD third-level representations are more similar to second-level representations (i.e., viewpoint-specific), but can be processed to become viewpoint-invariant according to need (e.g., task demands). This explanation is consistent with Ben Shalom's suggestion that individuals with autism can overcome their difficulty in integration via use of effortful logical processing of perception. In addition, our explanation is in agreement with Mottron et al.'s (2006) claim that high-level processing is automatic or mandatory among TD individuals, but optional among individuals with autism.

Another image copying study, using bistable ambiguous figures such as the duck/rabbit image, reveals viewpoint specific third-level representations in autism as well. Allen and Chambers (2011) examined implicit and explicit processing of ambiguous figures among participants with ASD who had cognitive delay and children with intellectual disability. First, participants were asked to copy ambiguous and non-ambiguous figures, after either being given a label for a presented figure (e.g., "draw this rabbit") or not ("draw this picture"). Afterwards, participants were asked several times what they see in the image, in order to assess spontaneous reversals. Then, participants who did not report perceiving the alternative interpretation of the figure were informed about it and informed reversals were assessed. Finally, they were asked to copy the image once again. Results indicate that when participants were not given a label before they drew the pictures, both groups provided similar figures before and after reversals. However, the groups were affected differently by the introduction of a label: participants in the learning disability group provided different drawings after a label compared to the first drawing (indicating that labeling one interpretation influenced their construction of the drawing), whereas participants in the ASD group provided two similar drawings regardless of the label. This may indicate, once again, that individuals with autism have third-level representations that are more similar to second-level representations. The two groups had comparable explicit interpretation reversals, and in both groups the number of reversals increased after participants were informed about the bistability of the figures. This suggests that effortful use of reasoning resources is typical in autism, consistently with Ben Shalom's claim that individuals with ASD compensate for lack of integration by using effortful reasoning, and with Mottron et al.'s suggestion that high-level processing can be achieved at will in autism. Allen and Chambers concluded that individuals with autism have typical perceptual representations but atypical conceptual representations. This conclusion is in line with our suggestion that third-level, rather than second-level, representations are atypical in autism.

Evidence for Atypical Use of Third-Level Precise Categorization in Autism

According to Marr (1982) and the ILH, third-level representations are important for categorization and conceptual processing. Thus, atypicality in viewpoint-invariant representations is expected to have implications for categorization. In her reduced generalization theory, Plaisted (2001) suggests that among people with autism discriminating features are more salient, while features held in common between objects are processed to a lesser degree, giving rise to atypicality in formation of categories and concepts. The ability to generalize across situations is reduced due to saliency of differentiating aspects of separate cases. Her account is supported by a personal description by Grandin:

> ". . .my concept of dogs is inextricably linked to every dog I've ever known. It's as if I have a card catalogue of dogs I have seen, complete with pictures . . ." (Grandin, 1996, p. 28).

O'riordan (2004) has added that generalization capacities are important for high-level processes, such as categorization and reasoning. Consistent with the reduced generalization theory, Church et al. (2010) found that high-functioning autistics use family resemblance (or a family prototype) less than controls during categorization of objects (e.g., when judging whether a non-social figure belongs to a newly learned category). Plaisted's explanation appeals to third-level integration atypicality. Thus, the reduced generalization theory is compatible with our suggestion that atypicality in integration among people with ASD is at the third level.

The change detection paradigm is one of the most commonly used in the study of perceptual consciousness. In this paradigm, subjects are presented with two pictures of a scene that may differ in one detail (e.g., one item has changed its color or disappeared), and are asked to detect the change. Findings consistently reveal a phenomenon called "change blindness": people fail to notice the change, even after re-viewing both pictures several times. The prevalent explanation is that changes in items to which attention is not allocated cannot be detected. One must compare the original image, stored in WM, with the new image, and thus an item must reach WM in order for change to be recognized. Some infer from this phenomenon that even though we think we have a rich experience of the world, we in fact have a sparse experience (e.g., O'Regan and Noë, 2001). This stance is usually supported by those who advocate the view that access consciousness and phenomenal consciousness are not dissociable. Others explain change blindness as stemming from failure in accessibility (e.g., Block, 2001; Prinz, 2011a; Smithies, 2011), so that the changed object is experienced,

yet the change is not detected due to deficiency in its storage in WM. According to Block (2001, 2008), this lack of accessibility is a result of failure in conceptualization of the changed item.

Several studies have examined differences in change blindness between TD individuals and individuals with autism. When change is perceptual and does not require precise categorization, people with ASD seem to perform similarly to TD people. For example, Burack et al. (2009) found similar accuracy and reaction times among subjects with ASD and TD subjects who were asked to indicate which of two images of objects presented simultaneously side by side has changed.[2] Since the objects depicted in their study were presented without a background scene, detection of changes could have been executed based on perception, without a demand to categorize the objects. Nonetheless, other studies, in which manipulations of context and semantic role were introduced, indicate impairments in processing of precise categories, although these results are not conclusive.

With regard to contextual influences on detection of changes in a scene, Loth et al. (2008) demonstrated that individuals with autism are less sensitive to influences of context. Performance of subjects in the TD and ASD groups was similar when changes were contextually-appropriate (either from the same general category, e.g., replacement of a kettle with a frying pan, or from the same precise category, e.g., replacement of a kettle with a different one). However, the groups differed when changes were contextually-inappropriate (e.g., replacement of a kettle in a kitchen with a football): While TD individuals detected changes in this condition faster than in contextually-appropriate conditions, individuals with ASD had similar performance in all change conditions. Contrary to Loth et al., Fletcher-Watson et al. (2006) found a similar pattern of results among subjects with ASD and TD subjects, and that both groups detected contextually-inappropriate changes faster than they detected contextually-appropriate changes. However, in Fletcher-Watson et al.'s version of the task, participants could control switches between the two images, so that they could choose when to look back at the original scene, and participants with ASD made more switches compared to TD participants. This methodological difference may account for the discrepancies in the results of the two studies.

This lack of benefit in detection of contextually-inappropriate stimuli may indicate a third-level deficit in categorization. Note that the kind of context that models such as Bar and colleagues' (Bar, 2004; Bar et al., 2006) and the 2SI model (Schendan and Kutas, 2007; Schendan and Stern, 2008) refer to is not relevant in this case, because in the case of contextually-inappropriate items, in which changes are detected more easily among TD individuals, early top-down contextual effects should not aid object recognition (on the contrary, these models will predict slower processing of these objects, see Bar, 2004). In Loth et al.'s (2008) and Fletcher-Watson et al.'s (2006) experiments, participants were provided with prolonged exposure to stimuli, and thus it is more reasonable that inappropriate items were processed bottom-up in a manner more in line with Marr's levels of processing. As was noted in the previous section, facilitation of object recognition based on context in the sense Bar refers to seems to be typical among individuals with autism (López and Leekam, 2003). The lack of difference between subjects with ASD and TD subjects in contextually-appropriate changes in Loth et al.'s (2008) study supports this conclusion as well.

Semantic processing is yet another kind of integration examined by using the change detection paradigm. Results regarding sensitivity to semantic roles of items in scenes are conflicting as well. Smith and Milne (2009) examined change detection according to the semantic role of items using short films. They found that, overall, subjects with ASD detect continuity changes in the films better than TD subjects. In addition, while participants in both groups detect central changes more accurately than marginal changes, the difference between the conditions is smaller among individuals with ASD, indicating less sensitivity to semantic information. On the other hand, Fletcher-Watson and colleagues (Fletcher-Watson et al., 2006, 2012) used still images of scenes and found that, similarly to TD participants, individuals with ASD detect changes in items with a central semantic role (e.g., a boat on the river) better than changes in items that had a marginal role in the scene (e.g., a tree among other trees). However, they found that participants in the ASD group were slower to detect changes in marginal items compared to participants in the TD group, and made more switches back to the original scene in this condition. Their results, as opposed to Smith and Milne's, indicate sensitivity to semantic information and greater saliency of semantically central items compared to semantically marginal items. Methodological differences may account for discrepancies in this case as well. Smith and Milne's task was more demanding: they used a dual task, in which in addition to change detection, participants also had to follow the plot of the scene and answer semantic question regarding what was going on. It could be that the lack of effect of semantic role in the ASD group was caused by high cognitive load on participants' WM, which could interfere with conceptual processing and effortful integration of precise categories and objects. Thus it could be argued that under low cognitive load, semantic processing can take place and an integrated representation of both the object and its precise category can be achieved, at least with regard to semantically salient objects. However, under high cognitive load or for semantically marginal objects, this integration is not achieved among individuals with ASD. In the case of high load, this could be due to lack of resources required for effortful integration or the creation of viewpoint-invariant representation of the object for identification. In the case of semantically marginal objects this could result from attentional processes. Fletcher-Watson et al. (2006) explained the finding

[2]It should be noted that in the TD group mental age was correlated with performance, whereas in the ASD group there was no such correlation, a result that may indicate different developmental trajectories. However, overall detection of changes in objects was similar in the two groups.

that individuals with ASD identified changes in marginal items slower than TD individuals as reflecting a deficit in attentional shifting between items or away from central items (which were selected first). In line with other findings reviewed above, this may point to a WM deficit: such an explanation involves updating the content of WM, because it requires the removal and substitution of central items with marginal ones.

Evidence for Atypical Neural Activity Attributed to the Third Level in Autism

Lamme (2004, 2006, 2010) addresses differences between the second and third levels in terms of patterns of neural activity. Second-level activity is characterized by local recurrent processing between visual areas, whereas third-level activity is more widespread and includes co-activation of frontoparietal areas as well. The literature on neural processing in autism points to atypical global connectivity and functioning of areas related to WM or the global workspace, in accordance with our suggestion of a third-level abnormality among individuals with ASD.

Ring et al. (1999) conducted an fMRI study that examined brain activity of subjects with ASD and TD controls during performance in the embedded figure task. In this task, which is thought to involve visual WM, subjects are presented with a complex pattern and a simple figure, and are asked to identify the hidden simple figure in the complex design. The general finding is that autistics outperform TD subjects in this task (Jolliffe and Baron-Cohen, 1997). Ring et al. found that participants with ASD and TD subjects had a similar pattern of activation in most brain areas. However, the ASD group had higher activation in association areas, whereas the control group had higher activation in frontoparietal areas associated with WM (the global workspace) and attentional allocation: the dorsolateral prefrontal cortex and the superior parietal lobule (Dehaene and Naccache, 2001; Baars, 2005). A comparable pattern of less activation in global workspace areas among subjects with ASD compared to TD subjects and similar activation in other visual processing areas was observed by Luna et al. (2002) as well, using a different spatial WM task. Ring et al. suggest that this pattern may indicate that subjects with ASD use more mental imagery when performing the embedded figure task, while TD participants rely more on their WM. We explain these results as reflecting use of third-level representations that are viewpoint-variant rather than invariant in WM among individuals with autism. This interpretation is supported by Ranganath's (2006) suggestion that the dorsal prefrontal cortex is in charge of the manipulation and reconstruction of complex stimuli, via reduction of the saliency of relations between features based on prior knowledge. Our explanation is consistent with typical explanations of superiority of individuals with ASD in this task, which appeal to less interference from the global shape and an ability to focus on local details (e.g., Happé and Frith, 2006).

Just et al. (2004) found that during sentence completion tasks there is less connectivity between the dorsolateral prefrontal cortex and parietal and occipital areas among participants with ASD compared to TD subjects. They suggest the underconnectivity theory, according to which autism is caused by lesser functioning of integrative circuitry in frontal integrating centers, especially when tasks require high-level abstraction and during high load. Although the task utilized in their study is not perceptual, and may seem irrelevant to our argument, the underconnectivity revealed in their study involves frontoparietal areas engaged in the global workspace, which is not specific to certain modalities or cognitive domains (Dehaene and Naccache, 2001). Similarly, Courchesne and Pierce (2005) have proposed that in autism there is increased local connectivity between close areas (including increased local frontal activity) and reduced long-distance co-activation between the frontal lobe and other regions. They suggest that this pattern leads to impairments in widespread processing and in integration of information from separate modules and in spreading of contextual feedback towards lower areas. Both descriptions fit impairment at the third-level as conceptualized by Lamme.

Conclusion and Implications

The Argument for Locating the Atypicality in Autism at the Third-Level

In line with Ben Shalom's model and other tripartite-models of perceptual processing (ILH and Lamme's model), we assume that processing of visual information can be usefully characterized as proceeding in three stages. The models differ with respect to the level at which certain categories are integrated with representations of objects. In agreement with Lamme's model and the 2SI model, we suggest that initial classification is achieved at the second level, yet objects are ascribed to their precise categories at the third level.

Based on empirical evidence, we have argued that autistics and non-autistics have similar viewpoint-specific second-level representations, characterized by feature binding, susceptibility to illusions and contextual facilitation. However, we suggest that individuals with autism have atypical third-level processing. First, whereas third-level representations in TD individuals seem to be viewpoint-invariant, data from studies examining shape constancy and copying impossible figures and ambiguous figures suggests that individuals with ASD have viewpoint-specific third-level representations, which are more similar to second-level representations. Second, there is some evidence for abnormality in third-level representations in individuals with autism that consists in a deficiency in the integration of perceptual representations of objects with precise categories. (We agree with Ben Shalom that individuals with autism can, at will, make up for the difficulty in categorization via effortful use of WM resources and use of logic and reasoning; they are capable of manipulating their third-level representations so that these would allow object recognition.) Third, individuals with autism seem to have atypical neural activity that is associated with third-level processing: lower global connectivity and lower activation in frontoparietal areas related to WM or to the global workspace in comparison with TD individuals. We conclude that atypicality

in integration in autism is better conceptualized as third-level atypicality than as second-level atypicality.

The debate regarding whether phenomenal consciousness and access consciousness are dissociable and our argument for the claim that the central atypicality in autism resides at the level of third-level rather than second-level representations are interconnected. On the one hand, the stance one takes with respect to that debate has implications for one's interpretation of our framework for understanding the atypicality in autism as a third-level atypicality—specifically, for whether this atypicality is understood as pertaining to phenomenal consciousness or to access consciousness. On the other hand, our argument may have implications for that debate—the commitment of a particular stance to attribute, or withhold attributions of, typical basic phenomenal states to autistics may be useful for evaluating its plausibility.

Understanding Phenomenal Consciousness in Autism

Different stances in the debate over whether phenomenal consciousness and access consciousness are dissociable may lead to different interpretations of our suggestion that individuals with autism have typical second-level processing but atypical third-level processing. That debate, recall, takes the form of a scientific controversy over whether second-level representations are phenomenally conscious (the dissociation view), or whether phenomenality requires that a representation be modulated by third-level processing, and is therefore restricted to third-level representations. Thus, if access consciousness and phenomenal consciousness are not dissociable, i.e., if the latter requires the former, then regardless of whether the atypicality arises already at the second level or is restricted to the third level, individuals with autism and TD individuals differ in their basic experiences. The non-dissociation view entails that every difference in access consciousness implies a difference in phenomenal consciousness, hence the fact that the access consciousness of autistics is atypical implies that their phenomenal consciousness is atypical as well. However, if the two sorts of consciousness are dissociable, atypicality of access consciousness does not imply atypicality in phenomenal consciousness. In that case, the view for which we have argued—namely, that the abnormality characteristic of autism is restricted to the third-level and that second-level processing and representations in autistics are intact—opens the door for the possibility that TD individuals and ASD individuals share their basic experiences. Due to our adherence to the dissociation view, it is this latter possibility that we endorse.

It should be noted that, even granted our claim that the atypicality in autism is located at the third-level, there is a possible middle position regarding the phenomenal states of individuals with autism. This position follows if one holds that second-level representations are phenomenally conscious, yet rejects the assumption (which we tend to endorse) that the contents of phenomenal states are *exhaustively* determined at the second level. That assumption is rejected by those who take the contents of perceptual phenomenal states to be (at least partly) conceptual, or, relatedly, to represent not only "simple" properties such as color, shape, illumination and motion, but also more "sophisticated" properties, such as plate, tree or eucalyptus (see, e.g., Siegel, 2006, 2010). Their view may still be compatible with the dissociation of phenomenal consciousness and access consciousness, provided that they hold that the contents of phenomenal states of TD individuals who are conceptually sophisticated typically involves two layers, the first of which is derived from the second-level and the second of which is derived from the third level. Conjoined with our claim that the atypicality in autism characterizes the third-level, that view would predict that the experiences of autistics have a lot in common with those of TD individuals, yet there are also some differences, due to difficulties autistics have applying certain specific categories at the third level.

Implications of the Case of Autism for the Overflow Debate

An important question for any account of phenomenal consciousness concerns the plausibility of its commitments regarding ascriptions of various phenomenally conscious states. That is, the question concerns the set of subjects (or creatures) to whom the account attributes any phenomenality, and (what is more relevant for our purposes) to whom it attributes phenomenality that is similar to that of typical (mature, human) subjects. Put in prevalent philosophical jargon, an account that is committed to attributions of phenomenal states similar to those of typical subjects to subjects who seem to lack them is said to be (too) liberal; an account that is committed to withholding such attributions from subjects who seem to have them is said to be chauvinist. Clearly, our pre-theoretic judgments regarding attributions of phenomenally conscious states form only a fallible starting point, which may be overturned by scientific and theoretical investigations. Yet, other things being equal, it is an advantage of a theory of mentality if it matches those judgments—we should strive for a reflective equilibrium between our pre-theoretic judgments on the one hand, and considerations regarding e.g., the explanatory powers of particular theories of phenomenality on the other hand.

A clear example that concerns ASD is the charge of chauvinism made by many philosophers against central versions of the higher-order thought (HOT) theory of consciousness. According to this theory, "a mental state is a conscious state when, and only when, it is accompanied by a suitable HOT" (Rosenthal, 1990/1997, p. 741), or, more specifically, if it is accompanied by a thought—grounded non-inferentially and non-observationally—to the effect that one is in that state. Autism is of course associated with theory of mind deficits, and specifically, individuals with autism have been claimed to have impaired ability to form HOTs about their experiences (see, e.g., Perner, 1998; Frith and Happé, 1999). Given that at least some low-functioning autistics cannot form any such thoughts, it follows from HOT that such autistics are not phenomenally conscious! While some (e.g., Perner, 1998; Carruthers, 2000) have bitten that bullet and accepted that consequence, it is considered by others to be a *reductio ad absurdum* of HOT.

Now, we by no means suggest that the charge of chauvinism that can be mounted against the non-dissociation view of the relations between phenomenal consciousness and access consciousness is as strong as the charge just described against the HOT. The non-dissociation view is not committed to denying that individuals with ASD are phenomenally conscious; it is committed only to their having quite atypical phenomenal states. Nevertheless, it seems to us that the non-dissociation view tends to exaggerate the differences between the mental lives of autistics and TD individuals. No doubt, there are significant differences. We believe that the dissociation view adequately accounts for those differences by taking them to be differences in access consciousness (rather than in phenomenal consciousness) i.e., by taking the bulk part of the atypicality in autism to pertain to the ways autistics access their experiences. The non-dissociation view, in contrast, is committed to interpreting the data described in this paper regarding those aspects of perceptual processing that are shared among subjects of the two groups as having little relevance to the personal level, and as scarcely reflected in the most basic ways in which they experience the world. This consequence of the non-dissociation view seems to us less plausible, and so as one that, other things being equal, should count against it.[3]

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[3]The charge of chauvinism against the non-dissociation view can be generalized so as to apply to its commitments regarding the phenomenal states of non-conceptual human subjects and non-human animals. For criticisms, in the same spirit, against the view that the contents of the experiences of mature humans are thoroughly conceptual—i.e., ones according to which that view overstates the differences between the sort of perceptual awareness enjoyed by mature humans on the one hand and non-conceptual creatures on the other hand—see, e.g., Jacobson and Putnam, 2015; Collins, 1998 and Ayers, 2004 (for weaker accusations along similar lines, see, e.g., Wright, 2002; Burge, 2003).

For a defense of the claim that the dissociation view is compatible with the claim that phenomenal states are "of the subject" and belong to the personal level, see Jacobson (2014).

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The Lateral Prefrontal Cortex and Selection/Inhibition in ADHD

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A previous paper from our lab (Shalom, 2009) presented evidence that the medial part of the prefrontal cortex is involved in the integration of raw, unintegrated information into coherent, wholistic mental representations such as perceptual objects, episodic memories, emotional states, and motor actions. It has used this analysis to classify some challenges encountered by people with Autism Spectrum Disorders, linking different types of difficulties in integration with different subareas of the medial prefrontal cortex. The current paper performs a similar analysis for the corresponding subareas of the lateral prefrontal cortex. It presents evidence that the lateral part of the prefrontal cortex is involved in the selection/inhibition of perceptual, memory, emotion, and motor aspects of processing. It then uses this analysis to classify challenges encountered by people with ADHD, linking different types of difficulties in selection/inhibition to different subareas of the lateral prefrontal cortex.

Keywords: ADHD, inhibition, selection, control, LPFC

INTRODUCTION

A previous paper from out lab (Shalom, 2009) argued that neurocognitive processing can be divided into three-levels: (1) a basic-level involving primary cognitive, emotional, and sensorimotor processing. For example, a loud unexpected sound that is perceived in primary auditory-sensory systems might trigger physiological emotional-responses, such as fear (fast heart beats, etc.). (2) an integrative-level, that combines the output of all primary processes from the basic-level, and forms a global-coherent meaning, experience, or behavior. For example, the mental representations of the various primary elements that constitute the fear emotional response results in a conscious feeling of being afraid. (3) A logical-level, which forms abstract logical rules (if-then rules) from the basic-level (e.g., "If I have fast heart beats and cold sweat, then I might be afraid"), and is also involved in selection and inhibition (e.g., controlling emotional urges). This three-level architecture was applied to four general psychological domains: emotion, memory, sensation-perception, and motor. Shalom (2009) focused on the second, integrative level and its relation to the four psychological domains. It also argued that these four types of integration are subserved by four different subareas of the medial prefrontal cortex: Brodmann Area (BA) 11 (perception), BA 10 (memory), BA 9 (emotion), and BA 8 (motor). Finally, it presented evidence that a selective deficit in these BA areas and these types of integrative processes underlie some of the common deficits in ASD (autism spectrum disorders).

The current review attempts to perform a similar analysis for the lateral prefrontal cortex (LPFC), shifting from the relevant medial prefrontal areas to their lateral counterparts: lateral BA 11/BA 47 (perception), lateral BA 10/BA 46 (memory), lateral BA 9 (emotion), and lateral BA 8 (motor) (**Figure 1**), (cf. the distinction between clusters 1, 2, 3, and 4 of the anterior cingulate in Beckmann et al. (2009). It brings evidence that a selective atypicality in these BA areas and

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a selective deficit in selection/inhibition processes in these four cognitive domains is involved in some of the common deficits in ADHD (attention deficit hyperactivity disorder), such as difficulties inhibiting motor responses (e.g., inability to inhibit inappropriate movements), perceptual focus (e.g., inability to ignore distraction) and emotional reactions (e.g., inability to control urges) (Barkley, 1997; Nigg, 1999).

PERCEPTION

Perceptual Selection and Inhibition and Lateral BA 11/47

There is evidence that perceptual selection and inhibition are supported by neural networks involving the lateral part of BA 11/47 in the LPFC. In a model proposed by Zsuga et al. (2016), the orbitofrontal cortex (OFC) is suggested to play a major role in the selection of visual stimuli according to task requirements.Specifically, they suggest that the medial part of the OFC plays a central part in integrating and categorizing information about stimuli from the environment and their context, while the lateral part of the OFC is involved in assigning and updating selection parameters according to task specific values of the available stimuli. In support of this claim, in one study, Howard and Kahnt (2017) showed that the lateral part of BA 11 is involved in encoding goal directed values of olfactory stimuli. They presented hungry participants with two preferred food smells and required them to choose whether to smell one or the other. Later, the participants were given one of the two foods to eat and were allowed to choose between the two smells once again. The change in preference toward the non-satiated smell was reflected by a change in activity in the lateral part of BA 11/47. Furthermore, it has been shown that lateral BA 11/47 is involved in the rejection of irrelevant stimuli (Kaufman et al., 2016).

Lateral BA 11/47 has been also shown to be involved in the maintenance of visual stimuli in working memory and guidance of visual selection. In one study, Soto et al. (2007), compared two conditions of a primed visual selection in which the prime was shown either once or twice. Lateral BA 11/47 activation was greater when the prime was shown twice, however, a reduction in activation was found when similar stimuli were passively repeated twice (without a visual selection phase, and therefore without task relevance).

Finally, according to Price (2007), lateral BA 11 is part of the sensory orbital network.

ADHD and Visual Selection and Inhibition

There is evidence that children and adults with ADHD have problems with inhibiting irrelevant visual and auditory stimuli. For example, ADHD adults have shown more interference effects (i.e., problems in inhibiting irrelevant stimuli) than controls when asked to complete a recall task while ignoring a background noise (Pelletier et al., 2016). Moreover, a positive correlation was found between task performance under conditions of irrelevant sound and the extent of attentional symptoms reported by patients on a clinical symptom scale. In another study, ADHD and control adults were asked to conduct a phone conversation while driving. The ADHD group showed significantly poorer driving skills during the phone conversation condition than in the silence condition when compared to controls (Reimer et al., 2010). Other studies have shown poor visual inhibition in ADHD individuals. For example, Forster et al. (2014) and Forster and Lavie (2016) found that ADHD adults performed a letter search task slower when irrelevant but salient cartoon characters were present on the screen, to a greater extent than controls. In a related manner, the Stroop interference task requires participants to attend a specific dimension of a visual stimuli while ignoring another. Studies found ADHD children to perform more poorly on the Stroop interference condition than controls (Sørensen et al., 2014), and that their performance correlated with their inattention and hyperactivity symptoms (Ikeda et al., 2013).

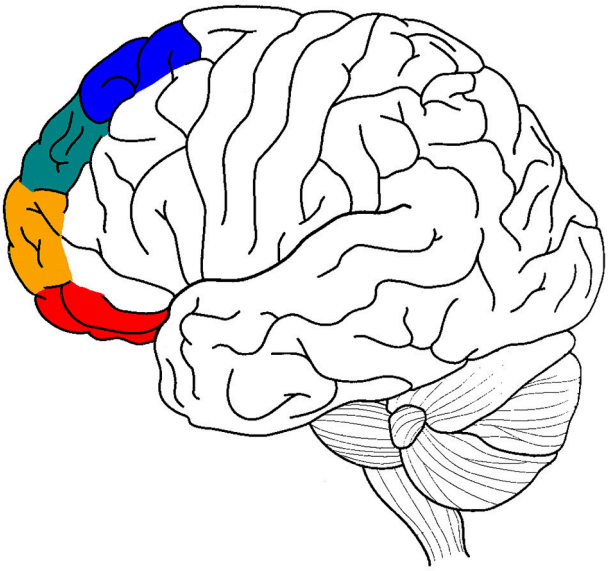

FIGURE 1 | A graphic summary of the main anatomical hypotheses of the article. Motor processing in blue, emotion in green, memory in orange, and sensory-perceptual in red.

ADHD, Visual Selection, and Inhibition and Lateral BA 11/47

In addition, several studies found specific evidence of atypical activation in lateral BA 11/47 in individuals with ADHD performing visual selection/inhibition tasks. Tsujimoto et al. (2013) asked children with and without ADHD to perform a working memory task with and without distraction. The ADHD participants showed significantly poorer behavioral performance, particularly under distraction, and showed significantly higher levels of activation in lateral BA 11/47 than controls. In a different study, Yasumura et al. (2014) tested ADHD and control children on both Stroop interference and reverse Stroop interference conditions, and found that in both conditions ADHD children performed more poorly and that performance correlated with lateral BA 47 activity. In another study where a salient yet irrelevant distractor was presented during a time estimation task, it was found that while the distractor assisted the ADHD

participants to the same degree as the controls, the lateral BA 11 activation which accompanied the distractor's appearance was significantly larger (Pretus et al., 2016).

MEMORY

Memory Selection and Inhibition and Lateral BA 10/46

While it is not a general consensus that BA10/46 is engaged in episodic memory functions, there is much evidence to support a role for BA 10/46 in the selection and inhibition of memory information. For example, Kim (2011), analyzed 74 studies that compared remembering and forgetting (i.e., successfully remembered items vs. distractors judged erroneously to have appeared), and found that the greatest bulk of studies overlapped at the frontal part of BA 46, near it's junction with lateral BA 10. In a later study, Kim (2013) performed a meta-analysis of 70 studies focusing on new and old items (i.e., hits vs. correct rejections). Results show that new>old comparisons yielded activations that spread across the middle part of the left lateral prefrontal. However, when focusing on source memory studies in which participants are required to retrieve not only the target item but also an additional detail related to the item from the learning phase (i.e., when selection demands are higher), specific activation was seen in the frontal part of BA46 including the rostral part of BA10.

A different line of evidence comes from a meta-analysis by Gilbert et al. (2006), in which 104 studies were analyzed focusing on BA 10, and found that the majority of studies involving the lateral part of BA 10 tested working memory and episodic memory retrieval, while studies involving the medial part of BA 10 tested mentalizing (i.e., attending to one's own emotions and mental states or those of other agents).

In addition, Cohen et al. (2014), employed the value directed remembering task, in which participants are presented with word lists in which some words are assigned more value than others, thus encouraging participants to attempt and select higher value items over low value ones during encoding. Results show specific activation of right lateral BA46/10, and very pronounced activation of left lateral BA46/10, when a cue predicting a high value word was appearing.

ADHD and Memory Selection and Inhibition

There are several studies that have found evidence for difficulties in the selection and inhibition of memory information in ADHD. For example, in a study by Pollak et al. (2007), adults with and without ADHD performed a difficult list learning task in which they had to memorize and recall five word lists on eight different occasions. Results show that the ADHD participants made more double recalls and intrusion errors (recalling words from the wrong list), which are examples of a difficulty in inhibiting the retrieval of task irrelevant items. In a similar study, Soliman and Elfar (2017), asked adults with and without ADHD to learn eight lists and were then presented with a recognition task. The ADHD group recognized less words correctly, produced more false positive responses (i.e., wrongfully selecting items that weren't learned) and were more confident in their mistakes. In a different study, Castel et al. (2011), asked children with and without ADHD to perform the value directed remembering paradigm mentioned above. Results show that children with ADHD recalled as many items as the controls, however they were less able to select which items to remember.

ADHD, Memory Selection, and Inhibition and Lateral BA 10/46

The literature search yielded only one neuroimaging study assessing selection or inhibition of memory functions in ADHD. In a study by Depue et al. (2010), adults with and without ADHD were taught a relation between face-picture pairs until mastery. They were later shown a picture of a face and were asked to either think of the related picture or to keep the related image from coming into consciousness. Results show that ADHD participants activated lateral BA 10 less than controls when comparing the "no-think" condition with the "think" condition.

EMOTION

Emotion Selection and Inhibition and Lateral BA 9

There is much evidence supporting the relation between emotion regulation (the inhibition of certain emotions and selection of others) and lateral BA 9. For example, in a study by Hallam et al. (2014), participants viewed emotion inducing films and were required to either suppress or reappraise their emotional reaction, or to simply watch the film. Results showed that both reappraisal and suppression compared to the passive condition showed activation of lateral BA 9. Similarly, two studies compared reappraisal and passive watching of pictures in people with PTSD and controls. Both studies found lateral BA 9 to be activated more during the reappraisal condition, but to a lesser extent in people with PTSD (Xiong et al., 2013; Rabinak et al., 2014).

In addition, two different meta-analyses were used to examine fMRI studies assessing emotion regulation. Buhle et al. (2014) found that reappraisal involving down regulation of negative affect consistently activated lateral BA 9; Frank et al. (2014) found that such reappraisal was accompanied by greater activation in lateral BA 9 and decreased activation in the amygdala.

ADHD and Emotion Selection and Inhibition

Several studies found emotion regulation deficits in children with ADHD. For example, several studies show that children with ADHD have a harder time suppressing their emotions than their typically developing (TD) peers. For example, in one study children underwent a peer competition task, in which half were requested to hide their emotions and half were not. According to assessments made by naive judges, results show that ADHD children were less able to mask their emotions than their peers (Walcott and Landau, 2004). Furthermore, a study assessing the performance of children with ADHD on an emotional Stroop task, found that the children with ADHD had a harder time

inhibiting responses to angry and frustrated faces (Yarmolovsky et al., 2016).

Additionally, in a meta-analysis of emotion regulation in ADHD performed by Graziano and Garcia (2016), they found four domains of interest, namely: recognition (i.e., ability to process and infer the emotions of others as well as one's self), reactivity (i.e., the threshold, intensity, and duration of one's affective arousal), regulation (i.e., effectively responding to emotional reactivity in a flexible manner that facilitates adaptive functioning), and empathy (i.e., the ability to experience another's affective state and/or express concern for another's position). Results show that while all four domains seem to be atypical in the ADHD population, the most notable deficiencies occur in the reaction and regulation domains. This means that (especially) children with ADHD tend to react more quickly, more intensely and for a longer period of time to aversive situations, and are less able to regulate these emotions even when they attempt to do so.

ADHD, Emotion Selection, and Inhibition and Lateral BA 9

There are several studies that show specific atypicalities in lateral BA 9 activation in ADHD participants performing tasks which require emotion regulation. For example, in a study by Passarotti et al. (2010a), children with bipolar disorder, children with ADHD and a group of age matched controls performed an emotional valence Stroop task. In this task, positive, neutral and negative words were presented, and participants were required to respond according to the word's color while ignoring its meaning. Results show that the bipolar group had difficulty ignoring positive words, while the ADHD group had difficulty ignoring negative words. Interestingly, lateral BA 9 activation was more pronounced for task condition that was successfully performed, i.e., for negative words in the bipolar group, and for positive words in the ADHD group. Furthermore, in a Stroop based emotional task, Hwang et al. (2015), asked children with and without ADHD to perform a numeric Stroop task after being shown pictures that were either positive, neutral or negative. While behavioral data did not show significant differences between the different emotional conditions, they did find that children with ADHD were less able to recruit lateral BA 9 when performing the task, a trait which also correlated with symptom severity as was measured by the Conner's parent scale.

MOTOR

Motor Selection and Inhibition and Lateral BA 8

There is much evidence that the inhibition of motor actions is supported by neural networks in lateral BA 8. The most common measure of motor inhibition is the Stop Signal Task (SST) in which participants are required to press a key when a stimulus is presented, but refrain from executing that key press if the stimulus is followed shortly by a signal. Studies show that inhibiting the key press involves activation in lateral BA 8 (Matthews et al., 2005; Smith et al., 2013; Hughes et al., 2014). Lateral BA 8 has also been shown to be specifically active when the selection of a motor response required attention or involved conflict. For example, Enriquez-Geppert et al. (2013), asked participants to press a key when a stimulus appeared on the screen, however, the response key changed in some of the trials. The Experimenters found lateral BA 8 to be specifically activated on trials in which the response key was different. Similarly, Lenartowicz et al. (2011), used a go/no-go task in which after a few practice sessions, the stimuli changed so that the previous go signal became a no-go signal (requiring more inhibition). They found lateral BA 8 to be specifically activated on those trials. In a similar study Albares et al. (2014), used a version of a go/no-go task in which a prime was presented before the go and no-go stimuli. However, while a green light indicated that a go stimulus will follow, a red light meant that any one of three conditions may occur, either a go stimulus, a no-go stimulus or no stimulus at all. The researchers reasoned that the red-light condition involves more complex motor planning than the green light, and found that lateral BA 8 was indeed more active during that condition.

ADHD and Motor Selection and Inhibition

There is robust evidence of motor selection and inhibition deficits in children with ADHD. Many studies to date have shown that children, adolescents and adults with ADHD show poorer performance on different versions of the stop signal task (e.g., Rubia et al., 1998; Lee et al., 2016; Bialystok et al., 2017; Dekkers et al., 2017), and that when children with ADHD are properly medicated and motivated using effective reinforcement, these differences may disappear (Rosch et al., 2016). Furthermore, in a very large study by Crosbie et al. (2013), ADHD symptoms were measured in over 16,000 general public children who performed the SST. Results showed that individuals with greater ADHD trait scores had worse response inhibition, slower response latency and greater variability, and also that this trend was highly heritable. Similarly, Alderson et al. (2007), performed a meta-analysis focusing on ADHD children and the SST and found greater mean response times, greater response variability and greater stop signal response time in the ADHD group.

ADHD, Motor Selection, and Inhibition and Lateral BA 8

There is also considerable evidence showing specific atypicalities in lateral BA 8 activation in ADHD participants performing tasks which require motor selection and inhibition. For example, two separate meta-analyses have explored fMRI studies assessing motor inhibition in children and adults with ADHD (Hart et al., 2013; Rubia et al., 2013). Both meta-analyses found lower activation in lateral BA 8 to be related to motor inhibition measures, and the study by Rubia et al. (2013), also found methylphenidate to increase activation in lateral BA 8 which was related to improved performance on motor tasks. In addition, studies which employed different versions of the SST and the go/no-go task found less activation in lateral BA 8 in the ADHD group during a simple no-go condition (Passarotti et al., 2010b; Mulligan et al., 2011), moments before an error occurred (Spinelli et al., 2011), as well as during a free choice condition in which participants chose whether to press a button or not when a stimulus was presented (Karch et al., 2010).

SUMMARY

The current paper presents evidence that the lateral part of the prefrontal cortex is involved in the inhibition, selection and manipulation of motor, emotional, memory, and perceptual-sensory information, a function that is helpful in everyday life through the ability to ignore distraction, select and retrieve specific information from our memories, identify and regulate our emotional state or plan a situation appropriate motor response. It uses this model to classify challenges encountered by people with ADHD, linking different types of difficulties in selection/inhibition to different subareas of the lateral prefrontal cortex.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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