BEYOND REWARD: INSIGHTS FROM LOVE AND ADDICTION

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BEYOND REWARD: INSIGHTS FROM LOVE AND ADDICTION

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It is an interesting topic to discuss addiction and love in the context of reward. In this e-book, we begin with an animal study of comparison between drug and natural reward. Then, some papers aim to understand the reward system underlying behavioral addiction focusing on technology, for example Internet addiction and mobile phone dependence. The third part of this e-book addresses the topic of love. Considered as a whole, this e-book demonstrates that drug and behavioral addictions are frequently related with negative consequences, while romantic love is related with a positive consequence. That's why romantic love may be considered as a natural addiction. We think that the notion of romantic love as a positive addiction may offer a new view for future research in the field.

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EDITORIAL
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Editorial: Beyond Reward: Insights from Love and Addiction

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Keywords: addiction, love, fMRI, EEG, reward system, sex

Editorial on the Research Topic

Beyond Reward: Insights from Love and Addiction

Rewarding stimuli promoting the learning of goal-directed behaviors tend to produce positive emotions, and subsequently repetition of those learned behaviors. Some kinds of drugs and behaviors are highly rewarding, and thereby, control human behavior by generating a state called addiction. The core feature of this state is compulsive behavior despite negative consequences. Addiction on a neurobiological level increases dopamine in the reward system and this is believed to underlie the rewarding effects. Large amount of studies in addiction have focused on the midbrain dopamine areas. Indeed, several researchers have defined addiction a disease of the reward system.

However, it has been argued that natural rewards can also induce an addictive-like state. For humans, natural rewards can be more complex than sex and food, and romantic love is interestingly proposed as a natural addiction. The following definition of romantic love as an addiction has been suggested: a positive addiction when one's love is reciprocated, non-toxic and appropriate, and a negative addiction when one's feelings of romantic love are socially inappropriate, toxic, not reciprocated, and/or formally rejected. Individuals in romantic love show many symptoms of drug and behavioral addictions, including tolerance, craving, emotional and physical dependence, relapse, and withdrawal. Human functional magnetic resonance imaging studies have shown that feelings of romantic love engage areas of the reward system, specifically dopamine-rich areas, including the midbrain, activated as well during drug and/or behavioral addiction.

It is an interesting topic to discuss addiction and love in the context of reward. In this e-book, we begin with an animal study of comparison between drug and natural reward. Duan et al. explore different effects of reward between morphine and food. A featured behavioral transition from psycho-activity to seeking behavior was shown during morphine abstinence, while only seeking behavior was displayed during food abstinence, suggesting that drug and natural rewards show some characteristics while mainly similarities exist. Lv et al. review cue reactivity in nicotine and alcohol addiction, suggesting that cultural cue reactivity may have an effect on addictive behavior through emotion and attention and is a field worth of exploring.

Some authors in this e-book seek to understand the reward system underlying behavioral addiction focusing on technology (mostly with internet addiction). Wang et al. find gray matter volume and white matter integrity altered in college students with mobile phone dependency. Li et al. present data showing that inhibitory control and reward functions, two associated cognitive processes, are impaired in problematic internet users, which strengthens the balance model of

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self-regulation theory. By using an addiction stroop task, Zhang et al. report that internet gaming disorder shows higher activations in brain areas involved in selective attention, visual processing, working memory, and cognitive control when facing internet gaming-related stimuli. Despite of local deficits, altered functional connectivity in internet addiction is also investigated. Lin et al. try to research the spontaneous brain activities of internet gaming disorder subjects and finds that these subjects show decreased functional connectivity in executive function and decision-making-related regions, which contributes to understanding the underlying pathophysiology. Treatment of internet addiction is an important area. Zhang et al. review studies on cue-induced behavioral and neural changes in internet gaming disorder, suggesting that mechanisms of internet gaming disorder mostly overlap with those of substance use disorder. The cue exposure therapy's effects in the treatment of addiction are also reviewed. Finally, an optimized paradigm for a probable treatment of internet gaming disorder is proposed.

The third part of this e-book addresses the topic of love. A review of addictive-like behaviors and brain systems associated with love is summarized by Fisher et al. A series of articles describe work aimed at understanding the neurobiology of love. Facial processing is closely related to romantic love. Wu et al. explore the effect of marriage style on the recognition of the beloved partner's face, especially in matriarchal societies. Marriage style affects the later stage processing of a beloved partner's face, which may be associated with greater affective arousal and familiarity. Another study by Sun et al. finds that facial attractiveness and expression are first processed in parallel for discrimination between stimuli. After the initial processing, more attentional resources are allocated to the faces with the most positive or most negative valence in both the attractiveness and expression dimensions. In the study by Song et al., early stage lovers show greater capacity for inhibiting action during presentation of negative emotional stimuli by comparing with individuals who are single, which may be related to the successful formation of romantic relationships.

Romantic love in a relationship is characterized by mate copying, attachment and intrasexual competition, which is investigated by several authors. Zhuang et al. confirm the mate copying effect in a behavioral experiment—greater increase in attractiveness ratings was observed for opposite-sex pictures in the interested than in the not-interested condition. And the fMRI results show that the DLPFC may be involved in the process related to mate copying. An electroencephalograph study by Hou et al. presents data suggesting that adult attachment styles affected individuals' recognition processing in response to love-related and sex-related images. Zheng et al. find that intrasexual competition can decrease pain empathic response to a same-sex "lucky guy" who has an attractive partner. Furthermore, right superior frontal gyrus and medial prefrontal cortex activations could predict participants' subsequent pain intensity ratings for the lucky guy.

Considered as a whole, the articles in this e-book demonstrate that romantic love may be considered a "natural addiction," which parallels "diseases" of the reward system like drug and behavioral addictions in some respect. Drug and behavioral addictions are frequently related with negative consequences, while romantic love may be a positive addiction when the relationship is reciprocated, non-toxic and appropriate. This Research Topic brought together a range of perspectives regarding love and addiction. We hope love as a positive addiction offers a new view for future research in the field and that readers feel inspired by the articles in this e-book that provides a sample of such work.

AUTHOR CONTRIBUTIONS

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

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ORIGINAL RESEARCH
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Addiction: From Context-Induced Hedonia to Appetite, Based on Transition of Micro-behaviors in Morphine Abstinent Tree Shrews

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Drug addiction is viewed as a maladaptive memory induced by contextual cues even in the abstinent state. However, the variations of hedonia and appetite induced by the context during the abstinence have been neglected. To distinguish the representative behaviors between hedonia and appetite, micro-behaviors in abstinent animal such as psycho-activity and drug seeking behaviors were observed in morphine conditioned place preference (CPP). To confirm the different effects of reward between drug and natural reward, a palatable food CPP paradigm was compared in current work. After a 10-day training in CPP with morphine or food, the preference was tested on day 1, 14, 28, and the changes of micro-behaviors were analyzed further. Our data showed that tree shrews treated with morphine performed more jumps on day 1 and more visits to saline paired side on day 28, which indicated a featured behavioral transition from psycho-activity to seeking behavior during drug abstinence. Meanwhile, food-conditioned animals only displayed obvious seeking behaviors in the three tests. The results suggest that the variations of micro-behaviors could imply such a transition from hedonic response to appetitive behaviors during morphine abstinence, which provided a potential behavioral basis for further neural mechanism studies.

Keywords: tree shrews, addiction, morphine, CPP, micro-behaviors, transition, palatable food

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INTRODUCTION

Drug addiction has been viewed as an aberrant learning of the association between drug and the context (Hyman, 2005). This association is so long-lasting that relapse could be triggered by the contextual stimuli even after long-term abstinence in human addicts (O'Brien, 1997; Daglish et al., 2001; Volkow et al., 2006). Thus, a better understanding of this association might be critical to the development of effective treatments against addiction (Crombag et al., 2008). However, the response induced by the context is controversial (Bolles, 1972; Carey and Gui, 1998; Bardo and Bevins, 2000; Huston et al., 2013). On one hand, the repeated use of drug in a particular environment generated the association between the context and the drug-induced affective effect such as hedonia (Carey et al., 2005). Thus the contextual stimuli might activate this hedonic effect directly by performing psycho-activity without drug. On the other hand, the association was also strengthened by the motivational properties of drug (O'Brien et al., 1993; Dalley et al., 2007) and the contextual stimuli might trigger appetite for drug or drug seeking in the drug-free state. It might be necessary to distinguish these two context-induced responses, because they depended on distinct anatomical and neurochemical substrates (Spiteri et al., 2000; Berridge et al., 2009; Smith et al., 2011).

The conditioned place preference (CPP) model was commonly used in preclinical studies to investigate the association between addictive drugs and the contextual stimuli. In CPP, the animal was alternatively confined in one chamber after drug injection or another chamber after saline injection. Following repeated conditionings, the animal was allowed free access to both chambers in a drug-free state, and the time stayed in drug-paired chamber was taken as the index of preference (Bardo et al., 1995). It was generally thought that the acquired place preference was driven by the motivation or appetite (Tzschentke, 2007), but morphine conditioned mice performed hedonic behaviors rather than appetitive behaviors in the preference test (Spiteri et al., 2000). The contrary results suggested it might be worthwhile to examine whether hedonia or appetite was actually induced by the context. Furthermore, the morphine CPP in rats could maintain at least 6 weeks (Mueller et al., 2002) and morphine CPP score in rats was even increased after a 2-week withdrawal (Smith and Aston-Jones, 2014). Meanwhile, cocaine self-administrated rats also performed the progressively increased seeking during abstinence (Lu et al., 2004). Moreover, clinical studies reported that cue-induced appetite was increased after an acute abstinence and the craving persisted even after a long period of abstinence (Gawin and Kleber, 1986). These results suggested that the abstinent state might increase appetitive behaviors, but the variation of hedonic behaviors was unknown. Therefore, we investigated whether hedonia or appetite was induced by context after morphine CPP training, and explored the variations of these responses during abstinence.

In addition to addictive drugs, many natural rewards including food could also form CPP (Tzschentke, 2007). A series of studies proved different brain mechanisms between the hedonic and appetitive effects of food (Berridge, 2009; Castro and Berridge, 2014) and mice displayed more seeking or appetitive behaviors after food conditioning (Spiteri et al., 2000). However, it was unclear whether the hedonic effect of food was induced by context after conditioning. Moreover, cue-induced appetite for sucrose in rats also increased during abstinence (Grimm et al., 2005), which implied the variation of context-induced responses might occur during food abstinence. Thus, we detected both hedonic and appetitive behaviors after palatable food training, then we examined the variations of these behaviors during abstinence. Both drug and food produced the reward effect through acting in the same reward circuits, but had different influences on the reward system (Pitchers et al., 2010). Therefore, the food CPP was used as a comparison for a better understanding about the responses induced by drug-related context.

In this study, we observed the micro-behaviors in tree shrews to investigate the variations of hedonia and appetite after morphine or palatable food conditioning. Tree shrews were suggested as potential candidates for addiction studies, phylogenetically close to primates (Fan et al., 2013). Based on the characteristic nature of tree shrews and previous behavioral studies, the psycho-activity characterized by number of vertical jumps was used as the index for hedonic behaviors, which was shown to increase significantly in tree shrews after morphine injection (Shen et al., 2014). Meanwhile, we counted the number of visits between different chambers as the index of seeking behaviors, which was widely used in rats to reflect the appetitive state (Mellgren and Olson, 1983; Mellgren and Elsmore, 1991). The observations were made on day 1, day 14, and day 28 following conditioning and compared with pre-test to investigate whether the context-induced responses were changed or not during abstinence.

MATERIALS AND METHODS

Animals

A total of eight male tree shrews (*Tupaia belangeri chinensis*; 12–18 months old; 130–160 g) from the breeding colony at the Animal House Center of the Kunming Institute of Zoology were used in the experiments. Animals were individually housed in stainless cages (395 mm × 300 mm × 595 mm) attaching to the nest boxes (246 mm × 158 mm × 147 mm) under standard conditions (a 12-h light/dark cycle with light on from 08:00 to 20:00; Room temperature at 25°C). Food and water were provided *ad libitum*. All experiments were conducted during the light phase. Animals were handled through opaque bags once a day for a week before the experiment, thus they were habituated to the treatment of the experimenter.

The experiments were conducted according to the National Institute of Health, Guide for the Care and Use of Laboratory Animals, and the protocols were approved by the Research Ethics committee of Institute of Psychology, Chinese Academy of Sciences.

Drugs

Morphine hydrochloride (Qinghai Pharmaceutical, China) was dissolved in sterile physiological saline (0.9% NaCl) to its final concentrations.

Apparatus

The CPP apparatus was composed of three stainless steel chambers (395 mm × 300 mm × 595 mm) as chamber A, C, and B in a row. The chamber C was in the middle and could connect with the nest box. The walls of chamber C were removable, separating chamber A and B, respectively. The apparatus were mainly featured with color cues in different sides of chambers according to the well-developed visual system in tree shrews (Petry and Harosi, 1990). Chamber A had a yellow floor with yellow and white horizontal stripes on the walls. In contrast, chamber B had a blue floor with blue and white vertical stripes on the walls. Chamber C just made by stainless steel without any decoration. All chambers had cameras mounted on the top to record the animals' behaviors.

Procedure

The procedures were made, respectively, in the morphine- and food-conditioned group. The procedures of two groups both consisted of three phases: pre-test, conditioning and post-tests on day 1, 14, 28 after last conditioning sessions. The difference in two groups was conditioning phase. The morphine CPP procedure was based on our previous study with minor modifications (Shen et al., 2014) and the food CPP procedure was referred to rat study (Kanoski et al., 2011). The timeline of the experiment was showed on **Figure 3A**.

Pre-test

The removable walls of chamber C were opened with a 5 cm width gap, and the tree shrews were placed in the chamber C through their nest boxes. Chamber C was the start for exploring the apparatus. Animals moved freely in the three chambers for 60 min on three consecutive days for habitation and pre-test. When the tree shrew was placed into the apparatus, it might hide in the nest box and did not explore the area for a while because it was sensitive to the change of the environment. Therefore, data acquisition started when the tree shrew first went out from the nest box and lasted for 30 min. Time spent in each chamber, the numbers of visits to each chamber and the numbers of vertical jumps on the third day was recorded as pre-test data. The biased procedure was used in our study, and the disliked chamber for each animal was used as the reward-paired chamber during conditioning training.

Conditioning

After the pre-test, the animals were randomly divided into two groups ($n = 4$ per group) to form morphine or food CPP, respectively. The details were described as follows.

Morphine-conditioned tree shrews were injected with 5 mg/kg (intramuscular injection, IM) morphine and placed in their paired chamber on the first conditioning day. This dose was only used for the first morphine injection and for the following morphine injection the dose increased to 10 mg/kg. This design was based on our previous results which showed that one morphine injection of 5 mg/kg could make tree shrews adapt to the strong pharmacology effect of morphine and avoid the potential harm induced by the increased dose in recent sessions. Twenty-four hours after the morphine injection, the tree shrews were injected with saline (1 ml/kg, IM, the same volume as the morphine injection) and confined to the other chamber. On the subsequent conditioning days, each tree shrew trained for eight consecutive days with alternate injection of morphine (10 mg/kg, IM) and saline. The interval between injection and putting animals into the chamber was 3045 min and the conditioning time was 90 min. The time was based on the previous study to make sure that animals stayed in high locomotor level after morphine injection.

The food CPP was designed to compare with the morphine and the only difference between the procedures was the rewarding event. Since food deprivation might change the motivational state and locomotor activity of animals, the palatable food CPP in the normal feed state of tree shrews was used in our study. Our preliminary study found that apple was their favorite among three kinds of food (dry yellow mealworm, apple and food pellets). Therefore, during the conditioning training (Day −9 to 0), tree shrews had free access to a piece of apple which was placed in the middle of the reward-paired chamber for 30 min and were conditioned with nothing in another chamber for 30 min on alternate day.

Test

After conditioning, the tree shrews freely explored the apparatus with the walls of chamber C opened to test their preference (P1-test). The procedure was similar to the pre-test phase. Moreover, to explore the preference and context induced behaviors during abstinence, tests were taken every 14 days (P14-test, P28-test).

Statistical Analysis

Conditioned place preference score [time in reward-paired chamber/(time in chamber A + time in chamber B)] was the index of preference. All data was shown as mean ± SEM. The statistical package SPSS 19.0 was used for data analysis. Paired *t*-test was performed to examine the establishment of CPP and behavioral changes between pre-test and P1-test. One-way ANOVA for repeated measures and LSD *post hoc* were performed to examine the persistence of the preference and the behavioral results within three abstinent time points in each group. The accepted level of statistical significance was $p < 0.05$.

RESULTS

Establishment of CPP and the Variations of Micro-behaviors after Conditioning

After five alternating conditioning sessions, CPP score in morphine-rewarded tree shrews was increased significantly compared with pre-test ($t = 15.560$, $p < 0.001$). And CPP score in food group also displayed a significant increase compared with their Pre-test data ($t = 3.215$, $p = 0.025$). The results indicated that both morphine CPP and food CPP were established in tree shrews (**Figure 1**).

During the expression of CPP, the behavioral data was further analyzed to distinguish hedonia or appetite induced by the context (**Figure 2**). In the morphine-conditioned group, the number of vertical jumps significantly increased compared with pre-test in morphine-paired chamber ($t = 2.665$, $p = 0.038$) but not in saline-paired chamber ($t = 1.071$, $p = 0.181$), indicating that the high psycho-activity induced by conditioned context occurred in P1-test. Meanwhile, the number of visits decreased significantly in saline-paired chamber ($t = 3.345$, $p = 0.019$), but no significant difference in morphine-paired chamber ($t = 0.051$, $p = 0.963$), compared with pre-test. The decreased visits implied that not obvious seeking behaviors were induced by context. In the food group, the number of vertical jumps in both chambers was low and not changed (in food-paired chamber: $t = 1.338$, $p = 0.136$; in no food-paired chamber: $t = 1.495$, $p = 0.116$; compared with pre-test, respectively), suggesting no significant psycho-activity induced by the context. Meanwhile, the number of visits in both chambers was also stable compared with pre-test (in food paired chamber: $t = 0.991$,

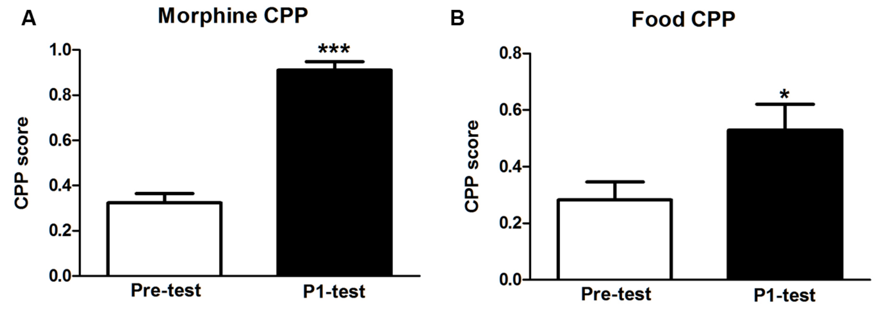

FIGURE 1 | Establishment of morphine and food CPP in tree shrews. (A) Morphine conditioned tree shrews showed a significant preference for morphine-paired chamber. **(B)** Tree shrews in food group showed a significant preference for food paired chamber. Blank and solid columns represent data from pre- and P1-tests, respectively. Data were expressed as the means ± SEM, $n = 4$. $^{*}p < 0.05$, $^{***}p < 0.001$.

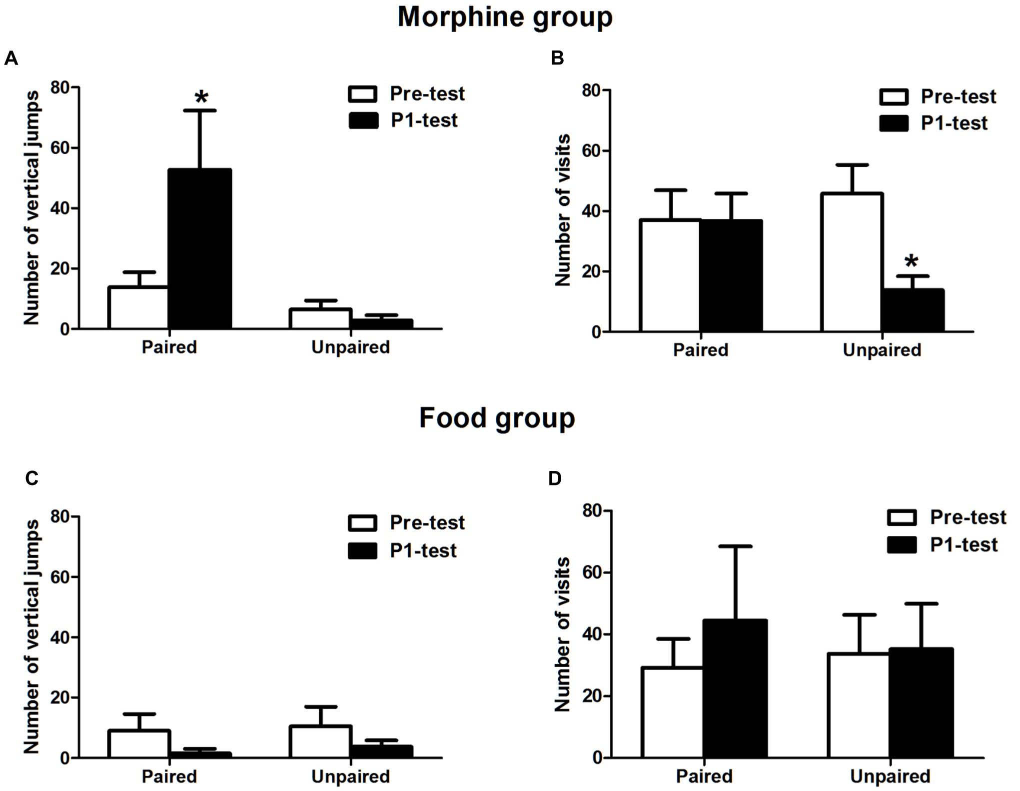

FIGURE 2 | Variations of psycho-activity and seeking behaviors on morphine and food CPP. (A) The vertical jumps of the morphine conditioned groups increased in morphine-paired chamber. **(B)** The visits number of the morphine-conditioned tree shrews decreased in saline paired chamber. **(C)** The vertical jumps number of the food-conditioned tree shrews was stable in both chambers and decreased compared to Pre-test. **(D)** The visits number in food group maintained stable. Data were expressed as the means ± SEM, $n = 4$. $^{*}p < 0.05$.

$p = 0.197$; in no food paired chamber: $t = 0.214$, $p = 0.422$). This result indicated that the food group expressed seeking behaviors, because the number of visits was not decreased even after habituation.

Above results showed that the morphine-conditioned group mainly performed hedonic behaviors, but the palatable food-conditioned group mainly performed appetitive behaviors on the expression of place preference.

The Rewarding Value of Morphine or Food during Abstinence

The CPP score was an index to reflect the rewarding value, which implied the strength of reward effects associated with the context. More importantly, both hedonia and appetite were induced by this reward effect. Thus, the place preference was examined every 14 days after conditioning (**Figure 3**). In the morphine-conditioned group, one-way ANOVA with repeated

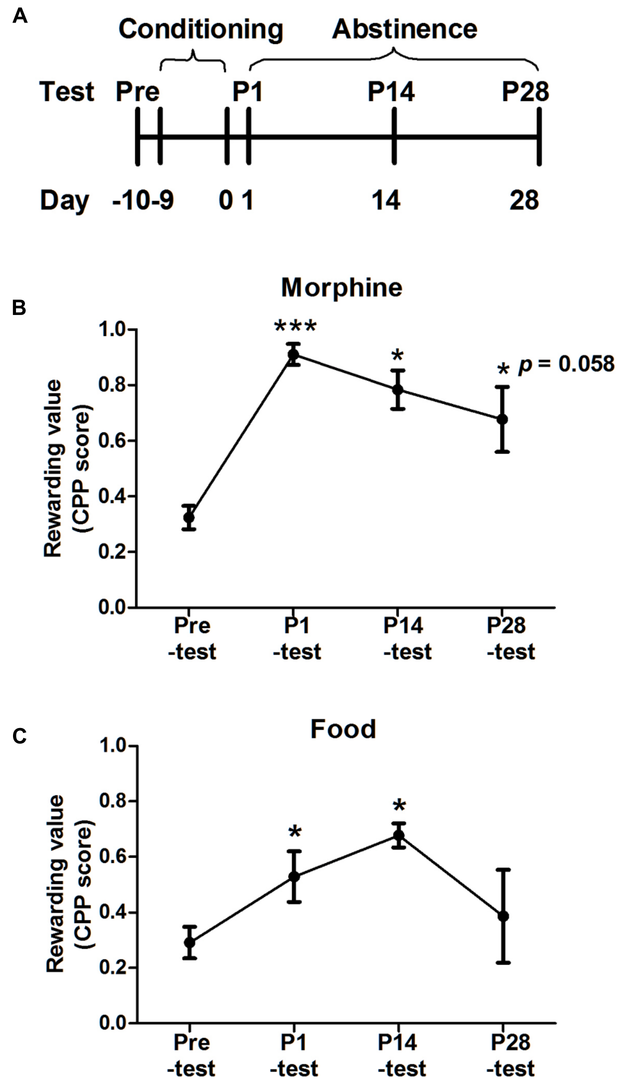

FIGURE 3 | Place preference induced by morphine or food during abstinence. (A) Diagram outlining the behavioral procedures. After conditioning and P1-test, both groups were tested for CPP every 2 weeks during abstinence. **(B)** Morphine conditioned group maintained preference for 28 days. **(C)** Food conditioned group maintained for 14 days. Data were expressed as the means ± SEM, $n = 4$. *$p < 0.05$, ***$p < 0.001$, compared with their pre-test.

measurement revealed a main effect of test time [$F_{(3,12)} = 13.040$, $p = 0.001$], and LSD *post hoc* analysis showed significant differences in P1-test ($p = 0.001$), P14-test ($p = 0.014$) and a marginally significant difference in P28-test ($p = 0.058$), compared with pre-test. In the food-conditioned group, the main effect of test time was significant [$F_{(3,12)} = 5.191$, $p = 0.024$], *post hoc* analysis found the significant difference in P14-test ($p = 0.005$) but not P28-test ($p = 0.519$), compared with pre-test.

Above results implied the morphine-induced place preference could maintain for almost 28 days in tree shrews and the palatable food-induced place preference could last 14 days. Thus, the further micro-behavior was analyzed till on day 28.

The Transition from Psycho-Activity to Seeking Behaviors during Morphine Abstinence

Beyond the results in the Section "The Rewarding Value of Morphine or Food during Abstinence," we recorded the micro-behaviors of tree shrews at 10 min intervals during four tests (Supplementary Figure S1). More detailed descriptions about this supplementary figure were in the discussion component. Based on these analyses on behaviors changing with time, we took the vertical jumps in reward-paired chamber as the index of psycho-activity, and took the number of visits in no reward-paired chamber as the index of seeking behavior. Both indexes in each group were displayed simultaneously (**Figure 4**).

In the morphine group, although there was no significant test time effect on the number of vertical jumps in morphine paired chamber [$F_{(2,9)} = 5.156$, $p = 0.106$], the number of jumps displayed a declining trend along with the abstinent time. It indicated that the psycho-activity was decreased during abstinence. Meanwhile, morphine-conditioned tree shrews displayed a time effect on the number of visits in saline paired chamber [$F_{(2,9)} = 9.582$, $p = 0.014$] and LSD *post hoc* showed significant difference between P1-test and P28-test ($p = 0.040$), and between P14-test and P28-test ($p = 0.011$). It suggested that the seeking behaviors in morphine groups continually increased during abstinence. In food-conditioned tree shrews, by contrast, the number of vertical jumps and visits was stable during the whole abstinence sessions, indicating that the responses were no changed during abstinence.

From above results, the increased seeking behaviors with decreased psycho-activity meant a transition from hedonia to appetite induced by context during morphine abstinence. However, food-conditioned group displayed no behavioral change during abstinence.

DISCUSSION

Our results indicated that morphine-conditioned tree shrews expressed more psycho-activity on short term-abstinence, but more seeking behaviors on long-term abstinence, implying a context-induced transition from hedonia to appetite. As a comparison, the food-conditioned group did not experience this transition during abstinence. There were still some questions to be discussed.

Both morphine and food CPP in tree shrews were established after five alternating sessions. However, the morphine-conditioned group showed higher CPP score than food group, in agreement with studies in rats (Duarte et al., 2003; Tzschentke, 2007). It implied greater magnitude of reinforcing effects in morphine. The reinforcing effects needed dopamine (DA) system participating in (Volkow et al., 2011) and preclinical studies showed that the higher and faster DA signals accorded with stronger reinforcing effects (Schultz, 2010). Morphine could activate DA system in a rapid access way, but food influenced the same circuits in two more indirect ways (Alonso-Alonso et al., 2015). Therefore, different reward effects might make

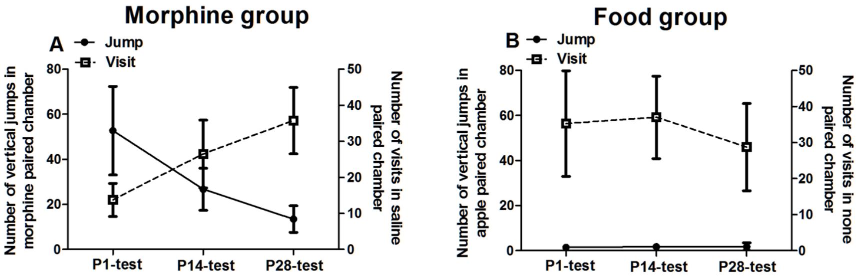

FIGURE 4 | Variations of psycho-activity and seeking behaviors during the abstinent state. The left *y*-axis showed the number of vertical jumps in morphine/food paired chamber and the right *y*-axis showed the number of visits to saline/no food paired chamber. **(A)** In morphine conditioned tree shrews, the jumps number in morphine-paired chamber expressed decreasing trend, however, the visits number in saline paired chamber expressed significantly increasing trend during abstinence. **(B)** In food-conditioned tree shrews, the number of jumps visits showed no change during the abstinent state. Data were expressed as means ± SEM, $n = 4$.

morphine evoke higher reinforcement than palatable food. Furthermore, the analyses on micro-behaviors showed that morphine-rewarded animals displayed more psycho-activity in drug-paired chamber, which was also observed in rats after morphine or heroin treatment (Parker, 1992; Paolone et al., 2007). On the contrary, the food-rewarded animals mainly displayed seeking behaviors, in agreement with the study in mice which found the food-conditioned animals mainly expressed seeking behaviors after training (Spiteri et al., 2000). The various influences on DA system between drug and food might be the neural basis of these different responses.

To explore whether the hedonia and appetite were changed or not with the increasing duration of abstinence, the most important thing was to find the appropriate behavioral indexes to represent the hedonic and appetitive responses. We counted the number of jumps and visits in both chambers at 10 min intervals during four tests (Supplementary Figure S1). The number of vertical jumps in the morphine-conditioned group was increased significantly in the P1-test, compared with pre-test. Moreover, the number in the morphine-paired chamber emerged an increasing trend (Supplementary Figure S1B), and the trend was the same as that of psycho-activity after morphine injection (Shen et al., 2014). Therefore, the number of vertical jumps in reward-paired chamber was taken as the index of psycho-activity. Meanwhile, the number of visits in different chambers was recorded, which was a common item as seeking behaviors in rats. However, the meaning of the visits to the reward-paired chamber was misleading (Huston et al., 2013). Both hedonic effects and the appetite could lead the approach to this chamber. Moreover, based on our observation, the trend of variation on visits number was different during each test. During the P1-test the visits number of the morphine-conditioned group performed significant differences in 0–10 min ($t = 4.621$, $p < 0.05$) and 10–20 min ($t = 5.62$, $p < 0.05$), compared drug-paired with saline-paired chamber (Supplementary Figure S1B). But during the P14-test, there was the significant difference only in the second 10 min ($t = 4.041$, $p < 0.05$; Supplementary Figure S1C), and there was no difference during the P28-test (Supplementary Figure S1D). It indicated that the difference on the visits to the morphine- and saline-paired chamber became disappeared, and the number in saline-paired chamber made the main contribution. Tree shrews performed more and more visits to saline-paired chamber, although still had the preference for morphine-paired chamber. It was indicated that the seeking behaviors occurred. Therefore, the number of visits in no reward-paired could be the appropriate index as appetite. In addition, we also found an interesting phenomena that when the animals showed high number of vertical jumps, the number of visits to no reward-paired chamber was low, and when performs low jumps, the visits number was high. It suggested that two responses might compete against each other.

During abstinence, the morphine-conditioned group implied a transition from hedonia to appetite. One of the possible reason for this transition was that the negative affective state was elicited because of morphine absence (Mucha, 1987). To get rid of the negative effects, animals might produce more appetite for drug and thus performed more seeking behaviors (Ahmed and Koob, 2005). Morphine-conditioned tree shrews in our study performed decreasing psycho-activity during withdrawal, which implied that some negative effects might emerge. However, to get rid of the negative state, the place preference would be turned into aversion. But the preference was still performed on our study. The alternative explanation for the increased appetite might be from the motivational shift during abstinence (Berridge and Robinson, 1995). Addictive drugs caused a sensitization in the brain systems which would be the biological base of the motivation bias induced by drug (Berridge, 2007; Kalivas, 2009). The sensitization could be long-lasting and even aggravated during withdrawal (Lee et al., 2013; Loweth et al., 2014). When tree shrews re-exposed to the context, the contextual stimuli might trigger the sensitized system into higher level of activation, and more appetite for drug might be also triggered. So the behavioral transition might reflect the variation in neural system. Further, the development of drug addiction has been believed to result in maladaptive neurobiological responses induced by drug within the mesostriatal DA systems and corticostriatal glutamate (GLU) systems of the brain (Tzschentke, 2001; Everitt and Robbins, 2005; Mameli and Lüscher, 2011), and two systems participated in different responses. DA release in nucleus accumbens (NAc) was necessary for psychomotor sensitization (Volkow et al., 2001; Everitt and Wolf, 2002), and imaging studies suggested increased DA in the striatum was associated with the "high" in humans (Volkow et al., 2007), implying the DA system activation was involved in the high positive effect. However, GLU was necessary for drug seeking behaviors (Cornish and Kalivas, 2000) and played a critical role of cue-induced appetitive behavior after long-term withdrawal (Loweth et al., 2014). Previous studies have shown reduced phasic dopamine function in (NAc) during drug withdrawal (Acquas and Chiara, 1992; Diana et al., 1995; Ahmed and Koob, 2005), whereas emerging evidences suggested that GLU system played more important role in long term synaptic adaptation during abstinence (Cornish and Kalivas, 2000; Kalivas et al., 2009). These results suggested that the neural change underlying addiction from DA system to GLU system, which might be reflected by the behavioral transition from hedonia to appetite.

As a contrast, the food conditioned group had no transition during abstinence. The stable number of jumps and visits implied that the appetite for food was continuously induced by the context. Although the same behavioral phenomenon was observed on mice study (Spiteri et al., 2000), the meaning might be different. In Spitert's study, the mice was on deprived state, and the appetitive behavior could be promoted by the food deprivation (Pyke, 1984). However, in our study the apple was as the palatable food to induce place preference and food was provided in their cages *ad libitum*. The high number of visits might suggest that the palatable food was as the goal conditioned with the context, which was related to the DA system (Carelli, 2002). When the food-conditioned group re-exposed to the context, the goal-seeking system was activated and animals performed seeking behaviors. Different from the morphine-conditioned group, the behaviors in food group was stable and had no transition. Drug and food both could activate the mesolimbic DA system, but the function of activations and the circuit which processed the reward effects were largely distinct (Carelli et al., 2000; Pitchers et al., 2010; Cameron et al., 2014). Moreover, although drug and natural rewards could both induce adaptive synaptic adaptation, the changes of GLU receptors were in opposite direction during withdrawal (Cameron et al., 2014). These different neurobiological mechanisms might explain the variable behaviors between drug and food, and the specific effects induced by drug might be the molecular target for this transition.

The main finding in our study was that the morphine abstinent tree shrew displayed a behavior transition from psycho-activity to seeking behaviors, implying that context induced hedonia after short-term abstinence but appetite after long-term abstinence. It might remind the significance to take the abstinence time as an important factor to make more effective target for treatment on relapse.

AUTHOR CONTRIBUTIONS

YD and FS designed the experiments, preformed the experiments, analyzed data and wrote paper; TG participated in the writing of the article; NS designed the experiments and had primary responsibility for final content.

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SUPPLEMENTARY MATERIAL

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MINI REVIEW
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Cue Reactivity in Nicotine and Alcohol Addiction: A Cross-Cultural View

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A wealth of research indicates that cue reactivity is critical to understanding the neurobiology of nicotine and alcohol addiction and developing treatments. Functional magnetic resonance imaging (fMRI) and electroencephalograph (EEG) studies have shown abnormal cue reactivity in various conditions between nicotine or alcohol addicts and the healthy. Although the causes of these abnormalities are still unclear, cultural effect can not be ignored. We conduct an review of fMRI and EEG studies about the cue reactivity in nicotine and alcohol addiction and highlight the cultural perspective. We suggest that cultural cue reactivity is a field worth of exploring which may has an effect on addictive behavior through emotion and attention. The cultural role of nicotine and alcohol addiction would provide new insight into understanding the mechanisms of nicotine and alcohol addiction and developing culture-specific therapies. We consider that culture as a context may be a factor that causes confusing outcomes in exploring nicotine and alcohol addiction which makes it possible to control the cultural influences and further contribute to the more consistent results.

Keywords: nicotine, alcohol, addiction, cross-culture, cue reactivity, context, emotion, attention

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INTRODUCTION

Addiction as one of the leading causes of poor health worldwide, has drawn the attention of public including researchers decades ago. Nicotine and alcohol addiction as two of the most common addiction are widely observed because of legalization. Nicotine addiction has been proved to lead to health problems, such as lung cancer, ischemic heart disease and esophageal cancer while alcohol addiction can also cause problems of our health and safety (Castellsagué et al., 1999; Koob and Moal, 2005; Florek and Piekoszewski, 2008; Patel and Feucht, 2010). Additionally, nicotine and alcohol addiction are proved to have an effect on cognition, such as attention and memory (Wiers et al., 2015). Evidence has shown that there existing abnormal functional and structural changes in the brain of nicotine or alcohol addicts (Williams, 1980; Ray et al., 2009; Zhang et al., 2009, 2011a; Vollstädt-Klein et al., 2010a; Bjork and Gilman, 2013).

Although the huge negative influences have been shown, the craving for smoking or drinking in nicotine or alcohol addicts is so difficult to overcome which can lead to relapse over and over again. As a result, the cessation rates remain low and researchers have done a lot to improve a successful cessation with the substance related cue-induced craving which is intense and episodic and can contribute to relapse of addiction (Sinha and Li, 2007; Ferguson and Shiffman, 2009). Although recently, findings show that factor such as trait impulsivity has been considered to partly cause cessation failure (Erblich and Michalowski, 2015) and craving has been proved to be not a necessary condition of relapse (Wray et al., 2013), cue reactivity still plays a very important role in addiction.

Culture as a kind of context may cause differences in behavior (Li et al., 2015). Different cultures may have contributed to different traits in nicotine and alcohol addiction which may provided new sight for the cue reactivity in addiction. We reviewed some reports using EEG and fMRI which try to explain the relationship between culture and the cue-induced activity in nicotine and alcohol addiction.

CUE REACTIVITY IN NICOTINE AND ALCOHOL ADDICTION

Cue Reactivity in Smoking or Alcoholic Behavior

As literature has shown, smoking or alcohol-related cues can elicit craving (Erblich and Bovbjerg, 2004; Vollstädt-Klein et al., 2011a; Yarmush et al., 2016) and facilitate the addictive behavior in nicotine or alcohol addicts (Wigmore and Hinson, 1991; Shiffman et al., 2013).

As noted earlier, cue exposure was associated with changes in cognitive function (Bates et al., 2002; Durazzo and Meyerhoff, 2007; Vollstädt-Klein et al., 2009, 2012; Wiers et al., 2013). Studies suggested that addicts show attention bias for the substance-related cues which caused by the expectation of the substance (Field and Cox, 2008; Luijten et al., 2011; Vollstädt-Klein et al., 2011b; Ramirez et al., 2014) and addicts represent the substance-related pathological memory with which the substance-related cues might obtain the power to motivate (Hyman, 2005).

In all, exposed to smoking or alcohol-related cues, smokers or alcoholics change their behavioral patterns. It seems that nicotine and alcohol addicts are susceptible to the substance-related context which may plays an important part in the abnormal addictive process and is worthy of exploring.

Cue Reactivity in Neural Responses in Nicotine and Alcohol Addiction

Cue Reactivity with EEG

As non-invasive measure of human brain function, EEG technique has been widely used in nicotine and alcohol addiction to detect specific sensory and cognitive event to specific cues. What's more, the P3 of the event-related potentials (ERPs) related to the involvement of motivational and arousal systems (Petit et al., 2015) and the Slow Positive Waves (SPWs) of the ERPs which reflect the brain's activation of motivational systems to emotional cues (Cuthbert et al., 2000) were most suggested. It is indicated that both P3 and SPW amplitudes in response to smoking cues are significantly more enhanced in smokers than in the healthy at frontal and central sites indicating that smokers show more attention bias for smoking cues (Namkoong et al., 2004; Littel and Franken, 2007; Marianne et al., 2012).

The larger amplitude of P3 was also observed in non-smokers in response to smoking cues than neutral cues (Mcdonough and Warren, 2001) while non-alcoholics show no significant differences in P3 amplitudes even though the larger P3 was observed in alcoholics when faced with alcohol-related cues than neural cues (Namkoong et al., 2004). One explanation is that non-smokers may get hurt from the secondhand smoking so that they are also sensitive to smoking cues while the non-alcoholics are not always concerned about alcohol given that the alcohol cannot hurt them directly. It seems that addiction has lead to a bit different consequences in motivation and arousal which may be caused by the different context between nicotine and alcohol addiction.

Cue Reactivity with fMRI

Abundant fMRI evidences have suggested that cue-induced reactivity among nicotine or alcohol addicts is different from the healthy which shows functional and structural abnormalities in the brain of addicts as stated earlier. Furthermore, brain regions associated with anterior cingulate cortex (ACC) and other regions in attentional network including orbitofrontal prefrontal cortex, default mode networks involved precuneus, salience network including insula and the reward network refered to amygdala and striatum appear to be stimulated abnormally by smoking cues (Due et al., 2002; Brody et al., 2007; Franklin et al., 2011; Zhang et al., 2011b) and alcohol-related cues (Vollstädt-Klein et al., 2010b; Claus et al., 2013; Dager et al., 2014).

With these results, researchers have explored the important functions of these regions in nicotine and alcohol addiction (Vollstädt-Klein et al., 2010b; Zhang et al., 2011a; Hayashi et al., 2013; Lerman et al., 2014). However, whether the role these regions played in nicotine and alcohol addiction are same or not is an open question.

The addiction severity of nicotine has been reported negatively correlated with smoking cue-induced activity in amygdala (Vollstädt-Klein et al., 2011a) while evidence showed that the severity of alcohol was positively associated with amygdala response to alcohol-related cues among alcoholics (Claus et al., 2011). As researches on amygdala showed significant association with the processing of learned reward values of conditioned cues and context (Robbins et al., 2008), the different role of amygdala in nicotine and alcohol addiction indicated that the sensitivity to context between smokers and alcoholics is different. As a result, context plays an important role in the formation of nicotine and alcohol addiction.

In addition, alcohol-related cue-induced activity in the ventral striatum showed positive correlation with self-reported alcohol craving (Myrick et al., 2004; Seo et al., 2011). As the correlation between cigarette craving and ventral striatum response to smoking cues yielded mixed results, with both negative correlations (Mcclernon et al., 2005) and null correlations (David et al., 2005) which is different from the results in alcohol addiction, we can infer that the ventral striatum plays different roles in the craving for smoking or drinking. The ventral striatum has been reported to make great contribution to behavioral conditioning reflecting the reward value predicted by discriminative cues (Schultz et al., 1997). It seems that the reward value of smoking cues to smokers is different from that of alcohol-related cues to alcoholics which may be due to the different craving elicited by the different context around them.

CULTURAL EFFECT IN GENERAL

General Cultural Effect on Behaviors

Behavioral differences between Eastern and Western cultures has been explored widely. It's said that East Asians and Asian-Americans pay more attention to the background than European Americans who tend to focus on the foreground and focal objects with several tasks (Goto et al., 2013). In line with that, East Asians are likely to attribute the behavior to social context while Westerners tend to attribute the same thing to their internal dispositions (Choi et al., 1998). Nisbett analyzed these findings and concluded that East Asian' cognitive styles are characterized as more holistic and European American cognitive styles are characterized as more analytic (Nisbett et al., 2001; Nisbett and Miyamoto, 2005). Besides, as for the social behavior, East Asians were interdependent and collectivism whereas Westerns were independent and individualism (Suh et al., 1998). Culture is closely related to our behavioral patterns and different cultures can induce different behavioral patterns.

Cultural Effect on Neural Responses

Cultural Effect with EEG

Research on cognition beyond observable behavioral performance with EEG revealed some neural differences in different cultures. To our knowledge, most of the research results are related to the Eastern and Western cultures indicating the huge differences between the two distinctive cultures while the cultural differences among different Western cultures are seldom revealed. Research results suggested that there is cultural effect in motivational responses to felt misunderstanding (Lun et al., 2010). Besides, there are fundamental differences in the distribution of EEG between Easterners and Westerners as EEG asymmetry between Japanese and Westerners is different (Moss et al., 1985).

One study utilizing the good time solution of EEG suggested that Chinese and Italian attend the commercials with the same theme in different moment reflecting the different span of attention (Vecchiato et al., 2011). Although the early ERP components in the processing of emotional pictures is not modulated by the cultures in European and Japanese, the late stage of the processing is different (Fleming et al., 2010). Further, huge evidence about cognitive differences between East and West with respect to emotion such as semantic affective processing (Goto et al., 2013) and expression of emotion with the N400 (Liu et al., 2015), and emotion suppression by the parietal late positive potential (Murata et al., 2012) indicating that Easterners are more sensitive to the relationship between context and objects than Westerners. In addition to emotion, the most discussed was cultural differences in self-construal which may be different from the processing of the emotion by the differences in N400, P3 and the early component N170 in various conditions (Lewis et al., 2008; Vizioli et al., 2010; Masuda et al., 2014).

Cultural Effect with fMRI

Quantitative fMRI studies has been conducted to examine cultural differences. Results have revealed specific regions related to cultural effect between Eastern and Western cultures in the neural responses to various stimulus. However, given the variation of the culture-specific task, the cultural effect can be concluded in general that social cognitive tasks such as cultural self-referential and self-representation are related the responses in the medial prefrontal cortex and ACC (Zhu et al., 2007; Sul et al., 2012). Non-social cognitive tasks such as processing of faces and attentional control are associated with the activation of attentional network (Gutchess et al., 2006; Hedden et al., 2008; Goh et al., 2010). Social effective tasks such as emotional pain perception, recognition of emotions, empathy, and fearful faces may refer to the different activation patterns of insula, amygdala and ACC (Moriguchi et al., 2005; Chiao et al., 2008; Derntl et al., 2009, 2012; Cheon et al., 2011, 2013; Greck et al., 2012).

Studies focus on the emotion among different Western cultures also have disclosed some rules. Firstly, there are similar neural activity in amygdala which is associated with emotion when viewing image of same or other-race faces among African-American and Caucasian-American individuals (Lieberman et al., 2005). However, Western cultures also showed neural differences which may be related to emotion as the fact that the neural correlation of empathic resonance for pain in participants with different Western cultures is different (Azevedo et al., 2013). Besides, during a social evaluative task, it is concluded that White Americans generally exhibited more activation in regions associated with conflict resolution and cognitive control, while African Americans (AA) exhibited activation mostly in areas associated with emotion and memory (Greer et al., 2012).

Summary

In all, culture between Eastern and Western have shown differences with respect to attention, emotion and self-construal while studies on Western cultural differences focus on the emotion factors. It seems that the emotional and attentional factors play important roles in general cultural differences while the self-construal-related context may play an essential role in cultural difference between Eastern and Western cultures but not among different Western cultures.

CULTURAL EFFECT IN NICOTINE AND ALCOHOL ADDICTION

Cultural Effect on Addictive Behaviors in Nicotine and Alcohol Addiction

Given the large influences on behavior stated earlier, culture may have an effect on addictive behaviors. Some direct evidences have shown that culture is a factor influencing the use behavior of alcohol (Zane and Sasao, 2010; Krentzman et al., 2012) and cigarette (Benowitz, 1996; Florek and Piekoszewski, 2008; Coleman-Cowger and Catlin, 2013). For example, AA smokers smoke fewer cigarettes per day, metabolize nicotine much lower, prefer mentholated cigarettes and have a higher level of nicotine dependence than Caucasians (CC) smokers (Benowitz, 1996; Coleman-Cowger and Catlin, 2013). As a result, it is more difficult for AA smokers to make a successful quit than CC smokers, although they were reported to make more quit attempts (Fiore et al., 1989). In addition, different cultures have caused various views on smoking (Finkenauer et al., 2009) or drinking (Caetano et al., 1998) and different motivation for smoking (Sánchez-Johnsen et al., 2006) or drinking (Nagoshi et al., 1994; Piko, 2007).

Take the essential emotion factors in nicotine and alcohol addiction and the fact that perceptions of emotion are not culturally universal (Gendron et al., 2014) into consideration, culture may be a factor that influences the neural responses of different addiction. For example, smoking and drinking in some Eastern cultures like Chinese are just a form of social contact which involves complex emotion while in Western cultures things are different as people usually smoke or drink by themselves. Given the fact stated above, the emotion factors in different cultures of nicotine and alcohol addiction may not always be the same.

Additionally, there are actually disparities of cognition for addicts regrading to different cultures. To our knowledge, a research showed that Dutch adolescents had an avoidance bias toward both smoking and neutral pictures, while American adolescents didn't have a significant bias toward either smoking or neutral pictures (Larsen et al., 2014).

Above all, culture has an effect on addictive behavior in nicotine and alcohol addiction and both emotion and attention which are related to cue reactivity play important roles in the cultural effect. It seems that cultural effect on cue reactivity of smokers and alcoholics are associated with emotion and attention.

Cultural Effect on Neural Responses in Nicotine and Alcohol Addiction

Furthermore, studies focusing on different neural responses among cross-cultural smokers have shown that cultural difference is a possible factor in modifying the effect of nicotine. Okuyemi et al. (2006) has done a research to examine whether smokers from different cultural background process smoking-related cues in a different way using fMRI. The experiment were conducted among AA and CC smokers which is related to racial effect. However, as the ethnicity is not the cause but the result of cultural phenomenon (Claude, 1952), it also have proved a strong cultural effect on neural responses by showing that the brain activation to smoking cues (versus neutral cues) of AA smokers is stronger than CC smokers in several priori regions of interest.

In addition, the disparities of cultural neural responses can also be tracked by the comparison of some studies. A study suggested that chronic smokers from China showed decreased activation in the left thalamus (Liao et al., 2012), while another study suggested smokers from Australia showed decreased thalamus activation in the right side (Almeida et al., 2008). It seems that the activation of several regions are different among smokers or alcoholics with different cultures which should be further studied.

Summary

Overall, culture as a kind of context influences the behavior and the neural activity in addiction and there may be two main ways. Firstly, culture affects the emotion of individuals which may causes different arousing to the emotional factors of the cues and elicits the culture-specific neural responses in nicotine and alcohol addiction. Secondly, culture may has an effect on the attention of the nicotine and alcohol addicts. And with the two factors associated with cue reactivity in nicotine and alcohol addiction, culture may have an effect on the cue reactivity.

UNSOLVED PROBLEMS

Although, we have found that culture could influence the cue reactivity in nicotine and alcohol addiction which is related to emotion and attention, some questions are still unclear. Firstly, causes of the differences between nicotine and alcohol addiction are uncertain. Although, we have supposed that the different context may be the reason, we can not exclude the possibility that nicotine and alcohol have different effects on nervous system given that there is no research comparing the effects of these incompatible substances directly. Secondly, we found that the differences between Western and Eastern cultures are more significant than among Western cultures, which we speculated may be caused by more commonalities within Western cultures. But it still needs more targeted research. Thirdly, there are cultural effect on nicotine and alcohol addiction, but literature focusing on the cultural effects on neural responses in nicotine and alcohol addiction is rare, the neural basis is far from fully understood. In addition, we have known that addicts with different cultures have different responses to the substance-related cues, but the cues used in these researches are not the same which may relate to culture-specific factors. Whether the addicts have stronger responses to the culture-specific cues still need further research.

With the solution to these questions, we could have a better understanding of the cultural effect on nicotine and alcohol addiction and the neural mechanisms of them, which would be beneficial to improve the treatments by developing culture-specific treatments of addiction. Besides, understanding the cultural effect would make it possible to control the cultural factor to resolve the inconsistencies caused by culture. At last, objective differences in neural responses caused by cultural effect may improve our rational knowledge of cultural differences in general which may further contribute to the elimination of misunderstandings among different cultures.

AUTHOR CONTRIBUTIONS

XZ supervised this study and revised each draft. WL and QW wrote this paper. XL, YC, HS, and LY provided suggestions on this paper.

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Altered Gray Matter Volume and White Matter Integrity in College Students with Mobile Phone Dependence

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Mobile phone dependence (MPD) is a behavioral addiction that has become an increasing public mental health issue. While previous research has explored some of the factors that may predict MPD, the underlying neural mechanisms of MPD have not been investigated yet. The current study aimed to explore the microstructural variations associated with MPD as measured with functional Magnetic Resonance Imaging (fMRI). Gray matter volume (GMV) and white matter (WM) integrity [four indices: fractional anisotropy (FA); mean diffusivity (MD); axial diffusivity (AD); and radial diffusivity (RD)] were calculated via voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) analysis, respectively. Sixty-eight college students (42 female) were enrolled and separated into two groups [MPD group, $N = 34$; control group (CG), $N = 34$] based on Mobile Phone Addiction Index (MPAI) scale score. Trait impulsivity was also measured using the Barratt Impulsiveness Scale (BIS-11). In light of underlying trait impulsivity, results revealed decreased GMV in the MPD group relative to controls in regions such as the right superior frontal gyrus (sFG), right inferior frontal gyrus (iFG), and bilateral thalamus (Thal). In the MPD group, GMV in the above mentioned regions was negatively correlated with scores on the MPAI. Results also showed significantly less FA and AD measures of WM integrity in the MPD group relative to controls in bilateral hippocampal cingulum bundle fibers (CgH). Additionally, in the MPD group, FA of the CgH was also negatively correlated with scores on the MPAI. These findings provide the first morphological evidence of altered brain structure with mobile phone overuse, and may help to better understand the neural mechanisms of MPD in relation to other behavioral and substance addiction disorders.

Keywords: mobile phone dependence, Mobile Phone Addiction Index scale, fMRI, gray matter volume, fractional anisotropy, axial diffusivity, impulsivity

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INTRODUCTION

As reported by eMarketer.com, the number of universal smartphone subscribers will reach 2,380 million in 2017, 672.1 million of which will be Chinese subscribers. Smartphones have many attractive characteristics that help foment its prevalent use in modern life, particularly for young adults. It is an inexhaustible source of fun and relaxation, a highly effective instrument for establishing and maintaining interpersonal relationships, and it is a convenient method for avoiding unpleasant mood states and 'killing' time (Choliz, 2010).

Increasingly, individuals perceive their world via this sophisticated, multifunctional, new 'organ.' However, more and more young adults are using smartphones in an out of control fashion. In recent years, physiological, social, behavioral, and even affective problems have been associated with extensive, uncontrolled, and excessive use of mobile devices, drawing a lot of attention to the potential negative effects of mobile phone overuse (Roberts et al., 2015).

Mobile phone overuse, as a disorder, can be considered a behavioral addiction (Billieux, 2012). The traditional general framework for addiction is based on a medical model that refers to bodily and psychological dependence from the consumption of substances such as tobacco, alcohol, or other drugs (McMillan et al., 2001). However, researchers have argued that addiction should be expanded to include pathological behavioral patterns that are analogous to substance dependence, and they have collectively referred to these as 'behavioral addictions' (Lemon, 2002). Behavioral addiction thus refers to behaviors, besides psychoactive substance ingestion, that produce short-term feelings of reward and engender further persistent behavior despite knowledge of adverse consequences. These behaviors include pathological gambling, skin picking, kleptomania, compulsive buying, and compulsive sexual behavior, to name a few (Grant et al., 2010). Behavioral addiction resembles substance addiction in many domains, including natural history, phenomenology (Roberts et al., 2015), tolerance (Leung, 2008), overlapping genetic contributions (Billieux, 2012), neurobiological mechanisms (Billieux et al., 2015a), comorbidity, response to treatment (Billieux et al., 2015b), and the common core feature of diminished control (Walther et al., 2012). With the advent and growing ubiquitous use of technology such as television, computer gaming, and the Internet, a new subclass of behavioral addiction that is non-chemical in nature, technological addiction, has been characterized as the problematic excessive use of technology involving human–machine interaction (Griffiths, 1996).

Mobile phone dependence (MPD), a subset of behavioral or technological addiction, shares lots of common features with other addiction disorders (Bianchi and Phillips, 2005; Billieux, 2012). These common characteristics are summarized by 'Brown's behavioral addictions criteria' (Brown, 1993), and include: cognitive salience, conflict with other persons or activities, euphoria or relief, tolerance or loss of control over the behavior, withdrawal, relapse, and reinstatement (Martinotti et al., 2011). Overall, MPD has been depicted as the excessive and uncontrolled use of a mobile phone to the extent that it affects an individual's real-life. For example, reminiscent of dependence and withdrawal, someone with MPD may feel uncomfortable and irritated in the absence of their phone, including feeling a physical and psychological void among other classical symptoms of withdrawal (Ling and Pedersen, 2006).

For many MPD individuals, a mobile phone can be so fascinating that it can dominate their life and interests (Chóliz, 2012). In fact, research has indicated that MPD is related to psychological distress, emotional instability, materialism (Beranuy et al., 2009), approval motivation (Takao et al., 2009), leisure boredom, sensation seeking (Leung, 2008), impulsiveness (Billieux et al., 2007, 2008), and risky behavior such as unprotected sex, illicit drug use, alcohol consumption, suspensions from school, and criminal activity (Yang et al., 2010). Furthermore, negative associations have been found between MPD and healthy introversion and conscientiousness (Roberts et al., 2015), working memory (Billieux et al., 2008), executive function (Billieux, 2012), self-control and self-monitoring (Takao et al., 2009), and even self-esteem (Yang et al., 2010). MPD may also cause lowered cognitive control, elevated reward seeking behaviors, increased tolerance to phone exposure, and impaired psychological health as well as lead to reduced work performance and even academic failure (Billieux et al., 2015a), similarly to other addiction disorders.

Importantly, trait impulsivity has been shown to play a key role in many kinds of dependence disorders including drug addiction (Moreno-López et al., 2012), gambling problems (Joutsa et al., 2011; Bickel et al., 2012), online game addiction (Han et al., 2012b), and even internet addiction (Cao et al., 2007; Lin et al., 2012). Thus, in the present study, we considered measuring possible underlying impulsivity in MPD as well.

Though some potential factors that may be related to MPD have been identified in previous studies, no body of research has yet been performed that investigates the underlying neural mechanisms or possible brain morphological alterations that are present in MPD individuals. There is tremendous promise for using Magnetic Resonance Imaging (MRI) to elucidate MPD's neural mechanisms (Yuan et al., 2011), and results may help the development of behavioral interventions or pharmacological treatments for this and other types of addiction in the near future (Hanlon and Canterberry, 2012). Thus, in the present study, we aimed to explore measures of brain morphology with MRI in individuals with MPD, particularly in young adult college students due to the increasing role that mobile phones play in this population.

Hypothesized common underlying neural patterns between MPD and other addiction disorders lend to the idea that by better understanding the mechanisms behind MPD, other types of addiction may be elucidated too (Billieux et al., 2015a). In a study of internet addiction in young adults, Zhou et al. (2011) found that compared with a healthy control group, internet-addicted young adults had lower gray matter density in the left anterior cingulate cortex, left posterior cingulate cortex, left insula, and left lingual gyrus. In a similar study looking at online game addiction in young adults, Weng et al. (2013) found gray matter atrophy in the right orbitofrontal cortex (OFC), bilateral insula, and right supplementary motor area, as well as reduced fractional anisotropy (FA) in the right genu of the corpus callosum, bilateral frontal lobe white matter (WM), and right external capsule in online game addicted-individuals. In research concerned with pathological gambling, there was higher gray matter volume (GMV) in the ventral striatum and right prefrontal cortex (Koehler et al., 2013), widespread lower FA, and higher mean diffusivity (MD) in the corpus callosum, the cingulum, the superior longitudinal fascicle, the inferior fronto-occipital fascicle, the anterior limb of the internal capsule, the anterior thalamic radiation, the inferior longitudinal fascicle, and the uncinate/inferior fronto-occipital fascicle in the group of pathological gambling patients (Joutsa et al., 2011). These reported regions are related to inhibitory control, reward processing, and impulsivity (Romero et al., 2010; Li et al., 2015). MPD may in theory also involve damage to some of these regions too (Hanlon and Canterberry, 2012), and exploring the similarities and differences among various addictions could deepen our understanding of the neural mechanisms of MPD behaviors and may help the development of specific interventions for it.

Many automated and objective MRI methods have been used to characterize healthy brain structural patterns, including T1-weighted structural imaging and diffusion tensor imaging (DTI). In the former, GMV can be inspected and further calculated by voxel-based morphometry (VBM) analysis. Based on the review above, we hypothesized decreased GMV in frontal lobe areas and thalamus in the MPD group relative to controls. We also supposed that the MPD group would be associated with impairment of WM fibers linked to emotional processing, executive attention, decision-making, and cognitive control. Four fiber integrity surrogates including FA, MD, axial diffusivity (AD), and radial diffusivity (RD), calculated via tract-based spatial statistics (TBSS) analysis (Yeh et al., 2009), are sensitive to the diffusion of water molecules in the brain (Basser et al., 1994), and are accurate qualified biomarkers for assessing the effectiveness of WM (Hasan et al., 2011).

In the present study, both GMV and WM integrity were explored using these measures in order to reveal potential discrepancies that may be present in young adults with MPD, with the potential to better understand its possible neural mechanisms.

MATERIALS AND METHODS

Ethics Statement

This research was approved by the Ethics Committee of Southwest University, and written informed consent was obtained from every participant. All participants were over 18 years of age, and were notified that their participation was completely voluntary and that they had the ability to secede at anytime.

Participants

Three hundred college students were recruited from Southwest University (SWU, Chongqing, China) by pamphlet and Internet advertisement. They were required to complete the Mobile Phone Addiction Index (MPAI) scale in which a score above 51 classified them as mobile phone dependent (MPD). This stratification led to an MPD group of 34 individuals (21 female, range: 18–27 years old). In order to match the MPD group, 34 non-MPD students (21 female, range: 18–27 years old) were randomly selected as the control group (CG). There were no significant differences in personal monthly expenses, age, gender, or years of education between groups (see **Table 1**).

Furthermore, all participants had no neurological disorders, history of psychiatric disorders, or metal parts, tattoos, or irremovable piercings on their body. They all had normal or corrected to normal vision, were right-handed, and were native Chinese speakers.

Questionnaire Evaluation

The MPAI scale (Leung, 2008), which consists of 17 items, was used to estimate the degree of MPD. A five-point Likert scale was used: 1 = 'not at all,' 2 = 'rarely,' 3 = 'occasionally,' 4 = 'often,' 5 = 'always.' The total score ranges from 17 to 85 in which according to a median split, 51 or more is considered indicative of phone dependence (Martinotti et al., 2011). The reliability of the scale as indicated by Cronbach's alpha is remarkably high at 0.90 (Leung, 2008).

The Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995) was administered to both groups to measure trait impulsivity. The BIS is made up of 30 items using a five-point Likert scale, where the higher the score, the stronger the impulsivity. The internal consistency reliability and retest reliability are 0.89, and 0.91, respectively (Li et al., 2011).

Scanning Acquisition

All imaging data were acquired using a 3T Siemens scanner (Siemens Medical, Erlangen, Germany) at the Brain Imaging

TABLE 1 | Economic status, demographics, MPAI and BIS scores of participants.

	MPD ($n = 34$)	CG ($n = 34$)	t	p
Monthly expenses (yuan)	954 (251)	928 (257)	0.43	0.67
Family income (yuan/months)	6265 (3028)	6559 (3228)	−0.39	0.70
Age (years)	21.60 (2.10)	21.73 (1.94)	−0.28	0.78
Years of education (years)	15.15 (1.37)	15.21 (1.37)	−0.18	0.86
Age of owning first phone	16.79 (2.41)	16.85 (2.22)	−0.10	0.92
Minutes of daily call-making	45.15 (30.34)	32.94 (16.93)	2.05	<0.05
Minutes of daily phone use	256.05 (100.95)	208.24 (90.40)	2.06	<0.05
MPAI scores	57.21 (5.98)	39.41 (6.45)	11.80	<0.01
BIS scores	47.50 (17.04)	37.60 (12.04)	2.77	<0.01

MPD, mobile phone dependency; CG, control group; MPAI, Mobile Phone Addiction Index; BIS, Barratt Impulsiveness Scale; Values presented are means (standard deviation).

Research Center of Southwest University. High-resolution T1-weighted anatomical images were obtained with a magnetization prepared rapid gradient echo (MPRAGE) sequence [repetition time (TR) = 1900 ms, echo time (TE) = 2.52 ms, field of view (FOV) = 256 mm, flip angle = 90°, in-plane matrix resolution = 256 × 256, slice thickness = 1 mm, slices = 176, voxel size = 1 mm × 1 mm × 1 mm]. 12-direction diffusion tensor images (DTI) were collected with a twice refocused spin echo pulse sequence, TR = 6000 ms, TE = 89 ms, FOV = 240 mm, matrix resolution = 128 × 128, slice thickness = 3 mm, slices = 45, b-value = 1000s/mm^2.

Structural Imaging Data Analysis

Each subject's structural imaging data was analyzed by Statistical Parametric Mapping software (SPM8[1]) in MATLAB R2014a (MathWorks Inc., Natick, MA, USA), and were first displayed to check for artifacts and gross anatomical abnormalities. Scans were manually co-registered and realigned to anterior commissure-posterior commissure line, then segmented into gray matter (GM), WM and cerebrospinal fluid (CSF) (Yin et al., 2013). Finally, the results were registered, normalized, and modulated using the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) toolbox, which uses a more sophisticated registration algorithm to achieve more accurate inter-subject registration. Its performance on non-linear registration algorithms is better than that of other similar toolboxes.

After these preprocessing steps, the study-specific brain template was created from all subject images (i.e., mean image), and the image intensity of each voxel was modulated by the Jacobian determinants to facilitate the determination of regional differences in the absolute amount of GM. The registered images were then transformed to Montreal Neurological Institute (MNI) space, and finally, the normalized and modulated images were smoothed with a 10 mm full-width at half-maximum (FWHM) Gaussian kernel to increase signal-to-noise ratio.

The difference in GMV between the MPD and CG group was assessed by two-sample t-test using SPM8 in which total GM volume as well as BIS scores were added for covariance, as trait impulsivity may be a confounding factor. Absolute voxel signal intensity threshold masking was set to 0.2 to minimize GM boundary effects (Duan et al., 2012). Significance levels were set at $p < 0.01$ with Alpha-Sim correction, calculated using DPABI software[2] (Chao-Gan and Yu-Feng, 2010). The resultant images were visualized with BrainNet Viewer (Xia et al., 2013).

In order to affirm differences associated with MPD relative to controls, the notably different GMV clusters between the two groups were selected as regions of interest (ROI), and the GMV values of these ROIs within the MPD group were then extracted by REST[3], and entered into a Pearson correlation analysis with MPAI scores with significance set at $p < 0.05$ (Song et al., 2011).

Diffusion Tensor Imaging Data Analysis

The diffusion-weighted imaging data were processed in the following way using the pipeline tool, PANDA[4]: estimation of the brain mask using the b0 image without diffusion weighting, cropping of the non-brain space in the raw images at 0.25 [fractional intensity threshold (0→1), where smaller values give larger brain outline estimates], correction of the eddy-current induced distortion and head motion during scanning by registering the diffusion weighted images (DWI) to the b0 image with an affine transformation, non-linear registration of all individual FA images in native space to the FA template in the Montreal Neurological Institute (MNI) standard space, warping of transformations used to resample the images of the diffusion metrics with 1 mm × 1 mm × 1 mm spatial resolution, execution of the TBSS procedure where all subjects' skeletons were created and every subregion's average FA, MD, λ_1 and λ_{23} value of the subjects' skeletonized WM were calculated according to the Johns Hopkins stereotaxic WM atlas – which comprises 50 core regions (Mori et al., 2008) – for further atlas-based count through multi-factor analysis of variance between the two groups while regressing out BIS scores. Finally, a Pearson correlation analysis was performed within the MPD group between the values from significantly different regions and MPAI scores with significance set at $p < 0.05$ (Cui et al., 2013). This method's statistical power was tested reliably (Oishi et al., 2009; Faria et al., 2010). The outcome was presented with FSLView using the FSL toolbox (FSL 5.0.0[5]), (Smith et al., 2006).

RESULTS

Questionnaire Performance

The MPD group had significantly higher scores on the MPAI than the CG. They also spent significantly more time on their mobile phone (see **Table 1**). As expected, BIS scores were significantly higher in the MPD group as well, showing that MPD individuals had higher trait impulsivity relative to controls.

Gray Matter Volume Difference between Groups

Compared with the CG, the MPD group had remarkably decreased GMV in the right superior frontal gyrus (sFG), right inferior frontal gyrus (iFG), bilateral medial frontal gyrus (mFG), right middle occipital gyrus (mOG), left anterior cingulate cortex (ACC), and bilateral thalamus (Thal) (see **Table 2**). Furthermore, within the MPD group, GMV of the right sFG, right iFG and Thal was negatively correlated with MPAI scores (see **Figure 1**).

DTI Discrepancy between Groups

For the atlas TBSS analysis, the FA and AD values for hippocampal cingulum bundle fibers (CgH) were significantly

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

[2] http://www.rfmri.org/dpabi

[3] http://www.restfmri.net

[4] http://www.nitrc.org/projects/panda/

[5] http://www.fmrib.ox.ac.uk/fsl/tbss

TABLE 2 | Notable gray matter volume (GMV) differences between mobile phone dependent (MPD) group and control group (MPD group < control group).

Region	Peak MNI Coordinates			Voxels	*t*
	X	*Y*	*Z*		
sFG_R	16.5	42.0	54.0	163	3.31
iFG_R	60.0	25.5	9.0	153	3.11
mFG_L	−10.5	37.5	28.5	288	2.94
mFG_R	13.5	43.5	−9.0	89	2.83
mOG_R	31.5	−88.5	18.0	407	3.42
ACC_L	−13.5	46.5	10.5	115	2.95
Thal (L and R)	−1.5	−12.0	9.0	291	2.85

sFG, superior frontal gyrus; iFG, inferior frontal gyrus; mFG, medial frontal gyrus; mOG, middle occipital gyrus; ACC, anterior cingulate cortex; Thal, thalamus; L, left; R, right; MNI, Montreal Neurological Institute.

decreased in MPD individuals, relative to controls (see **Table 3**). Furthermore, within the MPD group, FA of the CgH was negatively correlated with MPAI scores (see **Figure 2**).

DISCUSSION

As far as we know, the present study was the first attempt to explore altered neural morphology in college students with MPD. We compared GMV and four indices of WM integrity (FA, MD, AD, and RD) between MPD individuals and healthy controls. The results revealed that MPD individuals had decreased GMV, relative to controls, in the right sFG, right iFG, bilateral mFG, right mOG, left ACC, and bilateral thalamus (Thal). As far as WM integrity, the MPD group showed decreased FA and AD of bilateral hippocampal cingulum bundle fibers (CgH). Furthermore, GMV values of the right sFG, right iFG, and bilateral thalamus (Thal) were negatively correlated with MPAI scores in the MPD group, as were FA values of the CgH. Additionally, we confirmed that the MPD group had higher trait impulsivity as measured with the Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995).

These findings indicate possible underlying neurobiological mechanisms behind MPD, and simultaneously help in better understanding the underlying role of impulsivity in this kind of behavioral addiction disorder. The results also provide insight into the similarities and differences between MPD and other kinds of addiction disorders.

Decreased Gray Matter Volume in MPD

In the present study, we found decreased GMV in the MPD group, a finding that is consistent with our hypothesis based on findings from other drug and behavioral addiction studies where impulsivity is also hypothesized to play an influential role.

Functional neuroimaging studies of drug addiction reveal that drugs of abuse not only influence dopamine-rich subcortical structures such as the ventral tegmental area (VTA), nucleus accumbens (NAcc), caudate nucleus, putamen, thalamus and amygdala, but also disrupt cortical projection areas such as the prefrontal cortex (PFC), OFC, ACC and insula (Hanlon and Canterberry, 2012). Similarly to drug addiction, individuals with behavioral addiction are often characterized as having abnormal function in brain regions that include the prefrontal cortex, ACC (Grant et al., 2010), ventral striatal (Han et al., 2012a) and VTAs, NAcc (Grant et al., 2010), insula (Kuss and Griffiths, 2012) and thalamus (van Holst et al., 2010). Besides altered function in these areas, it is worth noting that altered brain morphology in these areas has also been reported in Internet addicts as well as gambling addicts. For example, studies have shown decreased GMV in these conditions in left ACC, left posterior cingulate cortex, left insula, left lingual gyrus (Zhou et al., 2011), right OFC, bilateral insula, and right supplementary motor area (Weng et al., 2013). These areas largely overlap with circuits related to inhibitory control (Ersche et al., 2011), reward processing, decision-making, and other cognitive functions (Romero et al., 2010).

In our study, decreased volume in three ROIs in the MPD group relative to controls was also correlated with the MPAI. That is, the sFG, right iFG, and thalamus. The sFG has been shown to be involved in many advanced cognitive functions such as inhibitory control, conscious decision-making, reasoning, working memory (Chase et al., 2011), aspects of voluntary top–down attentional control (Hopfinger et al., 2000), and modeling and prediction of the behavior of others (i.e., theory of mind) (Cui et al., 2012).

The right iFG is thought to serve as the control center for fronto-basal ganglia circuits involved with attention distribution, emotional processing, inhibitory control, and behavior monitoring and modulation (Moreno-López et al., 2012). Its injury is associated with behavioral disinhibition, and has been shown to play a key role in the maintenance and exacerbation of behavioral addiction (Grant et al., 2010; Kuss and Griffiths, 2012).

The thalamus, which extensively connects cortical and subcortical structures with one another, could arguably be one of the most crucial hubs of the brain, and has been shown to be related to reward expectation, attention, emotion, memory (Minagar et al., 2013), and executive function (Tuchscherer et al., 2010). Furthermore, thalamic atrophy has been previously found to be associated with cognitive impairment (Hanlon and Canterberry, 2012).

Contrary to our results, a study of patients with online game addiction showed that thalamic volume was actually increased in the addiction group, hypothesized to be the result of higher dopamine availability from the tremendous visual and auditory stimulation that is present in online game playing – altering the balance of mesolimbic circuits (Han et al., 2012b). This contradiction may also represent the difference in acquired habitual behaviors between dependent phone users and computer game-addicted players.

Abnormal White Matter Integrity in MPD

Besides decreased GMV, we found decreased FA and AD of hippocampal cingulum bundle fibers (CgH) in the MPD group.

TABLE 3 | Significant diffusion tensor imaging (DTI) index differences between MPD group and control group (MPD group < control group).

Index	Region	Central MNI Coordinates			*f*	*p*	η^2
		X	*Y*	*Z*			
FA	CgH_L	−22	−27	−18	5.98	<0.05	0.08
	CgH_R	24	−25	−19	7.76	<0.01	0.11
AD	CgH_L	−22	−27	−18	6.19	<0.05	0.09
	CgH_R	24	−25	−19	8.01	<0.01	0.11

CgH, cingulum bundle fibers in the hippocampus; FA, fractional anisotropy; AD, axial diffusivity; L, left; R, right; MNI, Montreal Neurological Institute.

The cingulum WM tract carries information from the cingulate gyrus to the hippocampus, and can be separated into two subregions at the axial level of the splenium of the corpus callosum: the cingulum in the cingulate gyrus above the splenium, and the cingulum in the hippocampal regions (CgH) below the splenium (Mori et al., 2008). The function of the CgH involves receiving different combinations of sensory, cognitive, and emotion regulation information. It provides major poly-sensory input to the hippocampus (Zhu et al., 2011), and contributes to reward pathways, and formation, maintenance and retrieval of working memory (Yuan et al., 2011) – information that is critical for cognitive control (Luck et al., 2010; Benedict et al., 2013). Furthermore, abnormal FA in the MPD group is consistent with findings in alcohol addiction (Yeh et al.,

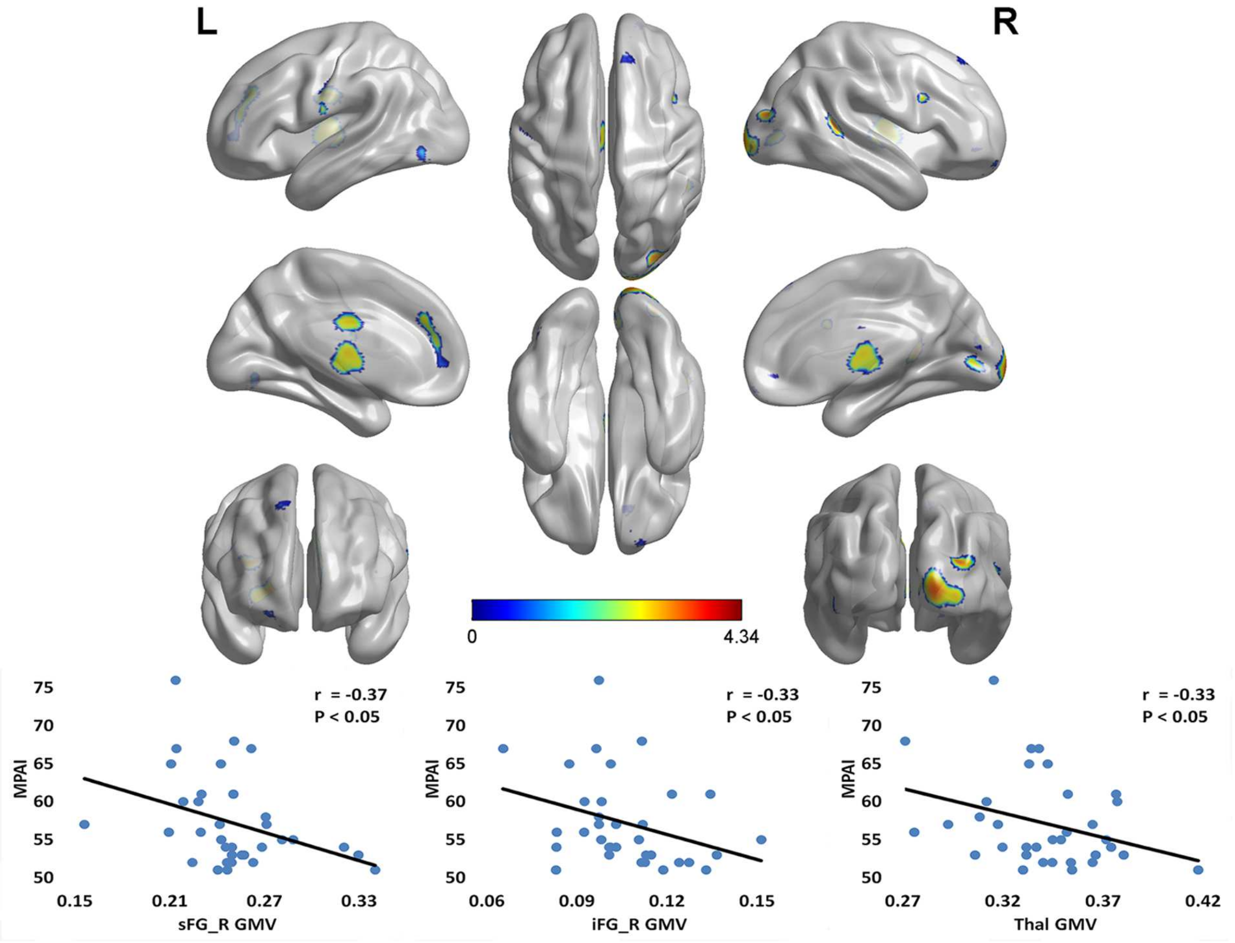

FIGURE 1 | Notable GMV differences between MPD group and control group (CG > MPD), and the negative correlation between GMV and MPAI scores within MPD group. Compared with the control group, the MPD group had remarkably decreased GMV in the right sFG, right iFG, bilateral mFG, right mOG, left ACC, and bilateral Thal. Furthermore, within the MPD group, the GMV of the right sFG, right iFG and Thal was negatively correlated with MPAI scores. sFG, superior frontal gyrus; iFG, inferior frontal gyrus; mFG, medial frontal gyrus; mOG, middle occipital gyrus; ACC, anterior cingulate cortex; Thal, thalamus; MPD, mobile phone dependency; CG, control group; MPAI, Mobile Phone Addiction Index; GMV, gray matter volume. L, left; R, right.

2009). Overall, decreased information transmission between the cingulate gyrus and hippocampus, as is suggested by the decreased CgH FA value in the MPD group, may be an underlying structural basis for functional deficits that leads to a solidification of addiction-related memories.

However, as far as we know, decreased FA in the CgH has not yet been reported in any behavioral addiction study. Our data indicates that the reduction of FA in the right CgH of the MPD group was mainly driven by a decrease in AD value, without divergence observed in the RD index. AD measures the magnitude of diffusivity along the principal direction of diffusion, which may index the organization of fiber structure and axonal integrity (Qiu et al., 2008). Thus, the main underlying mechanism of the WM injury in this area present in MPD may be due to subtle axonal injury rather than demyelination (Romero et al., 2010).

Impulsivity and Mobile Phone Dependence

Impulsivity can be defined as taking actions that are expressed prematurely, that are unduly risky, poorly conceived, and that could result in undesirable consequences (Bickel et al., 2012). It is closely related to a majority of addiction disorders (Romero et al., 2010), such as drug addiction (Moreno-López et al., 2012), pathological gambling (Joutsa et al., 2011), online game addiction (Han et al., 2012b), internet addiction (Lin et al., 2012) and MPD (Billieux, 2012). Interestingly, Walther et al. (2012) investigated the relationship between 12 different personality characteristics and five addictive behaviors including alcohol, tobacco, and cannabis substance use, problematic gambling, and problematic computer gaming, and found that high impulsivity was the only personality characteristic that was associated with all of the addictive behaviors that were investigated.

As expected, we found higher impulsivity in MPD individuals, consistent with previous research. Impulsivity may in fact be the strongest predictor of MPD (Billieux et al., 2008). It can predispose someone to spend extended periods of time on their phone, eventually leading to MPD, and in turn, can further deteriorate self-adaptation and self-control abilities (Billieux et al., 2007). Furthermore, high levels of trait impulsivity are associated with lower midbrain dopamine auto-receptor binding (Buckholtz et al., 2010). As for substance addicted individuals, continued use of stimulants, for example, is thought to further exacerbate impulsive traits (Moreno-López et al., 2012). Thus, because of the close link between impulsivity and addiction disorders, in order to improve treatment interventions that help promote more conscientious and less compulsive decision-making processes, and improve self-control abilities, therapists may focus on reducing traits related to impulsivity (Leung, 2008).

Nevertheless, due to the close relationship between impulsivity and MPD, the difference in BIS scores between the MPD and CG may have been a potential confounding variable in the comparative analysis of mobile phone use. Thus, in our study, BIS score was eliminated as a nuisance regressor in the GMV and FA group contrasts, and values from the resultant regions were then entered into correlation analyses with MPAI scores within the MPD group.

Limitations and Future Directions

Despite the novel results of the study, there are several limitations to be acknowledged. Firstly, due to the cross-sectional design of the study, and that potential psychological mechanisms

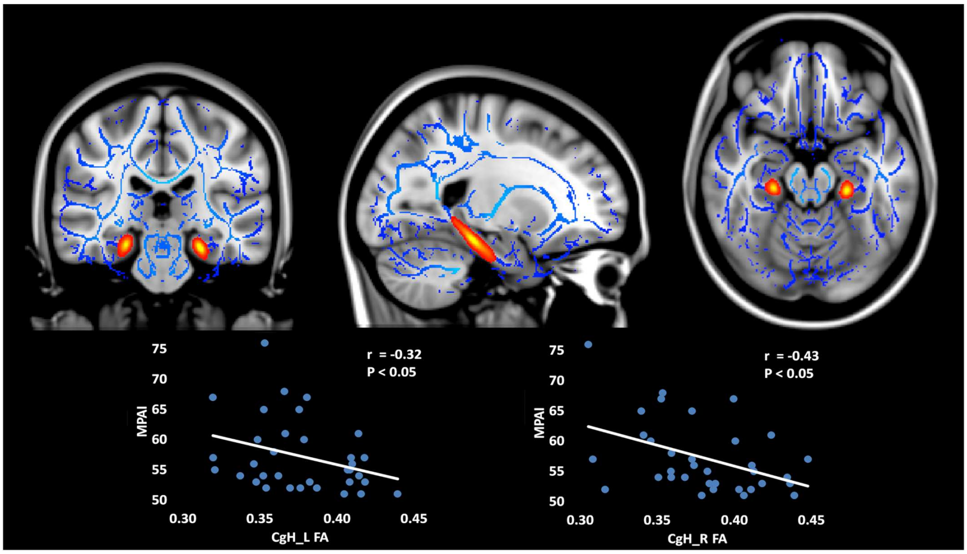

FIGURE 2 | Decreased FA and AD in bilateral CgH (subregions divided by Johns Hopkins stereotaxic atlases) in MPD group compared with control group (MPD < CG) and the negative correlation between FA and MPAI scores within MPD group. The FA and AD values of the CgH were significantly decreased in MPD individuals, relative to controls. Furthermore, within the MPD group, the FA of the CgH was negatively correlated with MPAI scores. CgH, cingulum bundle fibers in the hippocampus. FA, fractional anisotropy; AD, axial diffusivity; MPD, mobile phone dependency; CG, control group; MPAI, Mobile Phone Addiction Index.

are manifold, we cannot infer causality or direction of effect between mobile phone overuse and maladaptive structural alterations found in the MPD group. Thus, longitudinal studies would be very helpful in confirming possible psychological and physiological mechanisms of MPD, as well as provide the ability to measure the length and progression of MPD in participants. Secondly, though we found brain structural differences between the MPD and CG, we cannot know for sure what specific kinds of cognitive function deficits are related to these differences. Future studies should try to connect GMV (or WM integrity) differences in MPD to some psychological function (e.g., cognitive executive function) in order to better inform possible preventive measures and interventions for mobile phone overuse and dependence. Last but not least, despite regressing out BIS scores when performing group difference tests of GMV and FA, the underlying trait impulsivity found in the sample is inevitably an inextricable variable that cannot be completely isolated in the present study. Future studies that perhaps include a comparison between MPD individuals with high impulsivity vs. high-impulsivity non-MPD individuals may be helpful in dissociating MPD from trait impulsivity.

AUTHOR CONTRIBUTIONS

YW is responsible for the original experimental design, task procedure, data analysis and article writing. ZZ is responsible for the experimental process, data collection, and article writing. HS is responsible for experiment implementation and data analysis. XX is responsible for behavioral questionnaire data and experimental procedure plan. HW is responsible for chart and graph arrangement, including **Figures 1** and **2**, arrangement of data, and proofreading of the manuscript. FdU is responsible for manuscript writing, description of the functions of brain regions, copy editing, and content editing, as well as approval of the final version to be published. XH is responsible for experimental design and guidance throughout.

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Problematic Internet Users Show Impaired Inhibitory Control and Risk Taking with Losses: Evidence from Stop Signal and Mixed Gambles Tasks

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According to the balance model of self-regulation, dysfunction of the inhibitory control and reward processing might be a behavioral marker for addiction and problematic behaviors. Although several studies have separately examined the inhibitory control or reward processing of individuals exhibiting problematic Internet use (PIU), no study has explored these two functions simultaneously to examine the potential imbalance of these functions. This study aimed to investigate whether the self-regulatory failure of PIU individuals results from deficits in both inhibitory control [indexed with the stop signal reaction time (SSRT) in a stop signal task] and risk taking with losses (measured as the acceptance rates of risky gables or the ratio of win/loss in a mixed gambles task). The results revealed that PIU individuals, compared with controls, showed decreased SSRT and increased error rates as well as reduced risk taking with losses. Correlational analyses revealed a significant positive relationship between the SSRT and risk taking with losses. These findings suggest that both the inhibitory control and reward functions are impaired in PIU individuals and reveal an association between these two systems. These results strengthen the balance model of self-regulation theory's argument that deficits in inhibitory control and risk taking with losses may assist in identifying risk markers for early diagnosis, progression, and prediction of PIU.

Keywords: problematic Internet use, inhibition response, risk taking with losses, cognitive control, reward processing

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INTRODUCTION

The Internet plays a vital communication and social interaction role in modern life (Tonioni et al., 2012). However, some individuals are unable to control their Internet use, which can eventually cause serious mental health problems and a variety of negative psychosocial consequences (Ko et al., 2013b). This behavioral phenomenon is commonly referred to as problematic Internet use (PIU; Tsitsika et al., 2011). Although the description of PIU is based on the definition of substance dependence or pathological gambling, which are both examples of self-regulatory failure (Zhou et al., 2010), few studies have examined the self-regulatory failure of PIU.

Compared to the large number of individuals with online experience, why do only a few individuals become addicted? One possible explanation is that individuals who become addicted display deficits in self-regulation. According to the balance model of self-regulation, dysfunction of inhibitory control and reward processing might be a behavioral marker for addiction and problematic behaviors (Heatherton and Wagner, 2011). The balance model of self-regulation suggests that self-regulatory failure occurs as a result of a failure to appropriately engage top-down control mechanisms and bottom-up reward information. For instance, when self-regulatory resources are depleted (Gailliot et al., 2007; Muraven, 2010) or when impulse inhibition is impaired (Dong et al., 2010, 2012), people become prone to self-regulation failure in a top-down manner. Alternatively, when an individual is confronted with a strong impulse (e.g., an enticing dessert for someone on a diet), the likelihood of self-regulation failure in a bottom-up manner is increased. Thus, examining inhibitory control and reward processing in people with PIU might be an effective and useful way to understand their difficulty with self-regulation.

Several lines of research have identified an association between self-regulatory failure and impairments in inhibitory processes. For instance, several studies have found that self-reported impairments in control are reliably associated with greater past and future substance use (Gullo et al., 2014; Leeman et al., 2014a,b). Additionally, numerous studies using "go/no-go" or "stop signal" tasks provide converging evidence that individuals who are dependent on alcohol (Lawrence et al., 2009; Papachristou et al., 2013), cigarettes (Billieux et al., 2010), cocaine (Colzato et al., 2007), and food (Svaldi et al., 2014) display more difficulty inhibiting their responses than do controls, and deficits in behavioral response inhibition were found to be related to the severity of reported symptoms. Researchers have also observed inhibitory deficits in other addiction-like behavioral disorders that do not involve substance ingestion, namely, pathological gambling and PIU. For example, pathological gamblers exhibit performance deficits in go/no-go (Goudriaan et al., 2005; van Holst et al., 2012) and stop signal tasks (Goudriaan et al., 2006; Odlaug et al., 2011). Furthermore, a clinical study found that memantine treatment, which can reduce glutamate excitability and improve impulsive decision making, is associated with diminished gambling and improved cognitive flexibility (Grant et al., 2010). The link between inhibitory deficits and PIU have so far been mixed. Some studies have found that in comparison to controls, PIU individuals exhibit inhibitory deficits in the go/no-go task (Dong et al., 2010; Zhou et al., 2010; Liu et al., 2014) and stop signal task (Choi et al., 2013, 2014); in contrast, one study reported that PIU individuals performed better in the go/no-go task than controls (Sun et al., 2009). Notably, the reaction stimuli in this task are always go targets and no-go non-targets; therefore, the differences in these stimuli may reflect only aspects of the target (go)/non-target (no-go) decisions rather than the active suppression of motor responses. Given the limited amount of research, more research on inhibitory deficits in PIU individuals is warranted.

In addition to inhibitory control, exploring the relationship between self-regulatory failure and dysfunction of reward processing could have significant implications for research and treatment. Most research on addiction disorders has primarily focused on reward anticipation and reward outcome processing during gain and loss conditions; such studies have revealed that individuals with alcohol dependence (Wrase et al., 2007; Beck et al., 2009), cigarette smoking behavior (Rose et al., 2013), gambling problems (Dong et al., 2011; Ko et al., 2013a; Bustamante et al., 2014), and Internet addiction (Dong et al., 2011; Ko et al., 2013a,b) exhibit deviant reward processing. However, ambiguous findings have been reported for cocaine addiction (Jia et al., 2011; Bustamante et al., 2014). For example, some studies have observed increased anticipatory gain activity in a treatment-seeking group with cocaine dependence (Jia et al., 2011), whereas other studies have reported diminished anticipatory gain processing in cocaine-dependent patients with 1–2 years of sobriety (Bustamante et al., 2014). In fact, in addition to the clinical differences, which include treatment status, length of abstinence, drugs or drug metabolites, and other comorbidities, the varying sensitivity to gains and losses might be the key to explaining the variability among these findings.

Thus, risk taking with losses could also be a critical aspect of reward processing that provides vital insights into the self-regulatory failure of PIU and other behavioral disorders. When faced with a risky decision, individuals are often considerably more concerned with the potential loss rather than with the potential gain of the same magnitude. We are referring to this behavioral phenomenon as risk taking with losses. This phenomenon may result from an asymmetric sensitivity in reward responses in which losses "loom larger" than gains (Kahneman and Tversky, 1979). Risk taking with losses is associated with the "decision" utility of potential losses versus gains when a risky decision is being made (Tom et al., 2007). High risk taking with losses is an indication of the potential gain being more dominant for an individual than the potential loss. High risk taking with losses could reflect a decreased sensitivity to losses due to individual differences in reward processing (Tremeau et al., 2008; Lorains et al., 2014). A recent study demonstrated that problem gamblers took higher risks with losses than controls in a mixed gambles task (Lorains et al., 2014). Using the same task, another study found that pathological gamblers in earlier stages of therapy took higher risks with losses and accepted a higher number of gambles than did pathological gamblers in later stages of therapy; hence, sensitivity to risk taking with losses increased as a result of clinical treatment (Giorgetta et al., 2014). However, to our knowledge, no research has investigated the potential outcomes of risk taking with losses, a fundamental aspect of reward processing, in PIU individuals and those with substance addictions.

In the present study, we examined the inhibition control and risk taking with losses of PIU individuals in comparison to non-PIU individuals. As a measure of inhibition in substance use problems, the stop signal task has been found to be more sensitive to deficits than the go/no-go task (Smith et al., 2014), therefore, we used the stop signal task to capture the inhibitory deficits of PIU individuals. In general, performance in the stop signal task has been effectively modeled using the horse-race model (Band et al., 2003). This model assumes that stop (inhibitory) and go (executed) processes operate independently and that the response is stopped or executed depending on which set of processes wins the race (Kok et al., 2004). Hence, participants are more likely to fail at inhibiting their responses when the execute process finishes first. Moreover, to investigate risk taking with losses in PIU individuals, a mixed gambles task was used to investigate individual's reactions to potential losses versus gains during decision making (Tom et al., 2007). Based on the balance model of self-regulation, we hypothesized that PIU individuals would exhibit impaired functioning in inhibition control and/or risk taking with losses.

MATERIALS AND METHODS

Participants and Procedure

Right-handed participants were recruited via advertising posted on the Bulletin Board System and on campus. An experienced psychiatrist screened potential participants with the Structured Clinical Interview for DSM-IV, which excludes the axis I psychiatric disorders. The Young Diagnostic Questionnaire for Internet Addiction (YDQ; Young, 1998) was used to identify PIU individuals, 32 respondents who answered "yes" to at least five questions were classified as suffering from PIU (18 males; aged 18–24 years, $M_{\text{age}} = 21.13$, $SD_{\text{age}} = 1.60$; years of education: $M = 15.84$, $SD = 1.44$), and 34 age-, gender-, and education-matched healthy individuals with YDQ scores of less than or equal to four were selected as the control group (20 males; aged 18–24 years, $M_{\text{age}} = 20.97$, $SD_{\text{age}} = 1.64$; years of education: $M = 15.84$, $SD = 1.44$ years). Prior to the study, all participants voluntarily enrolled in the study and signed an informed consent statement in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Board of the Institute of Psychology of the Chinese Academy of Sciences. All participants completed the "stop signal" task and the "mixed gambles" task, with the order of the tasks counterbalanced across participants.

Behavioral Tasks

Stop Signal Task

A version of the stop signal task was administered to study the behavioral inhibition of PIU individuals. This task consisted of one deadline estimation block with 50 trials, one training block with 16 trials, and six testing blocks with 256 trials. During the deadline estimation block, the participants were asked to perform a letter discrimination task. Half of the participants in each group (control and PIU) were asked to press the "F" key with their left index finger in response to the letter "A" and to press the "J" key with their right index finger in response to the letter "B." The other half of the participants was trained to perform the opposite pairing. Each trial began with a fixation point in the center of the screen for 100 ms followed by a letter inside a green box for 1200 ms. The trial ended with a fixation point of 1500 ms.

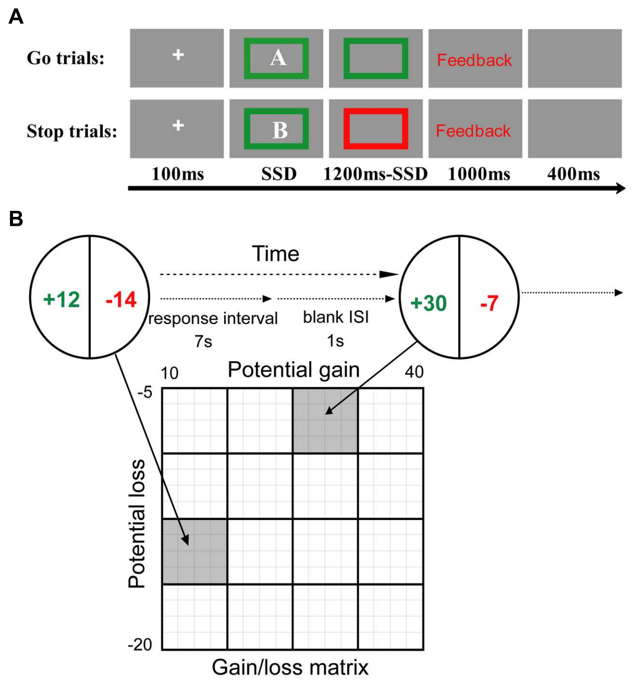

FIGURE 1 | Behavioral tasks. (A) The stop signal task. In this task, the participants were asked to discriminate between the letters "A" and "B." In 33.3% of the trials, the "stop" signal, a red box surrounding the letter (opposed to the box remaining green in the "go" trials), was presented at variable delays after the letter was displayed. The total duration of the onscreen display of the letter and color box was 1200 ms. The time interval between the go and stop signals (the stop signal delay, SSD), began at 300 ms and was updated with a step of 50 ms per trial using a staircase procedure. **(B)** The mixed gambles paradigm. The participants were asked to accept or reject mixed gambles offering equal (50%) chances of gaining or losing different amounts of money. All combinations of gains and losses were presented. ISI, interstimulus interval.

During the training and testing blocks, the participants continued to complete the letter discrimination task (**Figure 1A**); however, they were informed that some "stop" trials were added to the current task. That is, in the "go" trials participants continued completing the letter discrimination task as they had done in the deadline estimation block. In the "stop" trials, a "stop" signal (the green box surrounding the letter turned red) indicating that participants should withhold their response to the letter discrimination task was presented at variable delays after the letter was displayed. The "go" and "stop" trials were randomly intermixed, with "stop" trials constituting one-third of all trials. To ensure that participants would not improve their accuracy by reducing their speed, participants were told that slow responses would be regarded as "wrong." "Slow" responses were determined by estimating the 90th percentile of an individual's reaction time (RT) in the letter discrimination task during the deadline estimation block.

The trials in the training and testing blocks each began with a fixation of 100 ms followed by a letter in a colored box for 1200 ms, during which participants were allowed to respond up to a pre-estimated deadline from the onset of the letter. The response was followed by feedback (right, wrong, or slow) for 1000 ms. The trial ended with a 400 ms blank screen. The time interval between the go and stop signals, the stop signal delay (SSD), was initially 300 ms and varied from one stop trial to the next according to a staircase procedure. After a successful stop trial, the SSD was increased by 50 ms, and after a failed stop trial, it was decreased by 50 ms, thereby converging at a "critical" SSD and resulting in an approximately 50% successful inhibition rate (Levitt, 1971).

"Mixed Gambles" Task

A version of a "mixed gambles" task was used to study PIU individuals risk taking with losses. This task included four blocks. Prior to the "mixed gambles" task, all participants were given ¥50 for their participation in the questionnaire and the stop signal task. To convince the participants that they would be engaging in a real gambling task, they were told that one decision from each of the four blocks would be honored with real money, and an additional ¥50 was given for the present task.

In the mixed gambles task, the participants were offered a 50/50 chance of gaining one amount of money or losing another amount (**Figure 1B**). Possible gains ranged from ¥10 to ¥40 (in ¥2 increments), and possible losses ranged from ¥5 to ¥20 (in ¥1 increments), and these amounts were manipulated independently to allow for separate estimates of responses to gains and losses. All 256 possible combinations of gains and losses were presented randomly across the four blocks. The participants were asked to decide whether to accept or reject each of the gambles presented to them. If they accepted a gamble, the outcome was decided with a coin toss; if they rejected a gamble, then the gamble was not played. To encourage the participants to reflect on the subjective attractiveness of each gamble rather than to comply with a fixed decision rule (e.g., accept the gamble only if gain $\geq 2 \times$ loss), they were given 6 s to indicate the extent to which they accepted or rejected (i.e., strongly accept, weakly accept, weakly reject, and strongly reject) each gamble. This was done by pressing the S or D key with their left ring or middle finger to indicate that they either "strongly accept" or "weakly accept," or by pressing the K or L keys with their right middle or ring finger to indicate they either "weakly reject" or "strongly reject." When a participant made a choice, the chosen option was then highlighted by a thick red outline around the chosen rectangle for 1 s. The alternatives then disappeared, and a blank showed for 1 s. Due to the positive expected value of the gambles that the participants evaluated, no participant actually lost from these gambles. The average amount won from gambling was ¥15 (max gain = ¥24 and min gain = ¥4). Given the initial ¥50 endowment, all participants finished this task with a net gain ranging from ¥54 to ¥74.

Measures

After the experiment, the participants were asked to complete Chinese translations of the Barratt Impulsiveness Scale-11 (BIS-11; Patton et al., 1995) and the Behavioral Inhibition System/Behavioral Activation System questionnaire (BIS/BAS; Carver and White, 1994). The BIS-11 is a 30-item questionnaire assessing impulsiveness on a scale from 1 (rarely/never) to 4 (almost always/always). The BIS-11 includes three impulsiveness subscales: attentional, motor, and non-planning. The overall impulsiveness score is determined by summing the items from the three subscales, with higher scores indicating greater impulsivity. The BIS/BAS questionnaire has been widely used to assess individual differences in two motivational systems, the aversive and appetitive systems. The questionnaire is composed of 20 items that are divided into two primary scales: the BIS (seven items) and the BAS (13 items). The BAS scale includes three subscales: Reward Responsiveness (BAS-Reward; five items), Drive (BAS-Drive; four items), and Fun Seeking (BAS-Fun; four items). Each item is answered using a four-point Likert scale ranging from 1 (strongly disagree) to 4 (strongly agree). **Table 1** shows the demographic characteristics, descriptive statistics and group differences of the PIU and control participants on the BIS-11 and BIS/BAS.

TABLE 1 | Demographic information, means (and standard deviations), and group differences between Individuals with PIU and controls.

	Individuals with PIU	CON	*p*-value
Age (years)	21.13 (1.60)	20.97 (1.64)	0.7
Gender (M/F)	18/14	20/15	0.94
Education (years)	15.84 (1.44)	15.57 (1.36)	0.43
YDQ	5.69 (1.47)	1.71 (1.30)	<0.001
BIS-11	72.63 (13.41)	58.49 (11.19)	<0.001
Attentional	19.59 (3.94)	15.11 (3.64)	<0.001
Motor	24.19 (5.15)	19.51 (4.13)	<0.001
Non-planning	28.84 (5.73)	23.85 (4.55)	<0.001
BIS	21.16 (2.00)	20 (3.00)	>0.05
BAS	45.91 (4.55)	43.97 (3.20)	<0.05
BAS-Reward	18.72 (1.71)	18.06 (1.64)	>0.05
BAS-Drive	13.63 (2.08)	13.89 (1.49)	>0.05
BAS-Fun	13.56 (2.05)	12.03 (1.92)	<0.01

Mean group differences were examined with a two-sample t-test and a chi-square test was used for gender differences between groups. PIU, problematic Internet use; CON, controls; YDQ, Young's Diagnostic Questionnaire for Internet Addiction; BIS-11, Barratt Impulsiveness Scale-11; BIS, Behavioral Inhibition System Scale; BAS, Behavioral Activation System Scale.

Data Analysis

"Stop Signal" Task

Based on the horse-race model which asserts that the go and stop processes compete with one another in their race toward the finish line (Logan, 1994), the stop signal reaction time (SSRT) was computed by subtracting the critical SSD from the median RT in go trials. A longer SSRT indicates poor response inhibition. In the current stop signal task, an independent-samples *t*-test was used to compare the SSRT, RT in go trials, and percentage of errors in go trials of the PIU and control groups. Pearson correlation coefficients were used to examine the interrelatedness of SSRT and both rate of PIU and impulsivity.

"Mixed Gambles" Task

Statistical analyses were performed with MATLAB R2009b (http://www.mathworks.com). As a first step, the strong/weak responses of each participant were transformed into accept and reject categories. Next the acceptance rates of risky gambles (*P*) were computed. Then, a logistic regression was ran with the sizes of the potential gain and loss entered as independent variables and accept and reject categories entered as dependent variables. The risk taking with losses (λ) was computed as follows: $\lambda = -\beta_{loss}/\beta_{gain}$, where β_{loss} and β_{gain} are the unstandardized regression coefficients for the loss and gain variables, respectively (Tom et al., 2007). In the current mixed gambles task, the acceptance rates (P) and the size of log (λ) were compared between the PIU and control groups using an independent-samples t-tests.

Pearson correlation coefficients were utilized to examine the relationships between the participants acceptance rates (P) as well as their risk taking with losses log (λ) and their YDQ scores and SSRT. The alpha level was set at 0.05 for all analyses.

RESULTS

"Stop Signal" Task

The success rates of inhibition in the stop signal trials were 49.88% for the PIU group and 50.99% for the control group; the lack of group differences, $t(65) = 1.13$, $p > 0.05$, indicates that the current procedure was successful. The PIU group ($M \pm SD = 238 \pm 37$ ms) had slower SSRTs, $t(65) = -3.05$, $p < 0.01$, and higher error rates in go trials, $t(65) = 2.54$, $p < 0.05$, than the control group ($M \pm SD = 212 \pm 32$ ms). However, the groups did not significantly differ in their go trial RTs, $t(65) = -0.42$, $p > 0.05$ (**Figure 2**). Furthermore, the SSRTs of all participants were significantly correlated with their YDQ scores ($r = 0.32, p < 0.01$), as well as total BIS-11 scores ($r = 0.46$, $p < 0.001$) and its three subscales (attention: $r = 0.40$, $p < 0.01$; motor: $r = 0.43$, $p < 0.001$; non-planning: $r = 0.45$, $p < 0.001$). The YDQ scores were positively correlated with the total BIS-11 scores ($r = 0.63$, $p < 0.001$) and all three subscales (attention: $r = 0.66$, $p < 0.001$; motor: $r = 0.54$, $p < 0.001$; non-planning: $r = 0.56$, $p < 0.001$).

"Mixed Gambles" Task

The acceptance rates (P) of the PIU group ($M \pm SD = 71.54\%$ 19.28%) were significantly larger than that of the control group ($M \pm SD = 58.60\%$, $\pm$ 20.63%, $t(65) = 2.65$, $p < 0.01$). The control group's ratio of loss responses to their gain responses or their risk taking with losses λ ($M \pm SD = 2.27 \pm 1.10$) was consistent with previous findings (Tom et al., 2007). That is, similar to the difference observed for gambles in which the potential gain was twice the amount of the potential loss, the control group was slower and more hesitant in deciding whether to accept the gambles. However, the risk taking with losses λ ($M \pm SD = 1.54 \pm 0.51$) of the PIU group was significantly smaller than that of the control group, $t(65) = 4.02$, $p < 0.001$ (**Figure 3**).

In addition, for all participants, acceptance rates (P) were marginally significantly correlated with YDQ scores ($r = 0.23$, $p = 0.059$), and the risk taking with losses log (λ) was significantly correlated with YDQ scores ($r = -0.33$, $p < 0.01$), the Fun-Seeking subscale of the BAS (BAS-Fun: $r = -0.32$, $p < 0.01$), and the SSRTs ($r = -0.28$, $p < 0.05$; **Figure 4**).

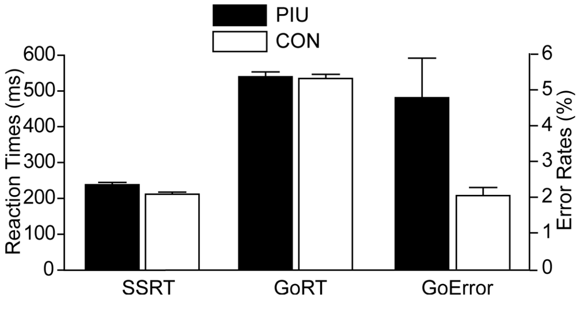

FIGURE 2 | Stop signal task performance group means and 95% confidence intervals for three measures: stop signal reaction time (SSRT; an index of response inhibition), reaction time in go trials (GoRT), and error rates in go trials (GoError). SSRTs and RTs were in ms (left y-axis), whereas error rates were in percentages (right y-axis). PIU individuals had significantly longer SSRTs and higher error rates than the control group, but they did not significantly differ in RTs measures.

DISCUSSION

This study was the first to simultaneously examine inhibitory control and reward processing in PIU individuals using a stop signal task and a mixed gambles task, respectively. Our study showed that PIU individuals, compared with controls, displayed an inability to inhibit responses and a diminished sensitivity to risk taking with losses. Moreover, the more individuals were able to inhibit their responses (shown through the SSRT), the lower their behavioral risk taking with losses was. Together, these results strengthen the argument that deficits in inhibitory control and risk taking with losses may offer promising opportunities to identify the underlying of excessive Internet use observed in PIU individuals. The present study indicates that PIU individuals might have more difficulty controlling their Internet use and be less sensitive to the negative consequences involved in excessive Internet use, and therefore, continue their behavior despite adverse consequences.

Using the stop signal task, which is an effective method to manipulate response inhibition, the present study identified the deficits in inhibitory and executed responses that underlie self-control in individuals with PIU. As previously mentioned, the horse-race model, which assumes that stop (inhibit) and go (execute) processes are in competition with one another, provides a quantitative interpretation of performance in the stop signal task (Band et al., 2003; Kok et al., 2004). In the present study, the time for stopping the response was estimated with the SSRT. We found that in comparison to controls, PIU individuals required more time to inhibit responses. Notably, the slower response inhibition among PIU individuals could not be attributed to in general faster response execution of controls, because both groups displayed similar mean RTs in go trials. The slower response inhibition could be the result of a general slowing of the inhibitory process, such that more time is required to inhibit a response. Furthermore, although PIU individuals did not differ from controls in their ability to execute responses (reflected in go-trial RTs), PIU individuals did display higher error rates in go trials, which demonstrates an impaired execution response in

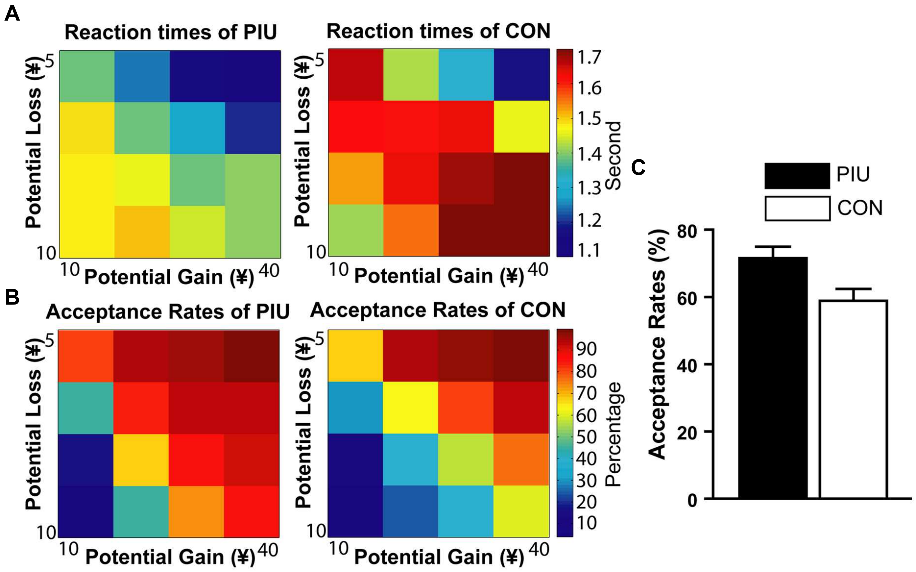

FIGURE 3 | Mixed gambles task performance at each level of gain/loss. (A) Color-coded heatmap of RTs for the PIU and control groups (red indicates slower RTs and blue indicates faster response times). **(B)** Color-coded heatmap of the percentage of gamble acceptance for the PIU and the control groups (red indicates a strong willingness to accept the gamble, and blue indicates a low willingness to accept the gamble). **(C)** PIU individuals had significantly higher acceptance rates of risky gables (*P*) than the control group.

PIU individuals. This finding is consistent with previous research (Zhou et al., 2014). Previous studies using variants of the go/no-go task have also found that individuals with severe PIU exhibit deficient inhibitory control, and this deficiency was confirmed by behavioral, electro-physiological brain potential and functional brain imaging (Dong et al., 2010; Zhou et al., 2010).

The present findings from the mixed gambles task are the first to directly compare quantifiable measures of risk taking with losses between PIU individuals and controls. We found that in comparison to controls, individuals with PIU decided more frequently to accept gambles during the mixed gambles task. Compared with controls, PIU individuals tended to exhibit higher behavioral risk taking with losses, and required less time to decide whether to accept gambles. These findings provide evidence of a specific increase in risk taking with losses in PIU individuals — a finding that is consistent with previous research which found that PIU individuals have enhanced reward sensitivity and decreased loss sensitivity compared to controls during a guessing task (Dong et al., 2011).

The exact reason for the increase in risk taking with losses in PIU individuals is still unclear. One possibility is that individuals with PIU had a diminished sensitivity to the potential loss. According to the regulatory focus theory (Higgins, 1997), people are usually guided by two distinct motivational systems. One involves a promotion focus for potential positive rewards (gains), such as advancements, growth, and accomplishments, and the other involves a prevention focus for potential negative rewards (losses), such as protection and safety. Accordingly, it seems that individuals with PIU have a strong system for promoting potential positive rewards and a lower system for preventing potentially adverse consequences (Dong et al., 2011). Within the present study, when individuals with PIU were confronted with a risky decision, they did not generate strongly negative reward responses, and they predominantly neglected to consider the negative aspect of the risk, and thus, they preferred adventure by exhibiting higher tendencies toward risk taking with losses. Another possibility is that non-PIU individuals were avoiding delay. Only accepting the gamble was associated with a delay (the coin toss), while rejecting it was associated with no delay. Thus, a decrease in risk taking with losses may simply reflect wanting to be done with the experiment faster (Silberberg et al., 2008). The third possibility is that PIU individuals are more likely to take risks (independently of gains or losses). The present study did not include a control task without losses and

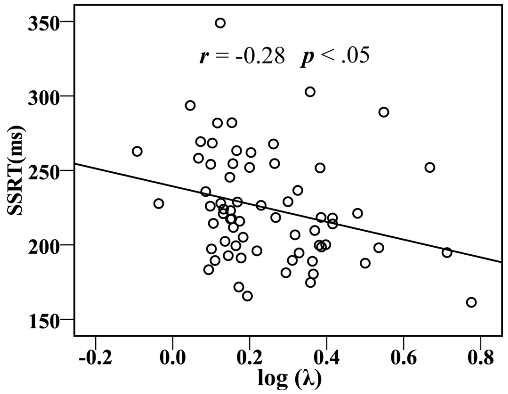

FIGURE 4 | Correlations between the SSRT and behavioral or the ratio of win/loss in risky gables (log λ).

therefore PIU individuals may simply have taken more risk in the sense of preferring variance over a fixed outcome (Yechiam and Hochman, 2013).

In addition, this study provided empirical evidence of the relationship between inhibitory control and reward processing in PIU individuals. Many previous studies have found a dysfunction in either the inhibitory control or reward processing of individuals with substance dependence (Parvaz et al., 2012; Kamarajan et al., 2013), problem gambling (Goudriaan et al., 2005; Lorains et al., 2014), and PIU (Dong et al., 2010, 2011), and such findings have supported the balance model of self-regulation. That is, dysfunction of inhibitory control or reward processing might be a behavioral marker for addiction or other behavioral disorders (Heatherton and Wagner, 2011). However, the neurobiological model of adolescent development proposes that top-down control and bottom-up reward systems should be considered together (Casey et al., 2008). The combination of heightened responsiveness to rewards and immaturity in behavioral control may bias adolescents toward seeking immediate gains rather than focusing on long-term losses, perhaps explaining their increased tendency to engage in various addictive and risky behaviors. Conforming to this model, the PIU individuals in our study demonstrated less effective inhibitory behavior and more excessive fun seeking. Furthermore, we found that individuals who took longer to inhibit their responses, tended to be less aversive to losses. This result suggests that impairment of the functions of inhibitory control and reward processing in PIU individuals is not independent but linked. Dysfunctions in both of these systems might be markers of risk for PIU and various risk behaviors.

The present study also included some limitations. This was a cross-sectional study so even though in comparison to controls, PIU individuals showed a dysfunction of inhibitory control and reward processing, it is hard to determine whether the dysfunction of these features preceded the development of PIU or were a consequence of the overuse of the Internet. Therefore, further studies should tease apart the causal relations between PIU and these features. Secondly, the sample size in this study was relatively small, which might reduce the power of the statistical significance and generalization of the findings. Owing to this limitation, these results should to be considered preliminary and need to be replicated in future studies with a larger sample size.

CONCLUSION

The present study revealed that inhibitory control and reward processing were simultaneously impaired in PIU individuals. Importantly, the present study illustrated an association between these two systems that suggested an imbalance of self-regulation in PIU individuals as a result of the diminished function of both systems. Moreover, the present results for PIU individuals may provide insight into a number of neuropsychiatric and behavioral disorders associated with self-regulatory failure, such as substance abuse, pathological gambling, and antisocial personality disorder. However, future studies should integrate methods related to both inhibition response and reward processing to gain greater insight into the mechanisms underlying the development of PIU. To promote the development of specific prevention and treatment procedures, further longitudinal research revealing the causes and consequences of PIU is needed to explore the role of inhibitory control and sensitivity to rewards in predicting the development of PIU.

AUTHOR CONTRIBUTIONS

QL designed the experiments and wrote the paper. JT and YZ edited this manuscript. WN and WD conducted the experiments and analyzed these data. XL designed the experiments and gave some suggestions to edit this manuscript.

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MINI REVIEW
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Cue-induced Behavioral and Neural Changes among Excessive Internet Gamers and Possible Application of Cue Exposure Therapy to Internet Gaming Disorder

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Internet gaming disorder (IGD) may lead to many negative consequences in everyday life, yet there is currently no effective treatment for IGD. Cue-reactivity paradigm is commonly used to evaluate craving for substance, food, and gambling; cue exposure therapy (CET) is applied to treating substance use disorders (SUDs) and some other psychological disorders such as pathological gambling (PG). However, no study has explored CET's application to the treatment of IGD except two articles having implied that cues' exposure may have therapeutic effect on IGD. This paper reviews studies on cue-induced behavioral and neural changes in excessive Internet gamers, indicating that behavioral and neural mechanisms of IGD mostly overlap with those of SUD. The CET's effects in the treatment of SUDs and PG are also reviewed. We finally propose an optimized CET paradigm, which future studies should consider and investigate as a probable treatment of IGD.

Keywords: Internet gaming disorder, excessive Internet gamers, cue-induced changes, substance use disorder, cue exposure therapy, mini-review

INTRODUCTION

Internet gaming disorder (IGD), is arguably the most problematic form of Internet use (Petry and O'Brien, 2013) and is different from other forms of problematic Internet use in terms of its prevalence rates, etiologies, characteristics of persons participating in them, and risks for harm (Ko et al., 2007, 2009b; van Rooij et al., 2010). IGD can also lead to comorbid disorders such as major depression, anxiety disorders, attention-deficit hyperactivity disorder, and schizophrenia (Ha et al., 2006). However, there is currently no effective therapy of this disorder.

Recent studies have shown that it is necessary to replace pharmacotherapy with intervention on sensitivity and reactivity to environmental cues in treating substance use disorders (SUDs; Perry et al., 2011). Cue exposure therapy (CET) is such an intervention and is based on Pavlov's theory of classical conditioning, in which an unconditioned cue (UCS) eliciting an unconditioned response (UCR) is consistently paired with a conditioned cue (CS) until the CS itself can evoke a conditioned response (CR) similar to UCR. The aim of CET is to diminish conditioned relation between an addictive cue (CS) and a physiological response (CR) by systematically pairing them in a treatment setting. Continual combination of a CR with a CS in absence of the actual substance or state it is formerly accompanied with can gradually weaken the CR to the CS, which eventually results in the extinction of the CS–CR association, consequently decreasing reactivity to addictive cues.

Cue exposure therapy is widely used in treating SUDs (Maltby et al., 2002; Hofmann et al., 2006; Costa et al., 2008; Reger and Gahm, 2008; Vögele et al., 2010). However, studies on its use in IGD are minimal. In this paper, we briefly review studies using game-related cues to induce behavioral or neural changes among excessive Internet gamers, and discuss possible adoption of CET in treating IGD.

MATERIALS AND METHODS

We searched for literatures on PubMed, Web of Science, and ScienceDirect with no date restrictions. Terms used were "Internet gam*" or "online gam*" or "computer gam*" in combination with "cue*" or "attention*" or "inhibit*" or "neur*". We finally selected most relevant papers for our review.

Studies on Cue-induced Behavioral Changes in Excessive Internet Gamers

In substance-related addiction and pathological gambling (PG), two behavioral tendencies associated with addictive disorders are usually studied. The first tendency is attentional bias in which addicted persons unconsciously allocate attention to addiction cues (Field and Cox, 2008), and is often investigated with stroop or dot-probe paradigms (Boyer and Dickerson, 2003; Lusher et al., 2004; Robbins and Ehrman, 2004; Field and Cox, 2008). The second is diminished response inhibition, in which addicted person's ability to suppress responses to addictive cues is diminished, and is commonly detected using go/no-go task (Goudriaan et al., 2006; Dawkins et al., 2009). Exploring the presence of the two behavioral tendencies in excessive Internet gamers may help us understand behavioral mechanism of IGD and possible therapeutic intervention.

The following three studies focused on both attentional bias and response inhibition toward game-related cues among people with IGD. The first study, by Decker and Gay (2011), used go/no-go task to examine existence of cognitive bias toward gaming-related words in players of World of Warcraft (WoW). The study found that WoW players had higher response disinhibition and cognitive bias toward WoW jargon in all conditions compared with non-players. The second study, by Zhou et al. (2012), used Internet game-shifting task, a variant of go/no-go task, in which game-related pictures and fruit pictures were set as targets and distracters, respectively, or in reverse, and subjects were required to respond to the targets but not respond to the distracters. They found that excessive gamers showed cognitive bias, response inhibition, and shifting deficits toward Internet game-related pictures, and length of addiction (number of years) was positively related to severity of cognitive bias. The third study, by Holst et al. (2012), also showed that higher levels of self-reported problematic gaming were related to more errors on both attentional bias and response inhibition to game cues among male adolescents. These results are consistent with findings of attentional bias reported in clinically recognized SUDs and PG (Boyer and Dickerson, 2003; Robbins and Ehrman, 2004).

Whilst the above three studies investigated both attentional bias and response inhibition, the following three studies focused on one of the two behavioral tendencies. The first study, by Metcalf and Pammer (2011), used a modified Stroop task to investigate the existence of attentional bias for gaming-related words in excessive Massively Multiplayer Online Role-Playing Gamers (MMORPGers). The modified Stroop task comprised of game-related, negative and neutral words presented in different colors and participants were required to indicate the words' color as quickly as possible. Results showed that excessive MMORPGers had attentional bias toward negative and MMORPG words. The second study, by Liu et al. (2014), examined deficit of response inhibition mechanism in game abusers and explored underlying neurological substrates related to abusers' implicit cognitive process. Results showed that brain activations of the superior parietal lobe and right dorsolateral prefrontal cortex (DLPFC) were negatively associated with performance of response inhibition among subjects with IGD. Similarly, the third study, conducted by Chen et al. (2014), not only validated the existence of response disinhibition in subjects with IGD, but suggested that dysfunctional activation of the supplement motor area in response disinhibiton is one of the candidate mechanisms in both IGD and SUD.

Not all of the studies exploring cue-induced behavioral changes in subjects with IGD use the terms "attentional bias" or "response inhibition" explicitly. Thalemann et al. (2007) employed the phrase "increased emotional processing" to indicate subjects' attentional bias and impairment of response inhibition toward addiction cues. They demonstrated that significant between-group differences in cue-induced event-related potentials found at parietal regions pointed to an "increased emotional processing" of these cues in excessive computer game players. The study further concluded that game-related cues had gained an "intrinsic motivational relevance" during learning process for excessive gamers. Yen et al. (2011) used another term "implicit cognition," a broader category encompassing attentional bias or response disinhibition. It is conceptualized and measured by various cognitive processes in abusers' performance such as response disinhibition, attentional bias, and memory associations (Stacy and Wiers, 2010; Decker and Gay, 2011). The IGD group responded faster to congruent pairing and had positive motivational implicit response to Internet gaming cues compared to the control group, which highlighted the important role of "implicit cognition" in young adults with IGD.

All the above studies demonstrate that Internet gaming abusers show attentional bias and response disinhibition toward game-related cues or emotional cues, which are considered typical behavioral characteristics of SUD and PG. (Coskunpinar and Cyders, 2013; Hønsi et al., 2013; Smith et al., 2014; Yau and Potenza, 2015).

Studies on Cue-induced Neural Changes in Excessive Internet Gamers

Neuroimaging studies have found that behavioral and substance addictions share neurocircuitry and that subcortical and frontal cortical areas, especially the ventromedial prefrontal cortex, contribute greatly to neural systems and neurobiological mechanisms of both behavioral and substance addictions (Power et al., 2011; Yau and Potenza, 2015). Existing studies on neurobiological mechanism of SUD and PG have adopted cue-reactivity paradigm, prompting researchers on Internet gaming to employ this paradigm to investigate the neural mechanism of IGD.

In three successive fMRI studies, using different methods and perspectives, Ko et al. (2009a, 2013a,b) concluded that cue-induced neural mechanism of IGD is similar to that of SUD. The first study compared brain activation between Internet game abusers and non-abusers presented with game-related pictures and mosaic pictures. Result showed that right orbitofrontal cortex, right nucleus accumbens, bilateral anterior cingulated and medialfrontal cortex, right DLPFC, and right caudate nucleus, known to relate to craving in SUD, were activated by gaming pictures in gaming abusers. The second study evaluated brain correlates of cue-induced craving to game-related cues in subjects with IGD, subjects in remission from IGD and controls. Results showed that bilateral DLPFC, precuneus, left parahippocampus, posterior cingulate and right anterior cingulate were activated in response to gaming cues in the IGD group and their activation was stronger in the IGD group than in the control group. Furthermore, the IGD group had stronger activation over right DLPFC and left parahippocampus than the remission group. Given that Internet abuse is often comorbid with problematic substance use (Ko et al., 2006, 2008; Yen et al., 2009), Ko et al. (2013b) conducted the third study evaluating brain correlates of cue-induced gaming urge and smoking craving among subjects with both IGD and nicotine dependence. Result showed greater activation in anterior cingulate, parahippocampus, and bilateral parahippocampal gyrus for both smoking craving and gaming urge among the comorbid group than the control group.

Two studies conducted in China further validated the similarity between IGD and SUD in terms of the neural mechanism. Sun et al. (2012) used fMRI to explore craving-related brain regions induced by game associated pictures in Internet game abusers. Results showed that game abusers' craving was induced by game cue pictures, which caused increased brain activation in some cerebral regions, including bilateral DLPFC, cingulated cortex, right inferior parietal lobule regions, and cerebellum. Increased imaging signal densities were significant and positively correlated with craving scores in the bilateral prefrontal cortex, anterior cingulate cortex and right inferior parietal lobe, all of which are related to cognitive and emotional processing. Given that there is a transition in processing of drug-related cues from the ventral striatum (VS) to the dorsal striatum (DS), Liu et al. (2016) conducted the first fMRI study to explore the function of both VS and DS in response to game-related cues among people with IGD. Results suggested that a transition from VS to DS processing may occur among people with IGD, which is consistent with studies in SUD.

Unlike studies conducted by Ko et al. (2009b, 2013a,b), Sun et al. (2012), and Liu et al. (2016), in which Internet game abusers were placed in one group, Han et al. (2010b, 2011) recruited only healthy subjects in their two cohort studies. The aim of their studies was to investigate cue-induced changes in cortex activity after a certain period of Internet video game play and if such cue presentation could activate similar brain regions observed in people with SUD or PG. The first study suggested that brain activity changes in the frontal-lobe areas after six weeks of extended Internet game play may be similar to those observed in early stages of SUD. In the second study, reported desire in subjects who played more Internet video game (MIGP) positively correlated with brain activation in right medial frontal lobe and right parahippocampal gyrus. The authors concluded that cue-induced activated brain regions in MIGP cohort are similar to those observed in persons with SUD or PG and cues appear to elicit activity in the DLPFC, orbitofrontal cortex, parahippocampal gyrus, and thalamus.

Some studies have suggested that brain activation decreases in response to cues among patients with SUD or PG after antidepressants treatment (Robertson et al., 2007; Chung et al., 2009; Hays et al., 2009). Han et al. (2010a) hence conducted the first bupropion treatment study in patients with IGD to find out if the same effect would be observed in people with IGD. Results showed that, after 6 weeks of bupropion sustained release treatment, both Internet gaming addiction (IGA's) craving for Internet video game and activity of DLPFC in response to video game cue stimulation decreased, and the former was positively correlated with the latter. The bupropion's therapeutic effect on IGD in terms of decreasing craving is hence similar to that on SUD or PG.

Based on the above-reviewed studies, activated brain circuit in people with IGD is similar to that in people with SUD. Further, craving for Internet games positively correlats with activated brain regions involved in cognitive and emotional processing. IGD seems to share similar neural mechanism with SUD and PG (Crockford et al., 2005; Goudriaan et al., 2014; Yau and Potenza, 2015).

Cue Exposure Therapy in the Treatment of SUDs and PG

Cue exposure therapy has been utilized in treating SUDs since 1980s, and appears to be effective in treating SUD although the effect is not significantly superior to other behavioral therapies (Conklin and Tiffany, 2002; Martin et al., 2010; Myers and Carlezon, 2012; Antoine et al., 2014). A meta-analytic review found insufficient evidence to validate CET's efficacy in treating SUD and the authors highlighted threats to extinction such as renewal, spontaneous recovery, reinstatement, and characteristics of the cues that may weaken the CET effect (Conklin and Tiffany, 2002). An updated review (Martin et al., 2010) found CET as effective in reducing individuals' craving in some studies. However, the review also obtained little evidence of CET's superior efficacy over other forms of treatment, although some studies in the review had made innovations including consideration of above-mentioned threats to extinction, attention to individual differences, use of virtual reality (VR) technology, and medication augmentation.

Subsequently, two other reviews focusing on CET combined with medication augmentation (Myers and Carlezon, 2012) and VR technology (Antoine et al., 2014) were conducted. Myers and Carlezon (2012) reviewed studies that examined the effect of D-cycloserine (DCS) on extinction of cue-induced conditioned responses in SUD. They concluded that existing data indicated less robust effects of DCS-coupled CET in SUD. Since medication augmentation measures bear some limitations, some neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are more favorable to augment CET effect. Similarly, studies combining CET with VR have also reported mitigated efficacy in treating SUD (Antoine et al., 2014). However, this review indicated that VR can improve actual assessment of craving in SUDs and can significantly help increase ecological cue validity so as to facilitate VR–CET efficacy at individual level. VR technology may have advantages if used in treating IGD because of its simulation of either the scenario of Internet game or the environments in which abusers play games, which can bring about subjects' visual stimulation as experienced in their gaming condition. Meanwhile, VR–CET can increase game-related cue's ecological validity and fulfill individualized treatment, which cannot be realized by standard cue-induced paradigms using common words, pictures, or videos.

A recent study explicitly confirmed CET's efficacy in treating SUD (Xue et al., 2012). This study reported a memory retrieval-extinction procedure that successfully decreased cue-induced craving in abstinent heroin abusers 1, 30, and 180 days later, and concluded that in extinction sessions, cue exposure can only work within a specific time interval termed "reconsolidation window" (Tronson and Taylor, 2007; Nader and Hardt, 2009) which is up to 2 h after memory retrieval.

Besides, results from studies adopting CET in treating PG also showed CET has its potential in the reduction or extinction of gambling urges. Two case studies adopting CET successfully reduced subjects' gambling behavior and urges (Symes and Nicki, 1997). Kushner et al. (2007) suggested that problem gamblers' intensity of gambling urges decreases with time when exposed to gambling cues, especially in the presence of gambling-relevant negative mood induction manipulation. Another study validated the use of VR in cue exposure, and showed that a number of exposure sessions are essential to trigger the extinction process (Giroux et al., 2013).

Cue's Possible Therapeutic Effect on IGD

To our knowledge, few studies have used standard CET paradigm to treat IGD and only two studies reviewed below indicate cue's possible therapeutic effect on IGD.

Lorenz et al. (2013) conducted an fMRI study using a dot probe paradigm with short-presentation (SP) trial used for investigating subjects' attentional bias and long-presentation (LP) trial used for investigating subjects' cue reactivity in eight male pathological computer game players (PCGPs) and nine healthy controls. The study found that PCGPs showed an attentional bias toward both game-related and affective stimuli with positive valence. Furthermore, activation brain areas in PCGPs were different between SP trial and LP trial, in which cue-induced brain responses can be inhibited by top–down inhibitory processes associating with the right inferior frontal gyrus. This implies that such cognitive inhibition processes in cue reactivity might be essential in therapy for the treatment of IGD. Kim et al. (2013) investigated the influence of a course with narrative characteristics and content borrowed from a MMORPG on game abusers' language expression and the course's therapeutic effect on gaming disorder. Analysis of P300 amplitude and sLORETA images before and after the course showed that game abusers had a processing bias toward game-related cues before the course and such bias was weakened after the course. Thus, game abusers' mental processing used for the course was changed and their craving decreased.

The above-mentioned two studies already take on some features of CET and the findings bear some implications for future CET's application in treating IGD. Lorenz et al. (2013) highlighted the possibility of inhibiting cue-induced brain responses and the importance of cognitive inhibition processes arising in cue's LP trial lasting for 2000 ms. This implies that there is a possible duration threshold for presenting cues in CET so that cognitive inhibition processes can take place. In the two-month study, Kim et al. (2013) used different forms of cues such as video game clips, images of game scenes, and written form of game story. Therefore, longer duration of study and more types of cues are worth consideration in future studies employing CET as treatment of IGD.

CONCLUSION AND FUTURE STUDY

In view of CET's efficacy in decreasing craving for substance-related cues, its extinction of cue-response association (Antoine et al., 2014) and the overlaps between IGD and SUD with regard to their neural and behavioral mechanisms, we suggest taking more studies on the effect of applying CET paradigm to the treatment of IGD. Given that CET's efficacy in treating SUD is overall mitigated, optimizing the traditional CET paradigm to ensure a better therapeutic effect is essential for future studies. Combining VR–CET with tDCS or conducting tDCS after VR–CET sessions may help ensure a long term effect in treating IGD. Further, when adopting CET paradigm in treating IGD, future studies should validate whether conducting the extinction process within the "reconsolidation window" can also help to weaken or even erase the original game-cue memory. Besides, some methodological problems such as threats to extinction, permission or forbiddance of online gaming between CET sessions, participants' individual differences, small sample size and high dropout rates should be considered so as to strengthen CET efficacy. If the proposed optimized CET paradigm, namely VR–CET coupled with tDCS, can work and bear long-term therapeutic effect, then it would be undoubtedly a more favorable treatment of IGD.

AUTHOR CONTRIBUTIONS

XZ supervised this study and revised each draft. YZ wrote this paper. YN proofread each draft. JH and LY provided suggestions on the structure of this paper. JC, YW, LH, JB, PZ, and YZ helped to collect the materials and resources needed for this study.

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Frequency-dependent changes in the amplitude of low-frequency fluctuations in internet gaming disorder

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Neuroimaging studies have revealed that the task-related functional brain activities are impaired in internet gaming disorder (IGD) subjects. However, little is known about the alternations in spontaneous brain activities about them. Recent studies have proposed that the brain activities of different frequency ranges are generated by different nervous activities and have different physiological and psychological functions. Thus, in this study, we set to explore the spontaneous brain activities in IGD subjects by measuring the fractional amplitude of low-frequency fluctuation (fALFF), to investigate band-specific changes of resting-state fALFF. We subdivided the frequency range into five bands based on literatures. Comparing to healthy controls, the IGD group showed decreased fALFF values in the cerebellum posterior lobe and increased fALFF values in superior temporal gyrus. Significant interactions between frequency bands and groups were found in the cerebellum, the anterior cingulate, the lingual gyrus, the middle temporal gyrus, and the middle frontal gyrus. Those brain regions are proved related to the executive function and decision-making. These results revealed the changed spontaneous brain activity of IGD, which contributed to understanding the underlying pathophysiology of IGD.

Keywords: internet gaming disorder, resting-state functional magnetic resonance imaging, amplitude of low-frequency fluctuation

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Introduction

Internet addiction disorder (IAD) has been defined as the individual's inability to control the excessive use of the Internet, even in the face of the negative consequences to psychological functioning aspects (Young, 1998; Fitzpatrick, 2008; Tao et al., 2008; Flisher, 2010). It has been proposed as a "behavioral addiction" according to its negative effects on social mental health (Kuss and Griffiths, 2012). However, little is known about the mechanism of IAD, and a uniformly definition of IAD hasn't been formed and the Diagnostic and Statistical Manual 4 (DSM-4) didn't include this behavioral disorder (Block, 2008). Along with the rapid spread of IAD, the DSM-5 is developed for internet gaming disorder (IGD) based on the definition of substance-use disorders and addictions (Frances and Widiger, 2012; American Psychiatric Association, 2013; Petry and O'Brien, 2013; Petry et al., 2014).

There are many different types of IAD due to the internet's diverse functions. In general, IAD consists of three subtypes: IGD, Internet pornography, and e-mailing (Block, 2007). Considering the definition of addiction, all these categories of IAD share four defining characteristics: excessive use, withdrawal, tolerance, and negative repercussions (Beard and Wolf, 2001; Block, 2008; Tao et al., 2010). As the most prevalent form of IAD (Dong et al., 2012a), IGD may share specific neuropsychological characteristics with other behavioral addictions, such as pathological gambling (Griffiths, 2005; Grant et al., 2010; Dong et al., 2012b; Han et al., 2012; Dong and Potenza, 2014).

Numerous imaging studies have investigated the characteristics of IGD using different tasks (Fowler et al., 2007; Dong et al., 2011a, 2012b; Han et al., 2011a; Xu, 2013), but it is difficult to compare data obtained from different experimental paradigms and draw clinically helpful conclusions from different cognitive tasks (Zang et al., 2007a). Resting-state fMRI studies have revealed some abnormalities of the brain activation in IGD (find more descriptions from a review by Weinstein and Lejoyeux (2015). IGD subjects have higher impulsiveness, which is a typical symptom of drug addiction; this symptom is related to the decreased activation of cingulate gyrus, which involves cognitive control (Dong et al., 2012a). An fMRI study also showed enhanced regional homogeneity (ReHo) in the brainstem, inferior parietal lobule, left posterior cerebellum, and left middle frontal gyrus that are related with sensory-motor coordination which might be relevant to the finger movement of playing internet games (Dong et al., 2012c).

Resting-state fMRI has been developed as a new technique since the Biswal's study (Biswal et al., 1995). They first reported the highly synchronous spontaneous low frequency (0.01–0.08 Hz) fluctuations in BOLD signal among motor cortices, concluding the amplitude of low-frequency fluctuation (ALFF) was a neurophysiologic indicator (Biswal et al., 1995). On the basis of ALFF, Zang et al. (2007b) promoted another tool to depict local brain activity - the fractional amplitude of low-frequency fluctuation (fALFF), which could detect the regional intensity of spontaneous fluctuations in BOLD signal (Zou et al., 2008; Zuo et al., 2010). Recently, fALFF was broadly used in mental disorder patients' studies, such as depression (Guo et al., 2013), schizophrenia (Bluhm et al., 2007), attention deficit hyperactivity disorder (Zang et al., 2007b), IGD (Yuan et al., 2013), and so on. It is still unclear whether the brain activity abnormalities of IGD are related to specific frequency bands. It is important to detect brain spontaneous fluctuations at specific frequency more than a broad frequency band. There are many diverse oscillations in the brain, the frequencies of them are ranging from very slow oscillations with periods of tens of seconds to very fast oscillations with frequencies exceeding 1000 Hz (Bullock, 1997). Buzsáki and Draguhn (2004) proposed an 'oscillation class' which contains 10 frequency bands extending from 0.02 to 600 Hz (Penttonen and Buzsáki, 2003). And Zuo et al. (2010) investigated the fALFF at four frequency bands and found that the oscillations are linked with specific neural processes (Buzsáki and Draguhn, 2004; Knyazev, 2007). They found that amplitudes of oscillations (0.01–0.027 Hz) at low frequency were most robust in the cortical structures and high frequencies were most robust in the subcortical structures such as the basal ganglia. Studies have revealed that schizophrenia patients had particular abnormalities of oscillations amplitudes in the slow-4 frequency band (Yu et al., 2014). Han et al. (2011b) also proved that abnormalities of brain function in amnestic mild cognitive impairment patients exposed different activation patterns in different frequency bands.

In the present study, we collected fALFF values of the frequency across 0–0.25, including six frequency bands of 0–0.01 Hz, 0.01–0.027 Hz, 0.027–0.073 Hz, 0.073–0.198 Hz, and 0.198–0.25 Hz in IGD, according to Buzsáki's "oscillation classes". We sought to compare the fALFF value between IGD and HC in different bands and address two issues: first, whether the IGD subjects show abnormal fALFF amplitudes when compare to healthy controls; second, whether the abnormalities of IGD are associated with specific frequency bands.

Materials and Methods

Participant Selection

The experiment conforms to The Code of Ethics of the World Medical Association (Declaration of Helsinki) and is approved by the Human Investigations Committee of Zhejiang Normal University. Fifty-two university students were recruited through advertisements [26 IGD, 26 healthy controls (HC)]. They were all right-handed males. IGD and HC groups did not significantly differ in age (IGD: $N = 26$, 22.2 ± 3.13 years; HC: $N = 26$, 22.28 ± 2.54 years; $t(50) = 0.1$, $p = 0.9$). Because of the higher IGD proportions among men, only males were included. Participants were required to sign the informed consent and all participants went through structured psychiatric interviews (M.I.N.I.) (Lecrubier et al., 1997) performed by an experienced psychiatrist with an administration time of approximately 15 min. All participants were free of Axis I psychiatric disorders listed in MINI. All the participants did not meet DSM-4 criteria for drug abuse or dependences, including alcohol, although all IGD and HC participants reported alcohol consuming in their lifetime. All participants were instructed not to use any substances, including coffee, tea, on the day of scanning. No participants reported brain damages or previous experience with illicit drugs (e.g., cocaine, marijuana).

The diagnosis of IGD was determined based on scores of 50 or higher on Young's online Internet Addiction Test (Young, 1998). As a special behavior addiction, the operational definition and diagnostic standards for IGD are still inconsistent. In the present study, the IGD group was composed of individuals who met the general IAD criteria (scores over 50 in the IAT) and reported "spending most of their online time playing online games (>80%)" (Blaszczynski, 2008; Weng et al., 2013). The IAT score of IGD group (72 ± 11.7) was much higher than the healthy controls [29 ± 10.4), $t(50) = 14$, $p = 0.000$].

Data Acquisition

After conventional localizer scanning, the T1-weighted images were obtained with a spoiled gradient recall sequence [TR = 240 ms; echo time (TE) = 2.46 ms; flip angle (FA) = 90°;

field of view (FOV) = 220*220 mm^2; data matrix = 256*256]. Then, resting-state functional images were acquired using an echo-planar-imaging sequence (TR = 2000 ms; TE = 30 ms; FA = 90°; FOV = 220*220 mm^2; data matrix = 64*64) with 33 axial slices (slice thickness = 3 mm and slice gap = 1 mm, total volumes = 210) in one run of 7 min. The subjects were required to keep still and not think about anything systematically during the scanning. At the end of the data acquisition, all subjects confirmed that they remained awake during the whole scanning period.

Data Preprocessing and fALFF Calculation

All of the functional image processing was performed with Data Processing Assistant for Resting-State fMRI [DPARSF (Yan and Zang, 2010)[1]] software. For each participant, the first 10 time points were excluded from further analysis, which is to avoid transient signal changes before magnetization reached steady state and to allow subjects to get used to the fMRI-scanning environment. The remaining 200 brain volumes were corrected for slice timing and realigned for head movement correction. Only participants with head motion less than 1.5 mm in the x, y, or z direction and less than 2 rotation about each axis were included. 26 HC and 26 IGD subjects were valid in the present study. Then, all of the realigned images were spatially normalized, and then resampled to 3 mm isotropic voxels and spatially smoothed (full-width at half-maximum = 6 mm), and the linear trend was removed. After preprocessing, fALFF was calculated using DPARSF. Briefly, for a given voxel, the time series was first converted to the frequency domain using a "fast Fourier transform." The square root of the power spectrum was computed and then averaged across a predefined frequency interval. This averaged square root was termed fALFF at the given voxel of predefined frequency bands (Zang et al., 2007a). We divided the full frequency range (0–0.25 Hz) into five sub-bands: slow-6 (0–0.01 Hz), slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz), and slow-2 (0.198–0.25 Hz) (35, 46, 30), and computed fALFF of each frequency bands.

Statistical Analysis

A two-way (group and frequency band) repeated-measures analysis of variance (ANOVA) was performed on a voxel-by-voxel basis with group (IGD and HC) as a between-subject factor and frequency band (slow-2, slow-3, slow-4, slow-5, slow-6) as repeated-measures. We also calculated the ROI-based correlation analysis following up the significant main effect and interaction between the severity of IGD and the fALFF values, and we picked fALFF values from specific bands.

Results

Main effects from the two-way repeated-measures ANOVA were shown in **Figure 1**, **Tables 1** and **2**. We used Alphasim correction for the multiple comparisons in imaging data. The corrected $p < 0.05$ corresponds to a combination of uncorrected $p < 0.05$ and cluster size >248 mm^3). ROI based correlation analysis was carried out between fALFF values and the severity of IGD (scores of IAT). The cerebellum showed significant negative correlation with IGD severity (slow-4: $r = -0.487$, $p = 0.000$; slow-5: $r = -0.485$, $p = 0.000$; see **Figure 2C**). The coordinate of ROI was defined by the activation peak of the survived cluster. The radius of ROI is 4 mm, and is made by the software REST[2].

Significant interactions between frequency band and group were observed in the cerebellum, the anterior cingulate, the lingual gyrus, the middle temporal gyrus, and the middle frontal gyrus. The middle frontal gyrus showed increased amplitude values and the middle temporal gyrus showed decreased amplitude values in IGD. In addition, ROI-based analyses presented dynamic alteration of fALFF in the cerebellum and lingual gyrus along with frequency adaption (see **Figure 3**). In IGD, the cerebellum showed decreased amplitude values in the higher frequency realm (slow-2, slow-3, slow-4) and increased amplitude values in the lower frequency realm (slow-6, see **Figure 3A**). Conversely, lingual gyrus showed increased amplitude values in the higher frequency realm (slow-2, slow-3) and decreased amplitude values in the lower frequency realm (slow-6, see **Figure 3B**). These two regions shared a transition point at slow-5 band for the alteration of amplitude.

Discussion

The present study investigated the abnormal spontaneous brain activity in IGD with the fALFF at different frequency bands. Main group effect revealed that the IGD demonstrated lower fALFF values in superior temporal gyrus and higher fALFF values in cerebellum. We presented BOLD fluctuation amplitudes in the whole frequency bands (0–0.25 Hz) and found a reversed pattern of changes in frequency realm in the cerebellum and lingual gyrus in IGD. These findings provide a full view of fALFF analyzes in frequency domain, and emphasize the importance of the selection of specific frequency for detecting abnormality related mental disorders.

Different fALFF in Cortical between IGD and HC (The Main Effect of Group)

Previous literatures believed that the signal of slow-2 reflects very low frequency drift, and the slow-6 reflects high-frequency physiological noises (Zang et al., 2007a; Xu, 2013). The analysis of main effect of group focused on the spontaneous neural activity at specific frequency bands (slow-4 and slow-5) in IGD. The main effect of group revealed that the IGD showed lower fALFF values at slow-4 and slow-5 in cerebellum. A negative correlation between the fALFF values in cerebellum and the severity of IGD was found in the present study. The cerebellum is commonly classified as a motor structure whose function is not confined to movement coordination or balance and it also plays an important role in higher cognitive processes (De Zeeuw

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[1] http://www.restfmri.net

[2] www.restfmri.net

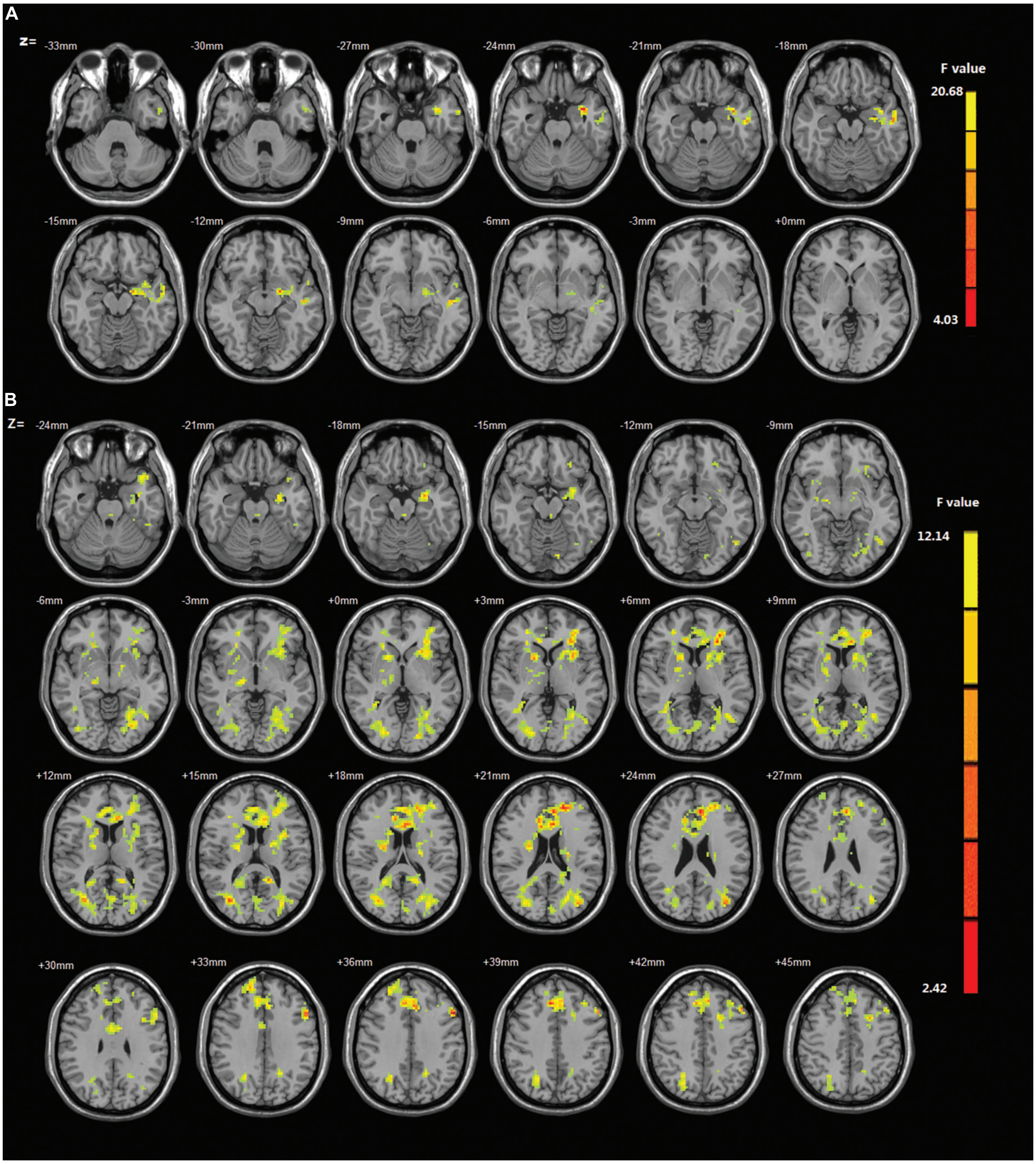

FIGURE 1 | (A) The main effect for group on amplitude of low-frequency fluctuation (ALFF). Brain regions in which the fractional amplitude of low-frequency fluctuation (fALFF) is different between Internet gaming disorder (IGD) and healthy controls. The IGD subjects showed increased ALFF in warm colored brain regions especially the cerebellum, whereas decreased ALFF in cool colored regions including the superior temporal gyrus. Map threshold of multiple comparisons were set at $p < 0.05$ using AlphaSim correction. **(B)** The interaction between frequency band and group on fALFF. The results were obtained by a two-way repeated-measures analysis of variance (ANOVA) calculated by AFNI.

et al., 2011; Stoodley et al., 2012). Evidence from anatomical, physiological, and functional imaging studies has proved that people with lesions to the cerebellum showed deficiency of cognitive executive functions and working memory (Raymond et al., 1996; De Smet et al., 2013). It receives input from sensory systems and other brain areas, and integrates these inputs to adjust motor activity (Doyon et al., 2003; Ito, 2006; Yuan et al., 2011). The potential role of the cerebellum in addiction has been addressed in a recent paper, which proposed that the cerebellum is a potential regulation center that is impacted by addiction (Moulton et al., 2013). Literatures have demonstrated that IGD subjects are associated with greater-than-normal ReHo (Liu et al., 2010; Dong et al., 2012c) and functional connectivity (Ding et al., 2013) over the cerebellum.

TABLE 1 | Brain regions with a main effect of group.

Region	BA	size	*x*	*y*	*z*	
Superior temporal gyrus	41,42	235	−33	3	−24	IGD<HC
Cerebellum		1180	0	−12	−51	IGD>HC

We list significant clusters of main effect of group. Shown are the Brodmann Area, the size of the cluster, the coordinates of the local maxima (in MNI space), and which group have the higher fractional amplitude of low-frequency fluctuation (fALFF) values. If multiple local maxima existed in the same region, only the maximum with the highest F score is shown.

TABLE 2 | Brain regions with interaction effect between group and frequency.

Region	BA	size	*x*	*y*	*z*
Left cerebellum		1348	−21	−51	−45
Bilateral anterior cingulate	24,32	1947	−6	36	24
Left lingual gyrus	18	680	−36	−78	24
Right middle temporal gyrus	21	648	−35	−75	15
Left middle frontal gyrus	46	264	−54	18	36

We list significant clusters of interaction effect between group and frequency. Shown are the Brodmann Area, the size of the cluster, the coordinates of the local maxima (in MNI space). If multiple local maxima existed in the same region, only the maximum with the highest F score is shown.

In the present study, a negative correlation between the fALFF values in cerebellum and the severity of IGD was observed (see **Figure 2C**), which also supports that the abnormal spontaneous neuronal activity in cerebellum is related with the inappropriate behavior of IGD.

The fALFF values were higher in superior temporal gyrus in IGD. Previous study showed that the IGD, compared to HC, showed decreased functional connectivity in the temporal area (Ding et al., 2013). Our previous study found decreased ReHo in the inferior temporal gyrus, and we infer it might be the results of a long duration of game playing (Dong et al., 2012c). The current findings are partially inconsistent with previous study, so we bring forward the hypothesis that increased fALFF in superior temporal gyrus may reflect higher level of brain activity correlating with the flexibility of movement in IGD, but the function of this area need further study.

Frequency Dependent Amplitude Changes in IGD

The interaction effects between groups and frequency bands were observed in the cerebellum, the anterior cingulate gyrus, the lingual gyrus, the middle temporal gyrus, and the middle frontal gyrus.

Higher fALFF Values in Middle Frontal Gyrus in IGD

In the present study, the IGD participants showed higher fALFF values in left middle frontal gyrus at different bands. The middle frontal gyrus plays an important role in coordinate different systems, such as learning and memory, which is strongly related to mental operations (Cardinal, 2006). In a previous study, we concluded that IGD subjects show enhanced synchronization in sensory-motor coordination related brain regions (Van Rooij et al., 2011) – the online game playing requires players to integrate several systems, including the sensory system, motor control, motor coordinate, and information processing system (Ito, 2006). The current findings also support this assumption. This result is also consistent with Liu's study (Liu et al., 2010), which found that subjects with IGD showed a significant increase in ReHo values in left middle frontal gyrus. So we draw the conclusion that the IGD participants showed higher fALFF values in left middle frontal gyrus, which might associate with the enhanced sensory-motor coordinate ability.

The Abnormality in Anterior Cingulate Gyrus in IGD

We found lower fALFF in anterior cingulate Gyrus at slow-6. The anterior cingulate region has been implicated in inhibition, controlling, and conflict monitoring (Paus, 2001; Goldstein et al., 2007) and the abnormalities have been mentioned in previous IGD studies (Liu et al., 2010; Moulton et al., 2013). As mentioned in introduction, the lower fALFF values may relate to decreased coordinating capability of long-distance neural activity. This assumption is supported by studies in this field: with a functional connectivity approach. Hong et al. (2013) reported reduced functional connectivity between ACC and PFC in IAD. Jiang et al. (2011) have proposed that the lower activities in the ACC may reflect the abnormal decreased spontaneous neuronal activity in this region and a functional deficit. Other task related studies have proved this point that the IGD always accompanied with cognitive dysfunctions, such as cognitive function deficiency (Dong et al., 2010, 2011b). So we believe the abnormality in ACC is related to the cognitive dysfunctions of IGD.

Reverse Pattern in Cerebellum and the Lingual Gyrus at Different Bands in IGD

It is important to note that the abnormalities of spontaneous neural activity in the IGD are dependent on specific frequency bands, especially in the cerebellum and the lingual gyrus. Comparing with the HC, the IGD showed decreased amplitude in the lower frequency bands (slow-4, slow-5, slow-6) and increased amplitude in the higher frequency bands (slow-2, slow-3) in the lingual gyrus. On the contrary, the IGD showed increased amplitude in the lower frequency bands (slow-6) and decreased amplitude in the higher bands (slow-2, slow-3, slow-4) in the cerebellum (**Figures 2A,B**). It has been revealed that different oscillatory bands are developed by different mechanisms and have different physiological functions (Bullock, 1997; Yuan et al., 2013). As previous studies have proved that the lower frequency fluctuations possess higher magnitude power and the higher frequency fluctuations have lower magnitude power (Baria et al., 2011; Yuan et al., 2013). The current findings might suggest that the IGD have increased coordinating capability of long-distance neural activity in the cerebellum and in the lingual gyrus. This assumption can be supported by previous study which reported that subjects with IGD exhibited increased functional connectivity in the bilateral cerebellum (Liu et al., 2010; Ko, 2014), and another study have detected gray matter density deficits in lingual gyrus which may relate to long-distance neural activity (Weng et al., 2013).

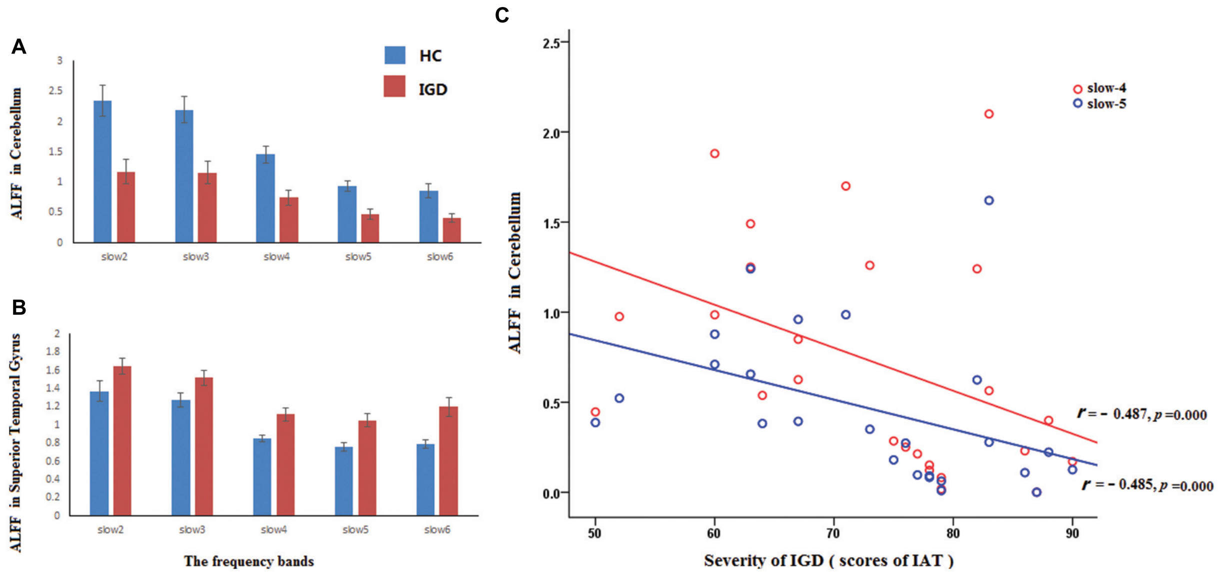

FIGURE 2 | The ALFF values in superior temporal gyrus and the cerebellum. The red and blue rectangle represented IGD subjects and healthy controls, respectively. The full frequency band (0–0.25 Hz) was divided into five bands. They were displayed in **(A,B)** [slow-6 (0–0.01 Hz), slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz), and slow-2 (0.198–0.25 Hz)]. **(C)** Reveled the ROI-based correlation between the severity of IGD and the ALFF values in the cerebellum, the red and blue line represented frequency slow-4 and slow-5, respectively.

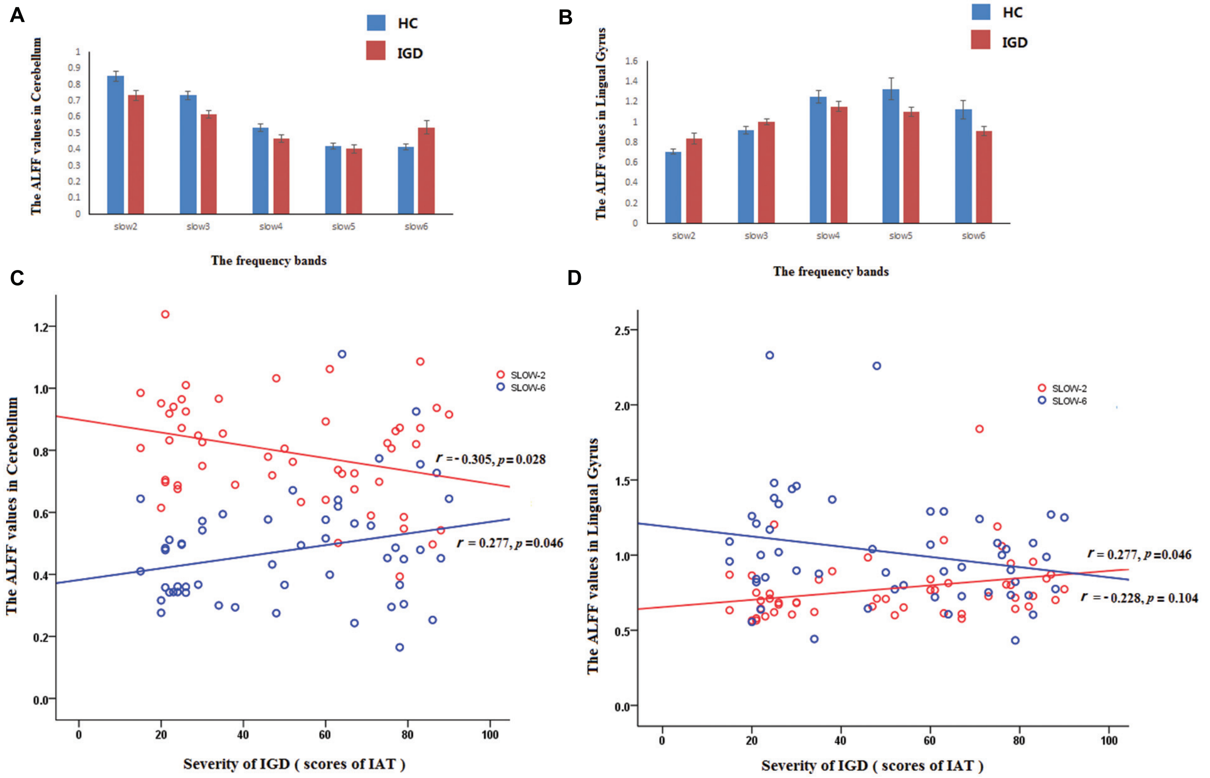

FIGURE 3 | Reverse pattern in cerebellum and the lingual gyrus at different bands in IGD. The red and blue rectangle represented IGD subjects and healthy controls, respectively. The full frequency band (0–0.25 Hz) was divided into five bands. They were displayed in **(A,B)** [slow-6 (0–0.01 Hz), slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz), and slow-2 (0.198–0.25 Hz)]. **(C)** revealed the reversed correlation between the fALFF of the cerebellum and the severity of IGD for different frequency (slow-2: $r = -0.305$, $p = 0.028$; slow-6: $r = 0.277$, $p = 0.046$), **(D)** revealed the reversed correlation between the fALFF of the lingual cyrus and the severity of IGD for different frequency (slow-2: $r = 0.277$, $p = 0.016$; slow-6: $r = -0.228$, $p = 0.104$).

Conclusion

The findings in the present study suggested that the IGD subjects showed abnormal fALFF in many brain regions, including the cerebellum (IGD < HC) and the superior temporal gyrus (IGD > HC). The present study can help to understand the pathophysiology of IGD and the full frequency amplitude analysis may potentially help to select specific frequency range for detecting IGD-related brain activities.

Author Contributions

XL analyzed the data, wrote the first draft of the manuscript; XJ contributed to data analyze, Y-FZ contributed to the guidance of Experimental methods, and improved the manuscript. GD designed this research, revised and improved the manuscript. All authors contributed to and have approved the final manuscript.

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Brain Activity toward Gaming-Related Cues in Internet Gaming Disorder during an Addiction Stroop Task

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Background and Aims: Attentional bias for drug-related stimuli is a key characteristic for drug addiction. Characterizing the relationship between attentional bias and brain reactivity to Internet gaming-related stimuli may help in identifying the neural substrates that critical to Internet gaming disorder (IGD).

Methods: 19 IGD and 21 healthy control (HC) subjects were scanned with functional magnetic resonance imaging while they were performing an addiction Stroop task.

Results: Compared with HC group, IGD subjects showed higher activations when facing Internet gaming-related stimuli in regions including the inferior parietal lobule, the middle occipital gyrus and the dorsolateral prefrontal cortex. These brain areas were thought to be involved in selective attention, visual processing, working memory and cognitive control.

Discussion and Conclusions: The results demonstrated that compared with HC group, IGD subjects show impairment in both visual and cognitive control ability while dealing with gaming-related words. This finding might be helpful in understanding the underlying neural basis of IGD.

Keywords: fMRI, internet gaming disorder, stroop, attentional bias

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INTRODUCTION

Internet gaming disorder (IGD) is rapidly becoming a prevalent mental health concern around the world over the last few decades (Dong et al., 2011). People often define IGD as an excessive or uncontrolled use of the internet-game followed by negative consequences (Beard and Wolf, 2001; Grant et al., 2010). IGD is also conceptualized as a "behavioral addiction" as its proposed diagnostic criteria are so closely parallel to substance use disorders and pathological gambling (Thaler and Shefrin, 1981; Targhetta et al., 2013; Thorens et al., 2014). Apart from considering substance-use and addictive disorders, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorder (DSM-5) has generated criteria for IGD in the Section Results containing disorders warranting additional study in 2013 (Petry and O'Brien, 2013; Dong et al., 2015).

Researches have demonstrated that attentional bias is the key characteristic for addiction, which contributes to people's motivation to take addictive substance. Various theories of addiction have argued that addictive behaviors are characterized by attentional bias for substance-related stimuli (Noël et al., 2005; Fields, 2008). Moreover, measuring attentional bias toward substance-related cues may be a valid method to identify people with heightened relapse vulnerability (Schouw et al., 2013). A wealth of researchers from the past two decades have found attentional bias for substance-related stimuli (presented verbally, pictorially, or as *in vivo* exposure) in users of alcohol and a variety of other substances, including nicotine, cannabis, opiates, and cocaine (Thaler and Shefrin, 1981; Koob and Volkow, 2010). For example, smokers show longer RT in naming smoking-related words than non-smokers. Therefore, the smokers exhibited more attentional bias for smoking-related words compared with the non-smokers (Fields, 2008). The similar features have also been observed in pathological gamblers (Kertzman et al., 2006), a type of behavioral addiction. As behavioral addiction, similar results have been found that the reaction time in IGD subjects is longer than that of HC group, which means that an attentional bias in IGD subject and the attentional bias in IGD subjects can be used to identify addiction (Metcalf and Pammer, 2011).

Although no chemical or substance intake is involved in IGD, excessive use of internet games can also lead to physical dependence, eventually causing psychological, social, or work difficulties, similar to other addictions (Griffiths, 2000; Holden, 2001; Murali and George, 2007). The IGD is currently positioned in the appendix of the DSM-V as a condition requiring further study and positioned as a behavioral addiction (Kaptsis et al., 2016; Király et al., 2015). As a behavioral addiction, IGD may share similar neuropsychological (i.e., development of euphoria, craving, and tolerance) characteristics with other behavioral addictions (Dong et al., 2010, 2011, 2013a,b). Considering the similarities in symptoms, the present study is set to explore whether behavioral aspects in IGD are commonly related to those found in substance-dependent persons and pathological gambler.

We used the addiction Stroop task in our study. It is a modified version of the classical Stroop task and a most widely used test of substance-related attentional bias (Cox et al., 2006). The goal of this study was to explore the relation between the attentional bias toward gaming-related stimuli and brain activation to gaming-related cues. In this task, attentional bias is inferred if participants' performance on a primary task (e.g., color-naming) is impaired when substance-related stimuli (e.g., gaming-related words) are presented simultaneously. It is indexed as the difference between mean color-naming response time (RT) on trials with substance-related and RT with neutral ones. It is supposed that longer RT to the substance-related words indicates the automatic processing of the semantic contents of the words and impair the color naming, or results from the attempts to avoid elaborative processing of substance-related words (Thaler and Shefrin, 1981; Cox et al., 2006).

Except behavioral evidences, researchers have also investigated the neurobiological underpinnings of disorders. Functional magnetic resonance image (fMRI) studies have identified that a number of brain regions are associated with addictive substance-related stimuli (Schouw et al., 2013; Yuan et al., 2014; Yang et al., 2015). For example, previous studies have found altered default network in brain regions, namely inferior parietal lobule, middle frontal gyrus, middle temporal, cingulate gyrus (Lin et al., 2012; Ding et al., 2013; Kim et al., 2015). Beside, studies using voxel-based morphometry (VBM) technique have demonstrated multiple structural changes of brain in internet gaming disorder (IAD) and IGD subjects, such as the bilateral dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC), middle temporal gyrus, insula and anterior cingulate (Yuan et al., 2011; Lin et al., 2015). Although recent studies have found the relation between the attentional bias and increased reactivity in the prefrontal cortex (Luijten et al., 2011; Ko et al., 2013), insula, the anterior cingulate cortex (Janes et al., 2010), the parietal gyrus and the temporal gyrus (Luijten et al., 2011), it still remains unknown whether these brain activation patterns are affected by attentional bias toward gaming-related words. Accordingly, in this study, we calculated the correlation between behavioral performance during the addiction Stroop task and the brain activation to gaming-related words vs. neutral words to find the potential relations between them.

IGD subjects with experience of playing online games would show automatic reaction toward gaming-related stimuli (Fields, 2008; Ko et al., 2015). Thus, they need to engage more cognitive resource in focusing their attention on the color rather than semantics of the gaming-related words to complete the task (coloring naming task). Therefore, we hypothesized that the IGD subjects would display different brain activities in regions responsible for enhanced efficiency of cognitive control, such as greater activation in the DLPFC (Ko et al., 2013).

METHODS

Participants

Participants were university students and were recruited through advertisements. Participants were right-handed males and had no difficulty in naming color (19 IGD subjects, 21 healthy controls (HCs)). The IGD subjects and HC group did not significantly differ in age [IGD: 22.2 ± 3.1 years; HC: 22.8 ± 2.4 years; $t_{(38)} = 0.694$, $p > 0.05$]. Only males were included due to higher IGD prevalence in men than that of women (Siomos et al., 2008; Gentile et al., 2011; Kamal and Mosallem, 2013; Adiele and Olatokun, 2014; Baggio et al., 2015). Defense of the Ancients (Dota) is mod built on the Real-Time-Strategy (RTS) games Warcraft III and is one of the most popular online games (Loh and Soon, 2006). And, the IGD subjects all reported to play the Internet game named "Dota." The IGD and HC participants did not meet DSM-V criteria for abuse of or dependence on substances, including alcohol and nicotine. All participants were medication free and were instructed not to use any substances of abuse, including coffee, on the day of scanning. Besides, all participants underwent structured psychiatric interviews (Lecrubier et al., 1997) performed by an experienced psychiatrist and all participants were free of active substance abuse, neuropsychiatric disorder and Axis I psychiatric disorder.

IGD participants met both Chinese IAT requirements: (1) spend more than 6 h online everyday aside from work, and (2) show symptoms such as psychological dependence, abstinent

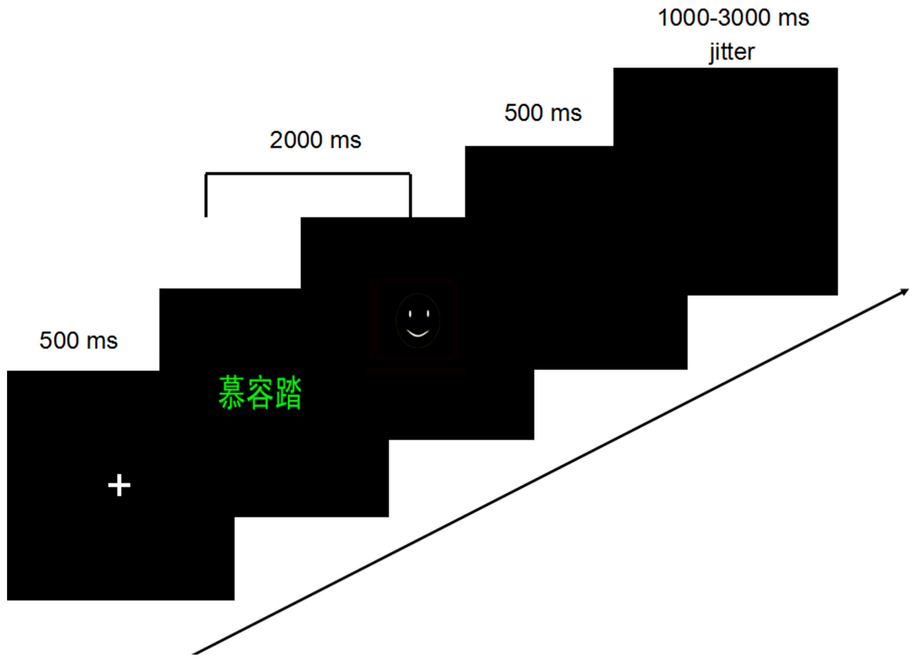

FIGURE 1 | The procedure of addiction Stroop task in present study.

reaction, compulsive use, social withdrawal, or negative effect on body and mental health for more than 3 months. All IGD participants spent most of their time online playing internet games. HCs all scored lower than 30 on Young's IAT (mean = 28.5, *SD* = 12.0) and did not satisfy either of the Chinese IAT requirements, while the IAT scoring all over 60 ((mean = 64.4, *SD* = 10.3). And the scores in IGD subjects were significant higher than HC group (*t* = -8.944, *p*=0.000).

Measures

The selection of IGD was based on Young's online internet addiction test (IAT) (Polezzi et al., 2008; Grant et al., 2010) scores of 50 or higher and at the same time, reach the criteria of the proposed 9-items IGD diagnostic scale based on DSM-V (Petry and O'Brien, 2013; Dong et al., 2015; Greenhow et al., 2015). Young's IAT consists of 20 items associated with online internet use including psychological dependence, compulsive use, withdrawal, related problems in school or work, sleep, family or time management. The IAT was proved to be a valid and reliable instrument that can be used to classify IAD (Widyanto and McMurran, 2004; Widyanto et al., 2011). For each item, a 5-point rating scale would appear on the screen and participants needed to choose from 1 to 5 (1 rarely, 5 always). Scores over 50 indicate occasional or frequent internet-related problems and scores over 80 mean "Your internet usage is causing significant problems in your life") (www.netaddiction.com). To classify IGD, individuals with IAD also needed to respond positively to the following question: "you spend most of your online time playing online games (>80%) (Yes)."

Procedure

An addiction Stroop task was administered. Two kinds of words (see in the supplementary document), including 30 internet gaming-related and 30 matched control words (matched in terms of semantic properties that affect reading speed, including word length, number of syllables per word), were presented randomly in red, green and yellow. Moreover, to control the familiarity of the words between the two groups, before the study, the familiarity of words have been evaluated among people who have played the game "dota" and who never have played (they all did not participant in this study). So the familiarity of gaming-related words and neutral ones which used in this study has no difference. In present study, the gaming-related words were common names of different categories, such as weapons, characters and tips in Dota. And the neutral words were selected from names of common tools, supplies etc., which are matched with the categories of gaming-related words. On each trial, a single word will appear in one font color (red, yellow, or green), and the participant will be instructed to name the color as quickly and accurately as possible using three buttons (i.e., green = thumb, red = index finger, yellow = middle finger) of a three-button response box (invivocorp.com/). The task was composed of 120 trials where the gaming-related words and neutral words with certain font color appeared randomly (Supplementary Material 1). Each word appeared twice and the same words or the words with same color did appear continuously. In each trial (see **Figure 1**), the stimuli were presented which would disappear once the participants pressed the button, after presenting a cross in the center of the screen as fixation point for 500 ms. Besides, the RT of the stimuli plus the duration of a followed black

TABLE 1 | Behavioral results of the Stroop task.

		RT (ms)		Accuracy rate	
		Neutral	Gaming-related	Neutral	Gaming-related
HC	*M*	622.038	642.040	0.978	0.986
	SD	119.850	113.997	0.024	0.027
IGD	*M*	579.301	590.622	0.975	0.984
	SD	101.600	105.421	0.041	0.027

M, arithmetic mean; SD, standard deviation; HC, healthy control group; IGD, internet gaming disorder.

screen are totally 2000 ms. Then a feedback would appear for 500 ms, the right response coming up with a smile face and a wrong one with a cry face. A black screen was presented for a random interval of 1000–3000 ms (average 2000 ms) between trials. Stimuli were presented and behavioral data were collected using E-prime software (Psychology Software Tool, Pittsburgh, PA.). A guaranteed 20 Yuan (about 3 dollars) would be given to participants.

Statistical Analysis

Image Acquisition and Pre-Processing

Structural images covering the whole brain were acquired with a T1-weighted three-dimensional spoiled gradient-recalled sequence (176 slices, $TR = 1700$ ms, $TE = 3.93$ ms, slice thickness = 1.0 mm, skip = 0 mm, flip angle = 15°, inversion time 1100 ms, field of view = 240×240 mm^2, in-plane resolution = 256×256). Functional MRI was performed on a 3 T scanner (Siemens Trio) with a gradient-echo EPI T2 sensitive pulse sequence in 33 slices (interleaved sequence, 3 mm thickness, $TR = 2000$ ms, flip angle 90°, field of view 220×220 mm^2, matrix 64×64). Participants were instructed to view the stimuli, which were presented on a screen in the head coil, through Invivo synchronous system (Invivo Company, www.invivocorp.com/).

Imaging analysis was conducted using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Images were slice-timed, reoriented, and realigned to the first volume. T1-co-registered volumes were then normalized to an SPM T1 template resulting in an isometric voxel size of $3 \times 3 \times 3$ mm^3 voxels. Finally, images were smoothed with a 6 mm full-width at half maximum Gaussian kernel.

Data Analysis

Response time and accuracy rate were computed with analysis of variance (ANOVAs) in two-by-two mixed ANOVAs separately, with group as a between-subject factor (IGD subjects; HC group) and word type as a within-subject variable (gaming-related words, neutral words). Besides, we also analyzed the attention bias (defined as the mean RT of the gaming-related words minus those of the neutral ones) between the two groups with an independent sample *t*-test.

For the fMRI data, pre-processed images were entered into a standard multiple regression (ordinary least squares) in NeuroElf (neuroelf.net), which included regresses for the conditions of interest. First, we examined the brain activation related to the main effect of group and words type separately. Then to assess the interaction effects, one-sample *t*-test was computed for the ((IGD Substance-related words - IGD Neutral words) - (HC Substance-related words - HC Neutral words)) contrast. For this contrast, we first identified clusters of contiguously significant voxels at an uncorrected threshold $p < 0.05$. Then we tested these clusters for cluster-level FWE (family wise error) correction $p < 0.05$ and the AlphaSim estimation indicated that clusters with 102 contiguous voxels would achieve an effective FWE threshold $p <$ 0.05. Besides, we extracted the BOLD signal within each cluster that demonstrated between-group differences (for each ROI, a representative BOLD beta value was obtained by averaging the signal of all the voxels within the ROI) and entered these data for the IGD subjects into correlation analysis with attentional bias (defined as the mean RT of the gaming-related words minus those of the neutral ones).

Ethics

All participants provided written informed consent. The experiment conformed to The Code of Ethics of the World Medical Association (Declaration of Helsinki). The Human Investigations Committee of Zhejiang Normal University approved this research.

RESULTS

Behavioral Performance

Error trials (in each participant: mean = 2.54, $SD = 2.93$) were excluded from the further analysis. To reduce the influence of outliers, 0.83% trials (mean = 1.00, $SD = 1.92$; the RT less than 300 ms or more than 1400 ms) were removed in order to eliminate anticipatory responses with no response or pressing by mistaken. And the number of trials excluded has no significant difference between the two groups (F=2.634, p=0.224).

Firstly, RT and accuracy rate were conducted with two factors repeated measures ANOVAs separately (see **Table 1**). The words type (gaming-related words vs. neural words) was a within-subject variable and group (IGD subjects vs. HC group) was a between-subject variable. For RT, this analysis revealed a main effect of the word [$F_{(1,\ 38)}$=4.558, p=0.039] with the mean RT of gaming-related words being shorter, compared with neutral ones for all participants together. The interaction effect was not significant [$F_{(1,\ 38)}$=0.432, $p = 0.515$]. Although IGD subjects showed longer RT than the HC group, it did not reach statistical significance [$F_{(1,\ 38)}$=1.527, p=0.224]. For accuracy rate, no main effects or interaction effect [$F_{(1,\ 38)}$=0.005, p=0.945] were found. The IGD and HC group did not significantly differ on accuracy

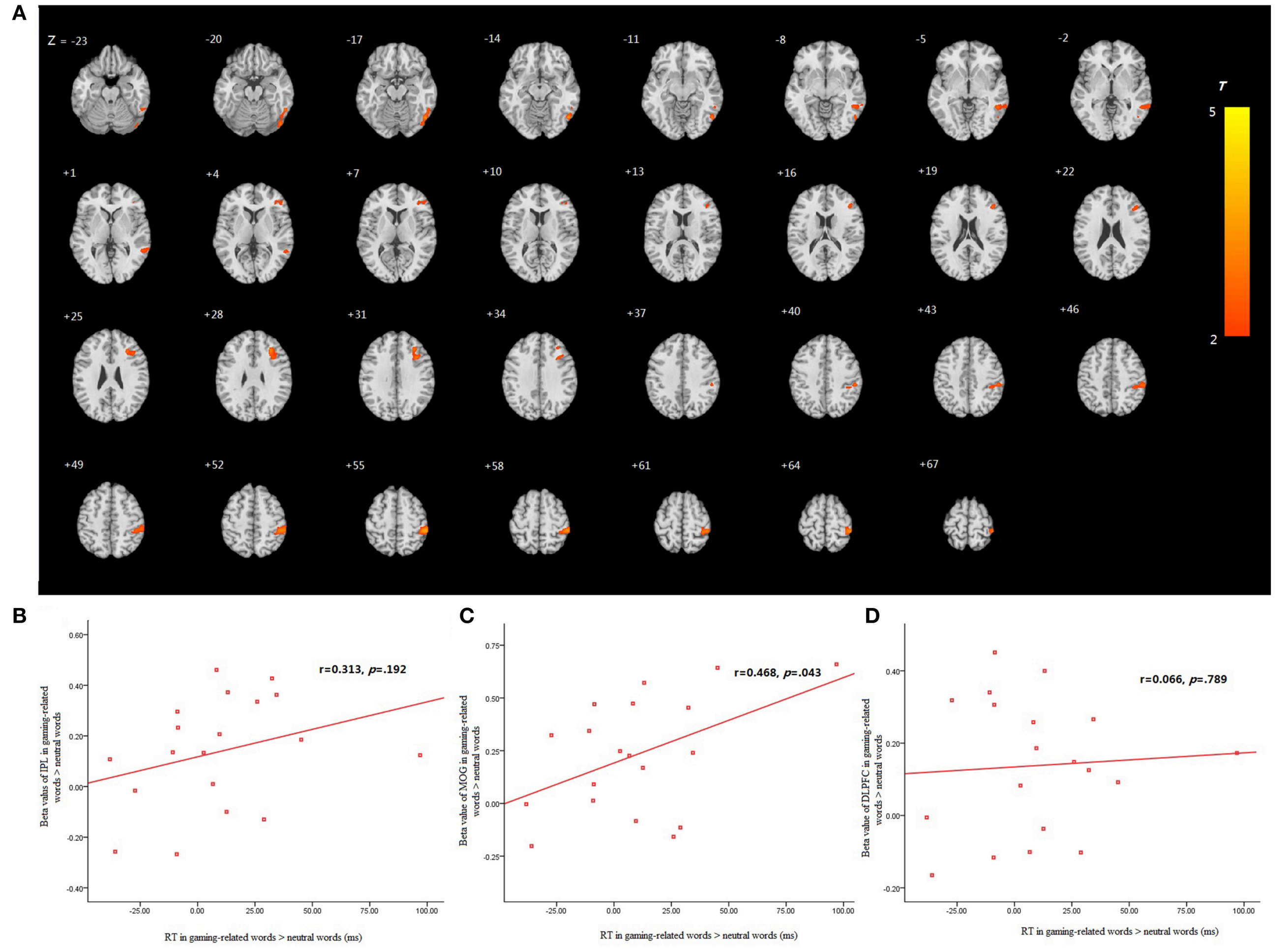

FIGURE 2 | Brain regions showing significant activation in the comparison of ((IGD Substance-related words - IGD Neutral words) - (HC Substance-related words - HC Neutral words)). Voxels size = $3 \times 3 \times 3\,\text{mm}^3$, $p < 0.05$ FWE (family wise error) corrected. **(A)** IGD subjects show increased activation in inferior parietal lobule, middle occipital gyrus and dorsolateral prefrontal cortex (DLPFC) than HC group in trials involved in gaming-related words minus neutral ones. **(B)** Correlation between RT (attentional bias: the mean RT of gaming-related words minus those of the neutral ones) and peak inferior parietal lobule activation among IGD subjects. **(C)** Correlation between RT (attentional bias: the mean RT of gaming-related words minus those of the neutral ones) and peak middle occipital gyrus activation among IGD subjects. **(D)** Correlation between RT (attentional bias: the mean RT of gaming-related words minus those of the neutral ones) and peak DLPFC activation among IGD subjects.

rate [$F_{(1,\ 38)}$=0.143, p=0.708]. And the accuracy rate for gaming-relate words and the neutral one showed no significant difference [$F_{(1,\ 38)}$=2.718, p=0.107]. In addition, to compare the attention bias between these two groups, an independent sample t-test was performed. The results revealed that the IGD subjects showed more obvious attentional bias than the HC group, although it did not reach statistical significant [$F_{(1,\ 38)}$=2.352, p=0.133].

Imaging Data

First, we found the fMRI signals in the left and right postcentral gyrus (Brodmann's areas (BAs) 2/3) and left temporal gyrus (BA 37) were significantly decreased for IGD subjects compared with HC group. We next determined the main effect of word type in brain regions in inferior frontal gyrus (BA 45) and the right pre-central gyrus (BA 6), with significant increased activation in gaming-related words than neutral words.

The blood oxygen level-dependent (BOLD) data for attention bias demonstrated significant between-group differences. Greater BOLD signals were found in the inferior parietal lobule, middle occipital gyrus and DLPFC in the gaming-related words relative to the neutral words, when comparing the IGD subjects to the HC group during the addiction Stroop process ((IGD Substance-related words - IGD Neutral words) - (HC Substance-related words - HC Neutral words)) (**Figure 2A**; **Table 2**).

Correlation Analyses

We analyzed the correlation between brain activity and attention bias (defined as the mean RT of the gaming-related words minus those of the neutral ones) in IGD subjects. The correlation

TABLE 2 | Regional brain activation for the contrast of ((IGD Substance-related words - IGD Neutral words) - (HC Substance-related words - HC Neutral words)).

x, y, z[a]	Hemisphere	Peak intensity	Number of voxels[b]	Region[c]	Brodmann's area
51, -36, 54	R	3.661	178	Inferior Parietal Lobule	40
51, -66, -15	R	3.473	135	Middle Occipital Gyrus	19
30, 30, 27	R	3.209	120	Dorsolateral Prefrontal Cortex	9

[a] *Peak MNI coordinates.*

[b] *We first identified clusters of contiguously significant voxels at an uncorrected threshold $p < 0.05$, as also used for display purposes in the figures. We then tested these clusters for cluster-level FWE correction $p < 0.05$ and the AlphaSim estimation indicated that clusters with 90 contiguous voxels would achieve an effective FWE threshold $p < 0.05$. Voxel size = $3 \times 3 \times 3mm^3$.*

[c] *The brain regions were referenced to the software Xjview (http://www.alivelearn.net/xjview8) and double checked with atlas.*

between attentional bias and brain activity in the inferior parietal lobule among IGD subjects is 0.313 (p=0.192) (**Figure 2B**). The correlation between attentional bias and brain activity in the middle occipital gyrus among IGD subjects is 0.468 (p=0.043) (**Figure 2C**). The correlation between attentional bias and brain activity in the DLPFC among IGD subjects is 0.066 (p=0.789) (**Figure 2D**).

DISCUSSION

In behavioral performance, consistent with previous studies which have demonstrated that attentional bias toward substance-related words across different types of addictions, such as alcohol use, smoking and gambling (Janes et al., 2010; Marhe et al., 2013), the present study revealed that participants' responses for gaming-related words were significantly longer than that of neutral words. It suggested that heightened gaming-related salience could result in undesired distraction and cognitive interference caused by the word content, rendering them slower to respond. However, since the accuracy rates were all over 90% among all the participants in present study, it is hard to claim whether the cognitive interference caused by executive control the positive feedback of the executive control. Besides, inconsistent with previous, IGD group did not show statistical difference on RT compared with HC group. Though, we have tried our best to control the familiarity of the gaming-related words and neutral ones between the two groups, this may be an important fact could affect the un-significant result. The online gaming represents a great deal of diversity in regards to the types of games played (Chen et al., 2008). Researches have proved that the attentional bias related to gaming-related stimuli may vary across subjects depending on their preferences and frequency of playing a particular game (Peters and Malesky, 2008). And the majority of previous studies, which have demonstrated an attentional bias in related addiction, have used generalized addiction-related stimuli but failed to find any special impact of personalized stimuli in the influence of generalized alcohol-related stimuli (Fridrici et al., 2013). Thus, the un-significant attentional bias in behavioral in IGD subjects may result from the familiarity on the material among the participants. In addition, previous researchers have demonstrated that frequent gaming may contribute to improvement of performance on tasks related to visual, selective attentional abilities and motor skills (Green and Bavelier, 2003; Boot et al., 2008), in which participants have to response as fast as possible. In present study people should press the corresponding button as fast as possible. Thus, another explanation may be that the accelerated reaction can weaken attentional bias toward gaming-related words, resulting in less significant difference between RT in gaming-related words and neutral ones.

Although we observed the un-significant behavioral results, however, in neuroimaging results, this study revealed several important findings that could deepen our understanding about the neural activities in IGD. We observed greater brain activation in IGD subjects relative to the HC group in the inferior parietal lobule, the middle occipital gyrus and the DLPFC during the addiction Stroop task. Our findings are in accordance with researchers using other addicted groups such as substance addiction and pathological gambling (Dannon et al., 2011; DeVito et al., 2012). Current theories of the inferior parietal lobule function suggest that the activation is involved in sustained attention to an important stimulus feature in the face of more salient and misleading stimulus features (Hassabis et al., 2007; Lutz and Widmer, 2014). A number of studies have demonstrated that parietal regions are activated during attention shifts when attention is reflexively drawn to prominent features of a stimulus (Chelazzi and Corbetta, 2000) and have been implicated in word reading (Vossel et al., 2006). In present study the participants had to perform a simple cognitive task (color-naming task) while salient but distracting information (gaming-related words) in the environment. Therefore, present finding (IGD subjects show higher brain activation in inferior parietal lobule) might suggest that the IGD subjects experienced more cognitive conflicts and need more (top-down) attentions during the addiction Stroop task (Peterson et al., 1999; Mitchell, 2005).

The DLPFC was demonstrated to be mainly related to cognitive control processing (MacDonald et al., 2000; Milham et al., 2003), word reading/production (Carpenter et al., 2000) and working memory (Ainslie, 1975; Odum et al., 2000; Alliance, 2013; Augustus Diggs et al., 2013). It has also implicated in response inhibition/interference (Casey et al., 1997; Pujol et al., 2001). Cognitive control and working memory capacity are critical in determining performance on the Stroop task (Grant et al., 1996), which affects attention (Lecrubier et al., 1997). Therefore, the higher activation in the DLPFC in IGD is in accordance with our hypothesis that the IGD subjects have to employ more cognitive resources in controlling their automatic response toward the semantic content of the words. In other words, the IGD subjects should engage extra endeavor to control their attention from gaming-related words to accomplish the primary task (color-naming) well due to their uncontrolled desire for recognizing the semantic of the words, which resulting from long-term experience of playing games online.

A significant positive correlation was found between attentional bias and activation of middle occipital gyrus in IGD subjects, which suggested that the more endeavors were engaged toward gaming-related words, the higher the brain activities in middle occipital gyrus. The occipital activity may be associated with word reading and visual attention processes (Tang et al., 2006). And it is demonstrated that the performance of the Stroop color-word task depends on three major processes including word reading, color naming and interference resolution (Adleman et al., 2002). Therefore, the activation of middle occipital gyrus might suggest the gaming-related words have attracted IGD subjects' attention during the addiction Stroop task. More importantly, occipital and parietal brain regions are thought to be critical in visual functions (Hu et al., 2013). The occipital gyrus is involved in visual process (Tam et al., 2008; Kojima and Suzuki, 2010; Dong et al., 2012). The parietal lobe also plays a role in visual attention (Yin, 1978; Yin and Mountcastle, 1978). As for the features of IGD, the activation in visual related regions might be altered by the experience of long-time game playing.

CONCLUSIONS

In summary, the current study shows that the gaming-related words are more interference to IGD subjects and they need to engage more endeavors to perform better for their attentions paid to the semantic rather than the color of the gaming-related words during the addiction Stroop task. More importantly, present study reveals that several abnormalities of brain regions might be implicated in underlying the pathophysiology of IGD in terms of neural results.

AUTHOR CONTRIBUTIONS

YZ programmed the experiment, analyzed the data, and wrote the first draft of the manuscript; XL and HZ contributed to data collection, and XL, JX revised and improved the manuscript. GD designed this research, revised and improved the manuscript. XD contributed to fMRI data collection. All authors contributed to and have approved the final manuscript.

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REVIEW
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Intense, Passionate, Romantic Love: A Natural Addiction? How the Fields That Investigate Romance and Substance Abuse Can Inform Each Other

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Individuals in the early stage of intense romantic love show many symptoms of substance and non-substance or behavioral addictions, including euphoria, craving, tolerance, emotional and physical dependence, withdrawal and relapse. We have proposed that romantic love is a natural (and often positive) addiction that evolved from mammalian antecedents by 4 million years ago as a survival mechanism to encourage hominin pair-bonding and reproduction, seen cross-culturally today in Homo sapiens. Brain scanning studies using functional magnetic resonance imaging support this view: feelings of intense romantic love engage regions of the brain's "reward system," specifically dopamine-rich regions, including the ventral tegmental area, also activated during drug and/or behavioral addiction. Thus, because the experience of romantic love shares reward pathways with a range of substance and behavioral addictions, it may influence the drug and/or behavioral addiction response. Indeed, a study of overnight abstinent smokers has shown that feelings of intense romantic love attenuate brain activity associated with cigarette cue-reactivity. Could socially rewarding experiences be therapeutic for drug and/or behavioral addictions? We suggest that "self expanding" experiences like romance and expanding one's knowledge, experience and self-perception, may also affect drug and/or behavioral addiction behaviors. Further, because feelings of romantic love can progress into feelings of calm attachment, and because attachment engages more plastic forebrain regions, there is a rationale for therapies that may help substance and/or behavioral addiction by promoting activation of these forebrain systems through long-term, calm, positive attachments to others, including group therapies. Addiction is considered a negative (harmful) disorder that appears in a population subset; while romantic love is often a positive (as well as negative) state experienced by almost all humans. Thus, researchers have not categorized romantic love as a chemical or behavioral addiction. But by embracing data on romantic love, it's classification as an evolved, natural, often positive but also powerfully negative addiction, and its neural similarity to many substance and non-substance addictive states, clinicians may develop more effective therapeutic approaches to alleviate a range of the addictions, including heartbreak–an almost universal human experience that can trigger stalking, clinical depression, suicide, homicide, and other crimes of passion.

Keywords: romantic love, addiction, ventral tegmental area, caudate

INTRODUCTION

We propose that romantic love is a natural addiction (Frascella et al., 2010) that evolved from mammalian antecedents (Fisher et al., 2006). Brain scanning studies show that feelings of intense romantic love engage regions of the brain's "reward system," specifically dopamine pathways associated with energy, focus, learning, motivation, ecstasy, and craving, including primary regions associated with substance addiction, such as the ventral tegmental area (VTA), caudate and accumbens (Breiter et al., 1997; Bartels and Zeki, 2000, 2004; Fisher et al., 2003, 2005, 2006, 2010; Aron et al., 2005; Ortigue et al., 2007; Acevedo et al., 2011; Xu et al., 2011). Several of these reward regions of the mesolimbic system associated with romantic love and substance addiction are also activated during non-substance or behavioral addiction, including viewing images of appealing food (Wang et al., 2004), shopping (Knutson et al., 2007), playing video games (Hoeft et al., 2008), and gambling (Breiter et al., 2001). Indeed, several researchers have taken the position that "addiction is a disease of the reward system" (Rosenberg and Feder, 2014). Moreover, men and women who are passionately in love and/or rejected in love show the basic symptoms of substance-related and gambling addiction listed in the Diagnostic and Statistical Manual of Mental Disorders-5, including craving, mood modification, tolerance, emotional and physical dependence and withdrawal. Relapse is also a common problem for those suffering with a substance and/or behavioral addiction, as well as among rejected lovers.

Because passionate romantic love is regularly associated with a suite of traits linked with all addictions, several psychologists have come to believe that romantic love can potentially become an addiction (Peele, 1975; Tennov, 1979; Hunter et al., 1981; Halpern, 1982; Schaef, 1989; Griffin-Shelley, 1991; Mellody et al., 1992). However, many define addiction as a pathological, problematic disorder (Reynaud et al., 2010); and because romantic love is a positive experience under many circumstances (i.e., not harmful), researchers remain hesitant to officially categorize romantic love as an addiction. But even when romantic love can't be regarded as harmful, it is associated with intense craving and can impel the lover to believe, say and do dangerous and inappropriate things.

All forms of substance abuse, including alcohol, opioids, cocaine, amphetamines, cannabis, and tobacco activate reward pathways (Breiter et al., 1997; Melis et al., 2005; Volkow et al., 2007; Frascella et al., 2010; Koob and Volkow, 2010; Diana, 2013), as do several of the behavioral addictions (see Cuzen and Stein, 2014); and several of these same reward pathways are also found to be activated among men and women who are happily in love, as well as those rejected in love (Bartels and Zeki, 2000, 2004; Fisher et al., 2003, 2010; Aron et al., 2005; Ortigue et al., 2007; Acevedo et al., 2011; Xu et al., 2011). So regardless of its official diagnostic classification, we propose that romantic love should be considered as an addiction (Fisher, 2004, 2016): a positive addiction when one's love is reciprocated, non-toxic and appropriate, and a negative addiction when one's feelings of romantic love are socially inappropriate, toxic, not reciprocated and/or formally rejected (Fisher, 2004; Frascella et al., 2010).

Romantic love may have evolved at the basal radiation of the hominin clade some 4.4 million years ago in conjunction with the evolution of serial social monogamy and clandestine adultery–hallmarks of the human reproductive strategy (Fisher, 1998, 2004, 2011, 2016). Its purpose may have been to motivate our forebears to focus their mating time and energy on a single partner at a time, thus initiating the formation of a pair-bond to rear their young together as a team (Fisher, 1992, 1998, 2004, 2011, 2016; Fisher et al., 2006; Fletcher et al., 2015). Thus, as products of human evolution, the neural systems for romantic love and mate attachment could be considered as survival systems among humans.

ADDICTION-LIKE BEHAVIORS IN EARLY STAGE, PASSIONATE LOVERS: EUPHORIA, OBSESSION, RISKY BEHAVIOR

Men and women in the early stage of intense passionate romantic love express many of the basic traits associated with all addiction (Tennov, 1979; Liebowitz, 1983; Hatfield and Sprecher, 1986; Harris, 1995; Lewis et al., 2000; Meloy and Fisher, 2005; American Psychiatric Association, 2013). Like all addicts, they focus on their beloved (salience); and they yearn for the beloved (craving). They feel a "rush" of exhilaration when seeing or thinking about him or her (euphoria/intoxication). As their relationship builds, the lover seeks to interact with the beloved more and more frequently (tolerance). If the beloved breaks off the relationship, the lover experiences the common signs of drug withdrawal, too, including protest, crying spells, lethargy, anxiety, insomnia, or hypersomnia, loss of appetite or binge eating, irritability and chronic loneliness. Like most addicts, rejected lovers also often go to extremes, even sometimes doing degrading or physically dangerous things to win back the beloved (Meloy, 1998; Lewis et al., 2000; Meloy and Fisher, 2005). Romantic partners are willing to sacrifice, even die for the other. Romantic jealousy is particularly dangerous and can lead to major crimes including homicide, and/or suicide. Lovers also relapse the way drug addicts do: long after the relationship is over, events, people, places, songs, and/or other external cues associated with their abandoning sweetheart can trigger memories and initiate renewed craving, obsessive thinking and/or compulsive calling, writing or showing up in hopes of rekindling the romance–despite what they suspect may lead to adverse consequences.

Passionate lovers also express strong sexual desire for the beloved; yet their yearning for emotional union tends to overshadow their craving for sexual union with him or her (Tennov, 1979). Most characteristic, the lover thinks obsessively about the beloved (intrusive thinking). Besotted lovers may also compulsively follow, incessantly call, write or unexpectedly appear, all in an effort to be with their beloved day and night (Tennov, 1979; Lewis et al., 2000; Meloy and Fisher, 2005). Paramount to this experience is intense motivation to win him or her. All these behaviors are common to those with substance addictions. However, not everyone exhibits these types of behaviors after a breakup, just as not everyone who uses a substance exhibits dependency and withdrawal effects (e.g., Shiffman, 1989; Shiffman et al., 1995; Shiffman and Paty, 2006; Haney, 2009).

THE BRAIN SYSTEMS ASSOCIATED WITH ROMANTIC LOVE

Neuroimaging studies of intense, passionate romantic love reveal the physiological underpinnings of this universal or near-universal human experience, and they all show activation of the VTA (Fisher et al., 2003, 2010; Bartels and Zeki, 2004; Aron et al., 2005; Ortigue et al., 2007; Zeki and Romaya, 2010; Acevedo et al., 2011; Xu et al., 2011). In our first experiment (Fisher et al., 2003; Aron et al., 2005), we used functional magnetic resonance imaging (fMRI) to study 10 women and 7 men who had recently fallen intensely and happily in love. All scored high on the Passionate Love Scale (Hatfield and Sprecher, 1986), a self-report questionnaire that measures the intensity of romantic feelings; all participants also reported that they spent more than 85% of their waking hours thinking of their beloved.

Participants alternately viewed a photograph of their sweetheart and a photograph of a familiar individual, interspersed with a distraction-attention task. Group activation occurred in several regions of the brain's reward system, including the VTA and caudate nucleus (Fisher et al., 2003; Aron et al., 2005), regions associated with pleasure, general arousal, focused attention and motivation to pursue and acquire rewards and mediated primarily by dopamine system activity (Delgado et al., 2000; Schultz, 2000; Elliott et al., 2003). These regions of the reward system are directly associated with addiction in many studies of drugs of abuse (Breiter et al., 1997; Panksepp et al., 2002; Melis et al., 2005; Volkow et al., 2007; Frascella et al., 2010; Koob and Volkow, 2010; Diana, 2013) and behavioral addictions (see Cuzen and Stein, 2014).

These data from several studies indicate that individuals who are happily in the early stages of passionate love express activity in neural regions associated with drug and some behavioral addictions.

There is also a difference between "wanting" and "liking/pleasure" suggested by Berridge et al. (2009). As in substance addiction, "wanting" the romantic partner is different from "liking" a pretty face and finding pleasure in a beautiful sight. We found that brain activation to an attractive face ("liking") was different from activation to the beloved partner ("wanting"): the former activated the left VTA, while the latter activated the right VTA (Aron et al., 2005). The result suggests the addictive aspects of romantic love are mediated through the right VTA, and that pleasure, or "liking" is different.

ADDICTION-LIKE BEHAVIORS ASSOCIATED WITH ROMANTIC REJECTION: CRAVING, RELAPSE AND DESTRUCTIVE BEHAVIOR

Cross-culturally, few men or women avoid suffering from romantic rejection at some point across their lives. In one American college community, 93% of both sexes queried reported that they had been spurned by someone whom they passionately loved; 95% reported they had rejected someone who was deeply in love with them (Baumeister et al., 1993). Romantic rejection can cause a profound sense of loss and negative affect (although this is not always the case e.g., Lewandowski and Bizzoco, 2007). Like many addictions, romantic rejection can also jeopardize one's health, because abandonment rage stresses the heart, raises blood pressure and suppresses the immune system (Dozier, 2002). It can also induce clinical depression, and in extreme cases lead to suicide and/or homicide. Some broken-hearted lovers even die from heart attacks or strokes caused by their depression (Rosenthal, 2002). The suite of negative phenomena associated with rejection in love, including protest, the stress response, frustration attraction, abandonment rage, and jealousy, in conjunction with craving and withdrawal symptoms, most likely also contribute to the high worldwide incidence of crimes of passion (see Meloy, 1998; Meloy and Fisher, 2005).

One pathology is also regularly associated with romantic love, stalking. There are two common types of stalkers: those who sustain pursuit of a former sexual/romantic intimate who has rejected them; and those who pursue a stranger or acquaintance who has failed to return the stalker's romantic overtures (Meloy and Fisher, 2005). In both cases, the stalker exhibits several of the characteristic components of all addictions, including focused attention on the love object, increased energy, following behaviors, and obsessive thinking about and impulsivity directed toward the victim, suggesting that stalking also activates aspects of the reward system in the brain (Meloy and Fisher, 2005) and may be akin to addiction. Another pathology, de Clerambault's syndrome, also known as erotomania, has not been associated with addiction. This syndrome is characterized by the patient's delusional notion that another person is madly in love with him or her; generally it is a young woman who believes that she is the love object of a man of higher social or professional standing. But because this syndrome has no direct association with reward system activity and may be a form of paranoid schizophrenia or other delusional disorder (Jordan and Howe, 1980; Kopelman et al., 2008) rather than addiction, discussion of this syndrome is beyond the scope of this paper.

It appears, however, as if evolution has overdone the negative response to romantic abandonment. But romantically rejected individuals have wasted precious courtship time and metabolic energy; they have lost essential economic and financial resources; their social alliances have been jeopardized; their daily rituals and habits have been altered; they may have lost property; and they have most likely experienced damage to their personal happiness, self-esteem and reputation (see Leary, 2001; Fisher, 2004). Most important, rejected lovers of reproductive age are likely to have lost breeding opportunities or a parenting partner for the offspring they have already produced—forms of reduced future genetic viability (Fisher, 2004). Thus, romantic rejection can have severe social, psychological, economic, and reproductive consequences.

ROMANTIC REJECTION ALSO ACTIVATES BRAIN REGIONS ASSOCIATED WITH DRUG CRAVING

To identify some of the neural systems associated with this natural craving state elicited by romantic rejection, we used fMRI to study 10 women and 5 men who had recently been rejected by a partner, but reported that they were still intensely "in love" (Fisher et al., 2010). The average length of time since the initial rejection and the participants' enrollment in the study was 63 days. All scored high on the Passionate Love Scale (Hatfield and Sprecher, 1986); all reported that they spent most of their waking hours thinking about the person who rejected them; and all yearned for their abandoning partner to return to the relationship.

Participants alternately viewed a photograph of their rejecting partner and a photograph of a familiar, emotionally neutral individual, interspersed with a distraction-attention task. Their responses while looking at their rejecter in the scanner included feelings of romantic passion, despair, joyous, and painful memories, rumination about why this had happened, and mental assessments of their gains and losses from the experience. Brain activations coupled with viewing the rejecter occurred in several regions of the brain's reward system. Included were: the VTA associated with feelings of intense romantic love; the ventral pallidum associated with feelings of attachment; the insular cortex and the anterior cingulate associated with physical pain and the distress associated with physical pain; and the nucleus accumbens and orbitofrontal/prefrontal cortex associated with assessing one's gains and losses, as well as craving and addiction (Fisher et al., 2010). Activity in several of these brain regions has been correlated with craving for cocaine and other drugs of abuse (Melis et al., 2005; Frascella et al., 2010; Koob and Volkow, 2010; Diana, 2013).

To understand the impact of right VTA activations associated with happy early stage relationships and romantic rejection, it is important to consider both "liking" (hedonic impact) and "wanting" (e.g., incentive salience) aspects of reward. That is, approach behavior and desired interaction with a person or a substance may or may not involve actual pleasurable experiences. In the context of addiction, it is often the case that a strong desire for the substance or a behavioral addiction, approach motivation and use, occurs even when the stimuli no longer provides a "high" and the reward-seeking behavior is associated with negative outcomes (e.g., the addiction is detrimental to the individual's health, career, social relationships etc.). Those who are rejected in love still "want" the ex-partner and experience approach motivation (e.g., desiring to contact the ex-partner) even when contact with the ex may be accompanied by negative outcomes and not pleasurable (e.g., experiences of sadness and pain). A distinction between hedonic impact and incentive salience has been explored in animal studies (Berridge et al., 2009). We also found that looking at the partners face activated the right VTA while left VTA activation correlated with the attractiveness of faces in the study (Aron et al., 2005).

ATTACHMENT

For those who stay in a relationship beyond the early stage, intense romantic phase, an important second constellation of feelings sets in, associated with attachment (Acevedo et al., 2011). In our studies of individuals who are happily in love (Fisher et al., 2003; Aron et al., 2005), we found that those in longer partnerships (8–17 months as opposed to 1–8 months) began to show activity in the ventral pallidum, associated with attachment in animal studies (Insel and Young, 2001), while continuing to show activity in the VTA and caudate nucleus associated with passionate romantic love. Thus, with time, feelings of attachment begin to accompany feelings of passionate romantic love (Fisher, 2004; Acevedo et al., 2011). Working in conjunction, these two basic neural systems for romantic love and attachment may constitute the biological foundation of human pair-bonding—and provide the context for the evolution of love addictions (Insel, 2003; Burkett and Young, 2012; Fisher, 2016).

EVOLUTION OF ROMANTIC LOVE AND ATTACHMENT

It has been proposed that the neural systems associated with feelings of intense romantic love and partner attachment evolved in conjunction with the evolution of the human predisposition for pair-bonding, serving as mechanisms to stimulate mate choice and motivating individuals to remain with a mate long enough to breed and rear their offspring through infancy as a team (Fisher, 2004, 2011, 2016; Fisher et al., 2006). This hypothesis suggests that the neural systems for romantic love and attachment are survival systems with evolutionary roots (Frascella et al., 2010).

Pair-bonding is a hallmark of humanity. Data from the Demographic Yearbooks of the United Nations on 97 societies canvassed in the 1980s indicate that approximately 93.1% of women and 91.8% of men in that decade married by age 49 (Fisher, 1989, 1992). Worldwide, marriage rates have declined since then; but today 85 to 90% of men and women in the United States are projected to marry (Cherlin, 2009). Cross-culturally, most individuals are monogamous; they form a sexual and socially sanctioned partnership with one person at a time. Polygyny (many females) is permitted in 84% of human societies; but in the vast majority of these cultures, only 5 to 10% of men actually have several wives simultaneously (Van den Berghe, 1979; Frayser, 1985). Moreover, because polygyny in humans is regularly associated with rank and wealth, monogamy (i.e., pair-bonding) may have been even more prevalent in the pre-horticultural, unstratified societies of our long human hunting-gathering past (Daly and Wilson, 1983), when the neural systems for intense early stage romantic love and partner attachment most likely evolved.

Data suggest that the human predisposition for pair-bonding (often preceded by romantic attraction) also has a biological basis. The investigation of human attachment began with Bowlby (1969, 1973) and Ainsworth et al. (1978) who proposed that, to promote the survival of the young, primates have evolved an innate attachment system designed to motivate infants to seek comfort and safety from their primary caregiver, generally the mother. Since these early studies, extensive research has been done on the behaviors, feelings and neural mechanisms associated with this attachment system in adult humans and other animals (Fraley and Shaver, 2000; Eisenberger et al., 2003; Panksepp, 2003a,b; Bartels and Zeki, 2004; MacDonald and Leary, 2005; Tucker et al., 2005; Noriuchi et al., 2008). Currently, researchers believe that this biologically based attachment system remains active throughout the human life course, serving as the foundation for attachment between pair-bonded partners for the purpose of raising offspring (Hazan and Shaver, 1987; Hazan and Diamond, 2000).

Pair-bonding could have evolved at any point in hominin evolution; and with it, various love addictions (Fisher, 2016). However, two lines of data suggest that the neural circuitry for human pair-bonding may have evolved at the basal radiation of the hominin stock (Fisher, 1992, 2011, 2016), in tandem with the hominin adaptation to the woodland/savannah eco-niche some time prior to 4 million years B.P. *Ardipithecus ramidus*, currently dated at 4.4 million years B.P., displays several physical traits that have been linked with pair-bonding in many species (Lovejoy, 2009); so Lovejoy (2009) proposes that human monogamy had evolved by this time. Anthropologists have also re-measured *Australopithecus afarensis* fossils for skeletal variations; and they report that by 3.5 million years B.P. hominins exhibited roughly the same degree of sexual dimorphism in several physical traits that the sexes exhibit today. Thus, some have proposed that these hominins were "principally monogamous" (Reno et al., 2003).

The emergence of bipedalism may have been a primary factor in the evolution of the neural circuitry for hominin pair-bonding (Fisher, 1992, 2011, 2016) and the concomitant evolution of romantic love (and possibly attachment) addiction. While foraging and scavenging in the woodland/savannah eco-niche, bipedal Ardipithecine females were most likely obliged to carry infants in their arms instead of on their backs, thus needing the protection and provisioning of a mate while they transported nursing young. Meanwhile, Ardipithecine males may have had considerable difficulty protecting and providing for a harem of females in this open woodland/savannah eco-niche. But a male could defend and provision a single female with her infant as they walked near one another, within the vicinity of the larger community.

So the exigencies of bipedalism in conjunction with hominin expansion into the woodland/savannah eco-niche may have pushed Ardipithecines over the "monogamy threshold," selecting for the neural system for attachment to a pair-bonded partner. And along with the evolution of pair-bonding and the neural system for attachment may have emerged the brain system for intense positive romantic addiction—serving to motivate males and females to focus their mating energy on a single partner and remain together long enough to trigger feelings of attachment necessary to initiate and complete their co-parenting duties of highly altricial young (Fisher, 1992, 2004, 2011, 2016).

HUMAN ROMANTIC LOVE AS A DEVELOPED FORM OF A MAMMALIAN COURTSHIP MECHANISM

Considerable data suggest that the human brain system for romantic love arose from mammalian antecedents. Like humans, all birds and mammals exhibit mate preferences; they focus their courtship energy on favored potential mates and disregard or avoid others (Fisher, 2004; Fisher et al., 2006). Moreover, most of the basic traits associated with human romantic love are also characteristic of mammalian courtship attraction, including increased energy, focused attention, obsessive following, affiliative gestures, possessive mate guarding, goal-oriented behaviors and motivation to win and keep a preferred mating partner for the duration of one's species-specific reproductive and parenting needs (Fisher et al., 2002, 2006; Fisher, 2004).

The brain system for human romantic love shows biological similarities with mammalian neural systems for courtship attraction. When a female laboratory–maintained prairie vole is mated with a male, she forms a distinct preference for him, associated with a 50% increase of dopamine in the nucleus accumbens (Gingrich et al., 2000). When a dopamine antagonist is injected into the nucleus accumbens, the female no longer prefers this partner; and when a female is injected with a dopamine agonist, she begins to prefer the conspecific who is present at the time of the infusion, even if she has not mated with this male (Wang et al., 1999; Gingrich et al., 2000). An increase in the activities of central dopamine is also associated with courtship attraction in female sheep (Fabre-Nys et al., 1997). In male rats, increased striatal dopamine release has also been shown in response to the presence of a receptive female rat (Robinson et al., 2002; Montague et al., 2004).

Because human romantic love shares many behavioral and biological characteristics with mammalian courtship attraction, it is likely that human romantic love is a developed form of this mammalian neural courtship mechanism (Fisher, 1998, 2004, 2011, 2016; Fisher et al., 2006). However, in most species courtship attraction is brief, lasting only minutes, hours, days, or weeks; while in humans, intense, early stage romantic love can last 12–18 months (Marazziti et al., 1999) or much longer (Acevedo et al., 2011). So in early hominin prehistory, activity in this mammalian neural system for courtship attraction may have become intensified and prolonged as pair-bonding evolved, eventually becoming the positive (or negative) romantic addictions experienced by men and women cross-culturally today.

ROMANTIC LOVE MAY ACT AS A REWARD REPLACEMENT FOR OTHER ADDICTIONS

High quality social relationships (including romantic relationships) can be extremely beneficial to those recovering from an addiction (e.g., Hänninen and Koski-Jännes, 1999). One potential mechanism for this benefit comes from the therapeutic approach to drug addiction of reward replacement. That is, when quitting one addictive substance or behavior, the addicted individual replaces this addiction with another form of rewarding behavior, often without prompting from an outside source, such as a clinician (Donovan, 1988; Marks, 1990; DiNardo and Lemieux, 2001; Haylett et al., 2004; Alter et al., 2006). Because of this, clinicians who treat addictions are known to effectively engage patients in new reinforcers (see Bickel et al., 2014), specifically healthy replacement reinforcers such as sports activities, new hobbies and more or new social interactions (e.g., Vaillant, 1983; Salvy et al., 2009; Liu et al., 2011).

Could early stage romance provide a replacement reward for those engaged in substance abuse (or a behavioral addiction)? To explore this question, Xu et al. (2012) put 18 Chinese overnight nicotine-deprived smokers who had just fallen madly in love into a brain scanner, using fMRI. These men and women looked at side-by-side photos, one of a hand holding either a lighted cigarette (cue) or a pencil (control) and one of their newly beloved or a familiar acquaintance (non-smokers so they were not cigarette-cues). Among those who were moderately addicted to nicotine, when the cigarette cue was presented next to the image of the beloved (compared to the acquaintance), less activation was observed in regions associated with cigarette cue-reactivity. Additionally, more activation in the caudate was observed during trials that included the beloved's pictures (compared to the acquaintance's).

These preliminary data provide more evidence that romantic love could be considered a powerful and primordial natural addiction because it can, under some circumstances, modify brain activations associated with a more contemporary addiction, nicotine.

"Self-expansion" and "incorporation of others into one's sense of self" may also act as reward substitutes for addictions, including love addiction.

First proposed by Aron and Aron (1986), the self-expansion model proposes that a basic human motivation is the desire to increase one's self-concept by engaging in novel, interesting, challenging and/or other exciting pursuits in order to gain resources and perspectives that can enhance one's self concept and capabilities (for review see Aron et al., 2013), as well as garner positive emotions and reward feelings (Aron et al., 1995, 2000; Strong and Aron, 2006). They propose that rapid self-expansion occurs during early stage romance.

This self-expansion, which is rooted in approach motivation (see Mattingly et al., 2012), may be beneficial when attempting to quit or reduce use of a substance or behavioral addiction because it offers a replacement and distracting rewarding experience. Self-expansion in the context of romantic love has been shown to attenuate perceptions of physical pain (Younger et al., 2010) via a reward mechanism (rather than distraction), which suggests that it might assist with the painful process of withdrawal after romantic rejection. Further, self-expansion may also be beneficial in the context of quitting any addiction because it facilitates self-concept change (e.g., starting to think of oneself as a writer, musician, bird watcher or whatever the self-expanding experience may be) into a new and healthier direction, and away from one's identity as a "user" (Kellogg and Kreek, 2005). In addition to providing distraction, replacement and redirection, engaging in self-expanding (i.e., novel, interesting, and/or challenging) activities may be biologically beneficial, because any form of novelty activates the dopamine system in the brain to facilitate energy and optimism, thereby potentially providing a replacement reward.

Indeed, three studies have directly investigating self-expansion in the context of nicotine addiction, each finding quite positive results. Ex-smokers reported that significantly more self-expanding experiences had occurred directly before they successfully quit smoking than did current smokers who reported on their unsuccessful attempts to quit (Xu et al., 2010). Even among the current smokers who relapsed, the number of self-expanding experiences occurring directly before their quit attempt was significantly positively correlated with how long they were able to abstain from smoking (Xu et al., 2010). Two fMRI studies of overnight abstinent smokers suggest that self-expansion via activities with a romantic partner attenuates cigarette cue-reactivity in the brain (Xu et al., 2012, 2014). These data suggest that when smokers engage in self-expansion, they are less responsive to smoking cues.

Another cognitive phenomenon that may play a role in attenuating romantic addiction is "inclusion of the other in the self" (IOS). This occurs when representations of the self change to incorporate aspects of a romantic partner. A scale has been developed to measure this cognitive process (Aron et al., 1992). Over time the partner's perspectives, identities, and resources become incorporated into the person's own sense of self and the distinction between self and partner blur. For example, people transition to more use of plural pronouns like "we" and "us"(Agnew et al., 1998), and become slower at distinguishing a partner's belongings or traits from one's own (Aron et al., 1991; for a review, see Aron et al., 2004). This growth of the self-concept can provide positive outcomes (e.g., additional resources, positive feelings), which may be effective in a therapeutic situation. Indeed, activation of the reward system through the VTA was correlated with a lover's IOS scores (Acevedo et al., 2011), which suggests that a moderate amount of positive identification with another person or group could be therapeutic–by boosting a positive self-image and providing a reward substitute for a substance or behavioral addiction that a person has given up.

IMPLICATIONS FOR TREATMENT OF ROMANTIC REJECTION AND ADDICTION

Clinicians have a host of strategies for helping lovers and drug addicts. However, when data on romantic love and substance abuse are considered together, some approaches have a particularly strong rationale.

Perhaps most important, like giving up a drug, rejected lovers should remove all reasonable evidence of their abandoning sweetheart, such as cards, letters, songs, photos, and memorabilia, as well as avoid contact with their rejecting partner, because reminders and partner contact can act as cues that induce craving and are likely to sustain the activity of brain circuits associated with romantic passion and thus interfere with the healing process. Self-expansion research also finds that positive outcomes such as personal growth and positive emotions are possible (even likely) following a break-up if the relationship had offered few self-expanding opportunities and if the newly single person engages in rediscovery of the self (Lewandowski and Bizzoco, 2007).

Close, positive contact with a friend or friends is rewarding and may also help to replace the craving for substances or a rejecting partner, because looking at a photo of a close friend activates the nucleus accumbens, associated with reward (Acevedo et al., 2011). Looking at a photo of a close friend also activates the periaqueductal gray, associated with oxytocin receptors and the calm of attachment. This suggests that group therapies, such as Alcoholics Anonymous and other 12 step programs, are successful because these group dynamics engage the brain's reward and attachment systems. Participating in group programs may be important for rejected lovers as well as for those addicted to substances like alcohol or those with a behavioral addiction, such as gambling.

Data suggest that rejected lovers should also stay busy to distract themselves (Thayer, 1996; Rosenthal, 2002). Physical exertion may be especially helpful as it elevates mood (Rosenthal, 2002), triggering dopamine activity in the nucleus accumbens to bestow pleasure (Kolata, 2002). Exercise also increases levels of β-Endorphin and endocannabinoids which reduces pain and increases feelings of calm and well-being (Goldfarb and Jamurtas, 1997; Dietrich and McDaniel, 2004). Also, engaging in a new form of exercise can be a self-expanding experience (see Xu et al., 2010). Because of these benefits of exercise, some psychiatrists believe that exercise (aerobic or anaerobic) can be as effective in healing depression as psychotherapy or antidepressant drugs (Rosenthal, 2002).

Self-expanding activities (e.g., hobbies, sports, spiritual experiences) can be helpful both in the context of addiction and heartbreak as they offer reward, benefits to the self-concept, and distraction. It is recommended that a person has more than one source of self-expansion in their life, thus should one no longer become available (e.g., a partner leaves), the other sources can help buffer the impact of that loss. It would also be helpful to have multiple and diverse sources of self-expansion in various domains of life (e.g., hobby, workplace, friends, family, volunteer organization, spiritual group, and academic interest etc.) and to have strong social networks to which one can turn for support in times of need (e.g., breakup, attempting to quit). It is important, however, to note that self-expansion should be pursued in a healthy manner with caution about potentially risky behaviors (e.g., seeking to fall in love with a new person immediately after the loss of a partner, picking up unhealthy habits or becoming an addict of another substance when quitting).

Similarly, it is important to remember that relationships and addictions can co-exist and influence each other and it may be especially difficult to have a strong and positive romantic relationship when issues of addiction need to be dealt with. As addiction often leads to less desire for and response to alternative rewards, it may be especially difficult for those dealing with addiction to engage in pro-relationship behaviors, and thus increase the risk of rejection. In addition, romantic rejection increases the risk of relapse, so close attention to romantic relationships during substance abuse withdrawal may be important.

Furthermore, smiling utilizes facial muscles that activate nerve pathways in the brain that can stimulate feelings of pleasure (Carter, 1998). Focusing on the positive may be effective too. A study by Lewandowski (2009) found that writing for 20 min on three consecutive days about a recent relationship break-up was beneficial when people wrote about positive feelings as opposed to when they wrote about negative feelings or wrote without expressing any feelings. Perhaps most important, time attenuates the attachment system. In our study of rejected men and women, the greater the number of days since rejection, the less the activity in a brain region (the ventral pallidum) associated with feelings of attachment (Fisher et al., 2010).

As disappointed lovers use strategies originally developed to quit a substance addiction, their love addiction is likely to eventually subside.

CONCLUSION

Researchers have long discussed whether the compulsive pursuit of non-substance rewards, such as uncontrolled gambling, eating, sex, exercise, Internet use, compulsive buying disorder and other obsessive behavioral syndromes can be classified as addictions (Frascella et al., 2010; Rosenberg and Feder, 2014). All can lead to salience, obsession, tolerance, emotional, and physical dependence, withdrawals, relapse and other traits common to substance abuse. Moreover, several of these non-substance rewards have been shown to produce specific activity in dopamine pathways of the reward system similar to drugs of abuse (see Frascella et al., 2010; see Rosenberg and Feder, 2014).

This suggests that uncontrolled use of these non-substances can be considered addictions. Romantic love is likely to be a similar addiction, with one exception. Unlike other addictions (that afflict only a percentage of the population), some form of love addiction is likely to occur to almost every human being that lives now and in our human past; few avoid the pain of romantic rejection either.

Romantic love appears to be a natural addiction, "a normal altered state" experienced by almost all humans (Frascella et al., 2010, p. 295) that evolved during human evolution to motivate our ancestors to focus their mating energy on a specific partner, thereby conserving mating time and energy, initiating reproduction, triggering feelings of attachment and subsequent mutual parenting, and assuring the future of their mutual DNA (Fisher, 2004, 2011, 2016; Fisher et al., 2006). Romantic love may be a positive addiction when the relationship is reciprocated, non-toxic and appropriate; but a harmful, negative addiction when unreciprocated, toxic, inappropriate and/or formally rejected.

To alleviate the negative symptoms of love addiction, addicted lovers are advised to remove the cues that fan their ardor, follow some advisories of a 12-step program, build new daily habits, meet new people, take up new interests, find the appropriate medication and/or therapist, and wait out the days and nights of intrusive thinking and craving, because feelings of attachment to a former romantic partner decrease over time (Fisher et al., 2010). Moreover, therapies that increase self expansion and incorporate new individuals into one's sense of self may also be useful in alleviated love addiction. Self expansion approaches may help drug and other negative addiction therapies, also.

If the public and the therapeutic, medical and legal communities come to understand that passionate early stage romantic love is an evolved drive (Fisher, 2004) and a natural addiction (Frascella et al., 2010) that can have profound social, economic, psychological, and genetic consequences (both beneficial and adverse), clinicians and researchers might develop more effective procedures for dealing with this powerful and primordial neural mechanism for mate preference and initial partner attachment, romantic love.

AUTHOR CONTRIBUTIONS

HF wrote half the text based on her ideas and data from previous studies and edited the final version. XX wrote twenty percent of the text based on her ideas and data from previous studies. AA contributed to the text based on his ideas and previous studies. LB wrote thirty percent of the text based on her ideas and data from previous studies and edited the final version.

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Event-Related Potential Responses to Beloved and Familiar Faces in Different Marriage Styles: Evidence from Mosuo Subjects

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Research on familiar face recognition has largely focused on the neural correlates of recognizing a beloved partner or family member. However, no research has explored the effect of marriage style on the recognition of a beloved partner's face, especially in matriarchal societies. Here, we examined the time course of event-related potentials (ERP) in response to the face of a beloved partner, sibling, or unknown person in a sample of individuals from the matriarchal Mosuo tribe. Two groups were assessed: intermarriage and walking marriage groups (i.e., couples in a committed relationship who do not cohabitate during the daytime). In agreement with previous reports, ERP results revealed more positive VPP, N250, and P300 waveforms for beloved faces than sibling faces in both groups. Moreover, P300 was more positive for beloved partner versus sibling faces; however, this difference emerged at fronto-central sites for the walking marriage group and at posterior sites for the intermarriage group. Overall, we observed that marriage style affects the later stage processing of a beloved partner's face, and this may be associated with greater affective arousal and familiarity.

Keywords: love, affective processing, familiar faces, event-related potentials

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INTRODUCTION

The experience of romantic love allows people to build passionate and intimate relationships. Based on previous theory, passion in romantic love is affected by intimacy and relationship duration (Baumeister, 1999; Graham, 2011). Generally, the early stages of romantic love involve intense and passionate emotions, and are later followed by companionate love and the formation of a stable commitment. Romantic love in a relationship is characterized by attachment, care-giving, and sexual attraction (Mikulincer and Goodman, 2006). Several neuroscience studies have proposed that the experience of love involves a neural network distinct from networks that process stimuli relevant to friendship or parental relationships (Bartels and Zeki, 2000, 2004; Aron et al., 2005; Ortigue et al., 2007). Other investigations have confirmed that the affective brain network (Bartels and Zeki, 2004) and reward pathway are correlated with the experience of romantic love (Fisher et al., 2002, 2005; Aron et al., 2005; Zeki and Romaya, 2010; Xu et al., 2011; Acevedo et al., 2012).

Event-related potential (ERP) studies on the visual processing of a beloved partner's face have provided temporal information regarding the dynamic neural mechanisms underlying familiar face perception. Numerous face-processing studies have identified several early face-related ERP components, including N170, VPP (or P2), and N200 (Bruce and Young, 1986; Luo et al., 2010). P300 has also been identified as sensitive to facial familiarity and emotional arousal, and is an important identifier for self-relevant processing (Grasso et al., 2009; Grasso and Simons, 2011). Previous ERP studies assessing the recognition of a beloved partner's face have demonstrated that beloved faces elicit a more positive P300 or late positive potential (LPP) than control faces. For example, the LPP was larger when viewing beloved faces than viewing friends' faces, which was interpreted as a greater reflection of motivational attention toward the beloved face (Langeslag et al., 2007). A subsequent study utilizing an oddball paradigm to dissociate love-related attention from task-related attention also found that P300 was more positive for beloved faces than for friends' faces, irrespective of whether the beloved face was the target or the distracter stimulus (Langeslag et al., 2008). The authors concluded that perception of a beloved face is accompanied by increased motivational attention for evolutionary reasons (i.e., reproductive). Additionally, it has been proposed that perception of a beloved face is associated with enhanced affective processing (Vico et al., 2006, 2010; Vila et al., 2006). A popular view suggests that emotional stimuli evoke a more positive P300 than neutral stimuli do (Schupp et al., 2004; Pollatos et al., 2005; Eimer and Holmes, 2007). To test this hypothesis, Vico et al. (2010) measured peripheral and central electrophysiological indices, including EEG, heart rate, skin conductance, and zygomatic activity, when subjects viewed five face categories: neutral, unknown, famous, babies, and beloved. Results showed that P300 could differentiate a beloved face from other faces, and furthermore related a larger P300 to the allocation of greater attentional resources. In agreement, it is documented that beloved faces evoke greater arousal of positive emotions (Guerra et al., 2011b). Therefore, despite inconsistent interpretations of P300, there exists a clear association of P300 with the processing of beloved and familiar faces.

The majority of the aforementioned studies placed a focus on passionate or intense romantic love by using the faces of dating partners, where dating can be assumed to describe the early stage of a romantic relationship (de Boer et al., 2012; Langeslag et al., 2015). A recent fMRI study explored the neural correlates of long-term romantic love by evaluating participants that had been married for more than 21 years (Acevedo et al., 2012). Results indicated that activation in reward regions (e.g., the ventral tegmental area and dorsal striatum) is similar in early stage love and long-term love. However, long-term love also involves attachment and pair-bonding-related brain networks (Acevedo et al., 2012). Therefore, it can be hypothesized that brain responses toward beloved faces shift with increasing intimacy and the stage of the relationship. However, few studies have examined brain responses following the recognition of a beloved partner in the context of a long-term relationship, wherein the spouse may be perceived as a family member. In consideration of "love phases" (de Boer et al., 2012), the present study included participants whose relationships had lasted at least seven years (Sternberg, 1987; García, 1998). Therefore, the first aim of the present study was to investigate neural face recognition responses among companionate love partners in stable relationships.

To our knowledge, few studies have investigated whether marriage style modulates the recognition of beloved and familiar faces. China's Mosuo tribe, which follows a matriarchal culture, provides a unique opportunity for the investigation of marriage style and partner face recognition. In the Mosuo tribe, women are often the head of the household, and inheritance is conveyed through the female line. More interestingly, members of the Muoso tribe are allowed to select between two marriage styles. Several members of the Mosuo tribe maintain a "walking marriage" lifestyle in which there are no husbands or wives, and romantic partners do not live together during the daytime (Yuan and Mitchell, 2000; Walsh, 2001). For instance, a man will stay with his partner during the night and return home early the next morning. The "walking marriage" relationship is somewhat secretive and accordingly does not include economic or childbearing responsibilities. Instead, siblings live together and rear each other's children, forming a family unit. In contrast, other Mosuo tribe members choose "intermarriage", which more closely represents a typical modern marriage. In an intermarriage, the married couple cohabitates and forms a core family unit that includes a husband, a wife, and children. Compared to intermarriage, a romantic partner in a walking marriage may be met with higher novelty and arousal. Therefore, different marriage and cohabitation styles may be associated with different neural responses to partner and family member faces. Specifically, we predicted that familiarity responses to a sibling should be higher for people who practice walking marriage than for people who practice intermarriage.

The present study used sibling faces as contrast stimuli to control for familiarity, age, gender, and affective affiliation. To explore neural responses to a beloved partner in Mosuo tribe members, we compared ERP responses to three types of faces (partners, siblings, and unknown persons) during a face discrimination task. We hypothesized that faces of a beloved partner would engender more attention or affective processing than sibling faces. Additionally, we predicted that familiarity processing of a family member's face would be modulated by marriage style.

MATERIALS AND METHODS

Participants

Forty-five healthy adult Mosuo tribe members participated in the study as paid volunteers. Four participants were excluded due to excessive artifacts or missing data, leaving 41 participants in the following statistical analysis. The walking marriage group consisted of 10 males ($M = 37.5$ years, $SD = 2.72$) and 10 females ($M = 34.4$ years, $SD = 5.89$). The intermarriage group consisted of 12 males ($M = 36.2$ years, $SD = 3.1$) and 9 females ($M = 33.4$ years, $SD = 6.44$). All participants were in a stable relationship for more than 7 years, had children with their partners, and reported an exclusive relationship. Signed informed consent was obtained from all subjects prior to testing in accordance with the Beijing Normal University Review Board guidelines.

Stimuli

For each participant, the stimulus set included seven digital images (the face of one's heterosexual lover, the face of one's opposite-sex sibling, and five faces of unknown opposite-sex Mosuo people). All photographs were taken before the experiment using the same digital camera and background. Faces showed a neutral expression and were processed by Adobe Photoshop CS4 to match brightness, contrast, and size within the stimulus set.

Procedure

Participants were seated 70 cm from the computer screen and stimuli were presented in the center of a 14-inch screen with a visual angle of 4.3° × 4.6°. A modified oddball and choice reaction paradigm was utilized. The beloved and sibling faces were targets, and the stranger faces were non-target stimuli. Participants were asked to press "F" or "J" in response to their beloved partner or sibling, respectively. The response button was counterbalanced across participants. That is, half of the participants pressed "F" to indicate a beloved partner while the other half pressed "J" to indicate a beloved partner. To evaluate P300, we also manipulated the ratio of face category presentation to be 1:1:5 (beloved partner vs. sibling vs. stranger) for three face categories. Each face was presented 60 times; accordingly, the study consisted of 420 trials. In each trial, a white fixation cross was first presented on a black background for 300 ms, followed by a randomly varied interval of 300–500 ms. Subsequently, a face was presented for 3000 ms and the participants were asked to respond to the target stimulus as soon as possible. The face disappeared upon response within the 3000 ms interval. The trial ended with a randomly varied interval of 300–500 ms.

Electroencephalogram Recording and Data Analysis

Electroencephalograms (EEGs) were recorded using a 64-channel BrainAmp MR with online reference to the left mastoid. Vertical electrooculograms (VEOGs) were recorded from two electrodes positioned above and below the left eye, and horizontal electrooculograms (HEOG) were recorded from two laterally placed electrodes for both eyes. All electrode impedance was maintained below 10 kΩ and the EEG signals were recorded with a band pass of 0.01–100 Hz and sampled at 500 Hz/channel. All electrodes were re-referenced to the average of the bilateral mastoids and filtered offline with a low pass of 30 Hz. EEGs were segmented from 200 ms prior to stimulus presentation until 1000 ms post-stimulus presentation. Trials containing blinks or eye movements (±80 μV) were excluded. The mean left trial number was 53.02 and 54.43 for the beloved partner and sibling conditions, respectively. The grand average ERPs suggested that the face of a beloved partner evoked a more positive potential than the face of a sibling from 200–600 ms (see **Figure 1**). We also observed VPP and N250 over fronto-central sites (Cz, C3, C4, Fz, F3, F4, FCz, FC3, and FC4). Therefore, we first averaged an individual's mean ERP over fronto-central sites, and then interpreted the local maximum between 150 and 200 ms to be the latency of VPP. Subsequently the amplitude at that specific latency was taken at each individual electrode to calculate amplitude of VPP. We also interpreted the local minimum between 200 and 300 ms to be the latency of N250, and the amplitude at that specific latency was qualified as the amplitude of N250. Considering that the trial number of stranger faces was far greater than that of the other two conditions, and did not require a motor response, we excluded stranger faces from the ERP analysis and focused on the distinctions between beloved partner and sibling face recognition. VPP and N250 were evaluated using a mixed ANOVA with group (walking marriage vs. intermarriage) as the between-subject variable and face category (beloved partner vs. sibling) as the within-subject variable. Given that P300 is a widely distributed component, and that previous studies have dissociated anterior P300 from posterior P300 (Halgren et al., 1998; Friedman et al., 2001; Gaeta et al., 2003; Bobes et al., 2007; Polich, 2007; Cano et al., 2009), we selected Cz, C3, C4, FCz, FC3, FC4, Fz, F3, and F4 in order to analyze the anterior P300 (mean amplitude, 350–600 ms), and Pz, P3, P4, POz, PO3, PO4, CPz, CP3, CP4 in order to analyze the posterior P300 (mean amplitude, 350–600 ms). The P300 amplitude was evaluated using a mixed ANOVA with group (walking marriage vs. intermarriage) as the between-subject variable and face category (beloved partner vs. sibling) and location (anterior vs. posterior) as within-subject variables.

RESULTS

Behavioral Results

Incorrect trials and individual response times (RTs) exceeding 3-times the standard deviation (*SD*) were excluded (less than 2%). Furthermore, preliminary analyses revealed no significant effect of gender (all $Fs < 3$, $ps > 0.09$) on any variable. Thus, all analyses were collapsed across gender. Accuracy and intra-individual mean RTs within categories were computed and entered into separate mixed two-way ANOVAs (face category by group). Since no significant effects were identified, we conducted planned paired *t*-tests (beloved partner vs. sibling) to examine within-group differences.

Response times were significantly different for beloved versus sibling face discrimination in the walking marriage group ($t_{19} = 2.66$, $p < 0.05$). Walking marriage participants showed longer response times for the beloved face ($M = 671$ ms, $SE = 23.48$) as compared to the sibling face ($M = 653$ ms, $SE = 21.24$). No significant differences were observed in the intermarriage group.

VPP

The ANOVA for frontal–central VPP amplitude revealed a significant main effect of face category, $F(1,39) = 14.73$,

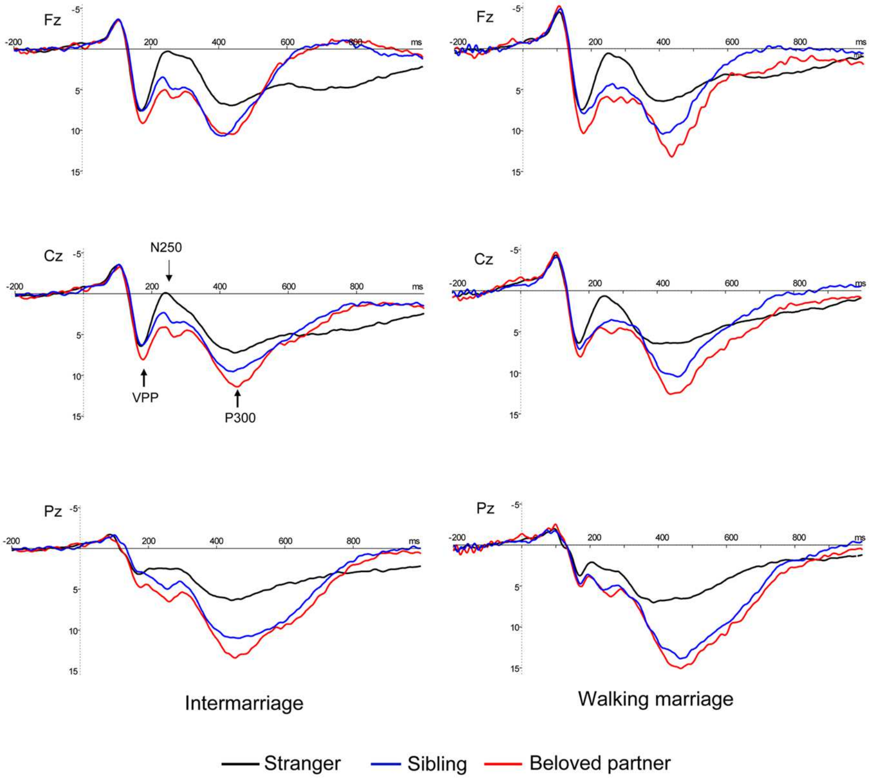

FIGURE 1 | Grand average ERPs at Fz, Cz, and Pz for two groups. Familiar faces (beloved and sibling) evoked more positive brain potentials than strangers from 200 to 600 ms for all sites. P300 (marked gray) was more positive for beloved face than sibling for both groups.

$p < 0.001$, $\eta_p^2 = 0.27$, indicating that beloved faces elicited larger VPPs ($M = 9.67$ μV, $SE = 0.69$) than sibling faces ($M = 8.24$ μV, $SE = 0.69$). No significant group effect was observed.

N250

Analyses of N250 also showed a significant main effect of face category, $F(1,39) = 5.71$, $p < 0.05$, $\eta_p^2 = 0.13$. Sibling faces evoked a larger N250 ($M = 0.26$ μV, $SE = 0.74$) than beloved partner faces ($M = 2.19$ μV, $SE = 0.70$).

Considering the observed effect of face category on VPP, we also measured the peak-peak amplitude of N250 to exclude any VPP influences. Results indicated no significant effect of face category and no group effect was observed, $Fs < 0.84$, $ps > 0.37$.

P300

P300 amplitude was evaluated using a mixed ANOVA with group (walking marriage vs. intermarriage) as a between-subject variable and face category (beloved vs. sibling) and location (anterior vs. posterior) as within-subject variables. We found a significant main effect of face category, $F(1,39) = 18.98$, $p < 0.01$, $\eta_p^2 = 0.33$, indicating an overall larger P300 for beloved faces. There was also a significant location effect, $F(1,39) = 10.51$, $p < 0.01$, $\eta_p^2 = 0.21$, which identified a larger P300 at anterior sites. While no significant group effect was observed, we did identify a significant three-way interaction, $F(1,39) = 5.77$, $p < 0.05$, $\eta_p^2 = 0.13$. *Post hoc* analyses indicated that, for the intermarriage group, the posterior P300 amplitude was larger for beloved faces ($M = 9.86$ μV, $SE = 1.17$) than sibling faces ($M = 8.78$ μV, $SE = 1.14$). For the walking marriage group, the anterior P300 amplitude was larger for beloved faces ($M = 9.93$ μV, $SE = 1.22$) than sibling faces ($M = 8.75$ μV, $SE = 1.23$).

Electrophysiological results for the P300 component in both groups and scalp voltage topography for the beloved *vs.* sibling difference waves (P300) are summarized in **Figure 2**. The topography map confirmed that the beloved vs. sibling P300 difference occurred mainly at posterior sites in the intermarriage group, while P300 differences only occurred at anterior sites in the walking marriage group. Interestingly, we primarily identified a differential pattern between beloved and sibling faces over the left frontal brain area. To validate this observation, we conducted an electrode side (left: F3, FC3, and C3 vs. right: F4, FC4, and C4) × face type ANOVA on the anterior P300. Results showed a significant electrode side effect on the anterior P300, $F(1,39) = 5.77$, $p < 0.05$, $\eta_p^2 = 0.13$, such that a more positive P300 was observed in the right fronto-central area versus the left.

DISCUSSION

The present study examined ERP responses to the face of a beloved partner or sibling in Mosuo tribe members practicing

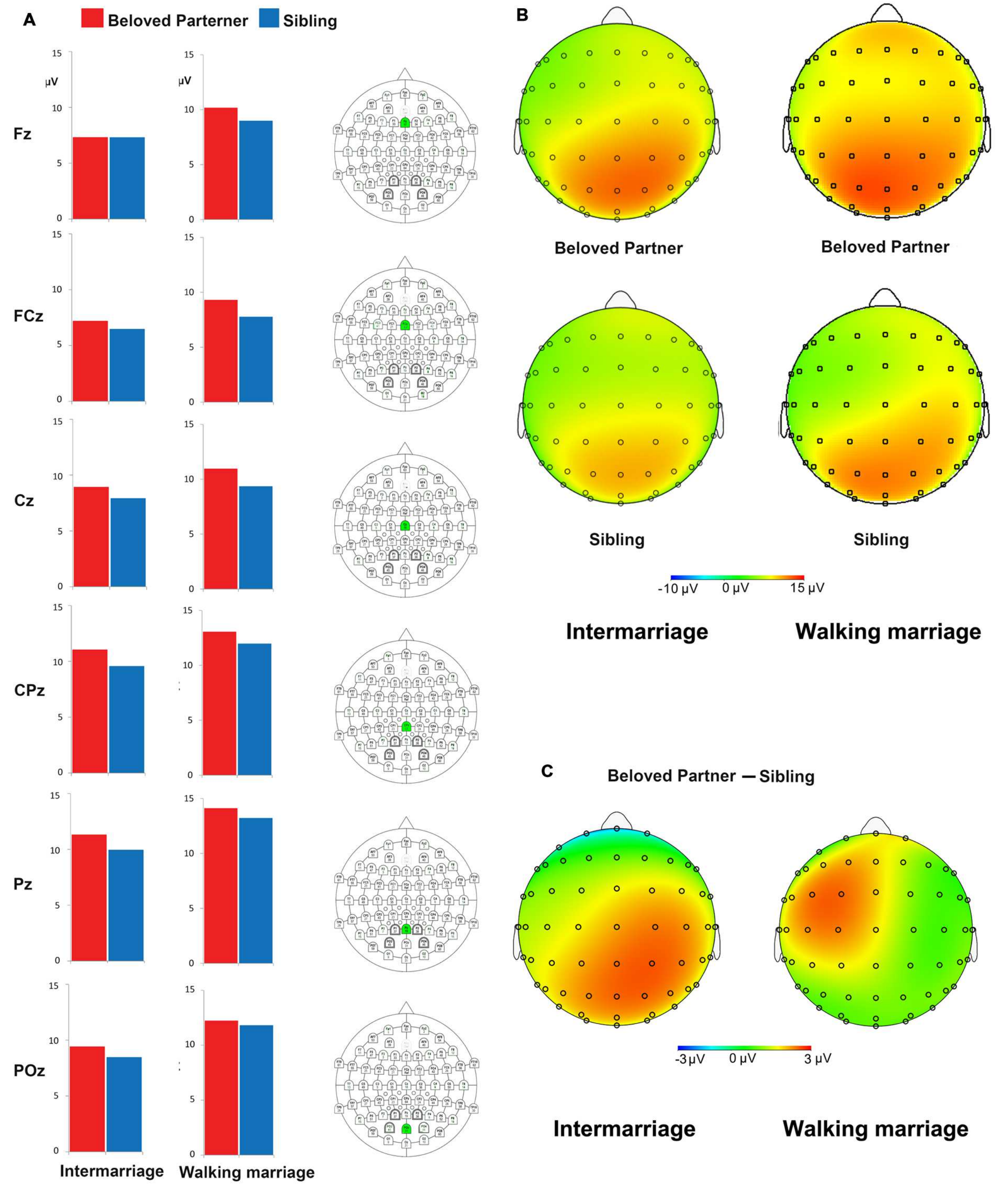

FIGURE 2 | (A) The P300 amplitude in the midline electrodes. The bars indicates the mean P300 amplitude at Fz, FCz, Cz, CPz, Pz, and POz (corresponding electrode was marked as green in column III); **(B)** The topography of P300 for grand averaged face conditions (beloved partner vs. sibling) for two groups; **(C)** The topography of difference wave of P300 (beloved partner vs. sibling) for two groups. The topography map indicated that the beloved partner vs. sibling P300 difference mainly occurs at posterior sites (also at some frontal sites) for intermarriage group while the difference only occurs at anterior sites for walking marriage group. The figure indicates that the beloved partner vs. sibling difference changes from the anterior to posterior sites. Such difference is larger at posterior sites for intermarriage group, while the difference is larger at anterior sites for walking marriage group.

walking marriage or intermarriage. Results indicated that individuals in the walking marriage group exhibited slower response times to beloved faces than sibling faces. One possible interpretation is that walking marriages represent a less secure relationship than a familial sibling relationship. The potential secrecy associated with a walking marriage may cause individuals to associate a beloved face with greater novelty, and thus lead to slower reaction times during an explicit face judgment task. Notably, we observed no differences in recognition accuracy between groups or between faces. This may suggest a "ceiling effect" in the face task, as mean accuracy (96.9%) was very high across groups and conditions.

With regard to ERP results, beloved faces were associated with more positive ERP potentials than sibling faces from 200 ms to the late processing stage (VPP, N250, and P300). VPP at centro-frontal sites, occurring between 150 and 200 ms post-stimulus presentation, is often regarded as similar to N170 (Rossion et al., 1999, 2003; Itier and Taylor, 2002; Jemel et al., 2003; Joyce and Rossion, 2005). Although some studies have reported that VPP is not modulated by emotional stimuli (Rossignol et al., 2005) or familiarity (Rossignol et al., 2005; Sui et al., 2006; Marzi and Viggiano, 2007), results from expression processing studies suggest that VPP is subject to modulation by affectively salient stimuli (Ashley et al., 2004; Williams et al., 2006; Foti et al., 2010). Therefore, enhanced VPP amplitudes observed in response to a beloved partner's face might reflect affective salience in early perception.

VPP enhancement in response to a beloved face likely influenced the effect observed for N250, as the peak-peak N250 amplitude revealed no significant effect. N250 (or N300 in some studies) has been reported to be sensitive to facial familiarity (Schweinberger et al., 1995; Tanaka et al., 2006; Krigolson et al., 2009) and affective features (Eimer and Holmes, 2002, 2007). While N250 results are in accordance with previous studies demonstrating that beloved faces (fathers and romantic partners) are associated with smaller N200s (Guerra et al., 2011a), we conjecture that the N250 effect in our study was due to VPP enhancements after viewing the face of a beloved partner.

Clearly, the P300 component discriminated the perception of familiar faces from unknown faces in our study, as familiar faces elicited a more positive P300. This effect is consistent with several previous studies (Langeslag et al., 2007, 2008; Guillaume et al., 2009). Furthermore, enhancements in the amplitude of P300 were greater in response to the face of a beloved partner versus a sibling. We speculate that a beloved partner provides more intimate/self-relevant significance, regardless of marriage type. We did however identify a dissociation of anterior P300 from posterior P300 based on marriage type. An enhanced posterior P300 amplitude was observed for beloved partner versus sibling faces in the intermarriage group, while the anterior P300 amplitude was more positive for beloved partner versus sibling faces in the walking marriage group. The anterior and posterior P300 components may reflect differences in psychological significance. The posterior P300, which is more akin to classic P300 (e.g., peaking at parietal sites), may reflect face familiarity or a memory process that discriminates the familiar from the unfamiliar (Miyakoshi et al., 2007; Guillaume et al., 2009). On this premise, it is unsurprising that the intermarriage group showed widely distributed differences in P300 response to beloved partners versus siblings, especially in the posterior P300 (see **Figure 2**). Compared to the walking marriage group, a beloved partner in the intermarriage group may be of higher familiarity than siblings as a result of cohabitation and child rearing. There was no significant beloved partner versus sibling difference in the posterior P300 for the walking marriage group. This is likely because familiarity was more closely matched between one's beloved partner and sibling in the walking marriage group, relative to intermarriage group. Consequently, the posterior P300 result could be interpreted as a memory-related component in which a person of higher familiarity is correlated with larger P300 amplitudes.

The anterior P300 over fronto-central sites is more akin to a P3a component, which reflects orientation responses toward novel stimuli (Friedman et al., 2001; Polich, 2007; Weisman et al., 2012). Our most remarkable finding was that the anterior P300 was enhanced in response to beloved partner versus sibling faces in the walking marriage group. This anterior P300 effect fits well with our hypothesis of a partner-viewing novelty effect in the walking marriage group, wherein limited contact (i.e., only at night) produces enhanced arousal toward the beloved partner's face. The beloved partner versus sibling difference was not significant for the anterior P300 in the intermarriage group. This may be attributed to the cohabitation environment, as intermarried couples have extensive contact with their partner, which is likely to decrease partner-face novelty.

On the other hand, neuroimaging studies have demonstrated that romantic love involves affective state-related brain regions, including the anterior cingulate cortex, the orbitofrontal cortex (OFC), and the striatum/reward system (Aron et al., 2005; Fisher et al., 2005; Xu et al., 2011; Acevedo et al., 2012). These regions, mostly within fronto-central areas, may contribute to the perception of beloved faces. Given the observation of differences in the response of anterior P300 to beloved partner versus sibling faces, we agree with Guerra et al. (2011b) that the frontal P300 may relate more specifically to the perception of a beloved partner's face.

Interestingly, we also observed overall left-right anterior P300 differences in the walking marriage group for responses to beloved versus sibling faces (see **Figure 2**). Lateralization over left fronto-central cites may be indicative of emotion-motivation system involvement, as asymmetric frontal cortical activity is correlated with affective experience (Harmon-Jones et al., 2011). Specifically, approach motivation is more significantly associated with left frontal cortical activity (Hewig et al., 2004). Another previous study demonstrated that appetitive pictures evoke a larger LPP than neutral pictures over left frontal sites (Gable and Harmon-Jones, 2010). Therefore, our observation that the face of a beloved partner produces a larger P300 over left fronto-central sites is supportive of our interpretation that the anterior P300 reflects an orienting response toward motivational stimuli.

One limitation of present study is the absence of familiarity and affect ratings from both groups. We chose not to collect this data due of the conservative nature of our population and the "taboo" nature of sex-related questions. Therefore, we cannot definitively attribute P300 effects to familiarity or affective feelings. Further studies using subjective ratings and behavioral data are needed to validate our findings. Further, the lack of a normal, non-Mosuo marriage group to control for minority or tribe-related effects limits our ability to make inferences regarding P300 in other populations.

In summary, the present study provides a unique examination of companionate and sibling love, and reveals that ERPs can differentiate beloved partners from siblings in the early and late stages of processing. The VPP and N250 ERP components are thought to discriminate the perception of familiar individuals from unfamiliar individuals. In our study, more positive VPP and N250 values were not only observed for familiar versus unknown faces, but also for beloved partner versus sibling faces; thus, these components indicate early face configuration and identification processing of a beloved partner. In line with previous studies, P300 was also sensitive to beloved faces, and furthermore we differentiated anterior and posterior P300s in individuals with different marriage styles. The present study therefore demonstrates that early processing of a beloved partner's face is conserved across various relationship types, but affective or familiarity processing is subject to divergence in the late phase.

AUTHOR CONTRIBUTIONS

YJL and HW conceived the experiment, HW, LL, JD, and SY conducted the experiment, LL and HW analyzed the results. HW, NW, SY, and YJL wrote the paper. All authors reviewed the manuscript.

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Are Happy Faces Attractive? The Roles of Early vs. Late Processing

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Facial attractiveness is closely related to romantic love. To understand if the neural underpinnings of perceived facial attractiveness and facial expression are similar constructs, we recorded neural signals using an event-related potential (ERP) methodology for 20 participants who were viewing faces with varied attractiveness and expressions. We found that attractiveness and expression were reflected by two early components, P2-lateral (P2l) and P2-medial (P2m), respectively; their interaction effect was reflected by LPP, a late component. The findings suggested that facial attractiveness and expression are first processed in parallel for discrimination between stimuli. After the initial processing, more attentional resources are allocated to the faces with the most positive or most negative valence in both the attractiveness and expression dimensions. The findings contribute to the theoretical model of face perception.

Keywords: face, attractiveness, expression, ERP, P2, LPP

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INTRODUCTION

Romantic love is closely associated with mate choice (Fisher et al., 2005), in which facial attractiveness plays a critical role (Little et al., 2011; Little, 2014). The effect of facial attractiveness has been found to be modulated by facial expression. For example, a smile was evaluated as more attractive than a neutral expression (Otta et al., 1996), and the preference for attractive faces was enhanced by happy expressions (Main et al., 2010). However, the classical theoretical models of face perception (Bruce and Young, 1986; Haxby et al., 2000) do not clarify whether the perceptions of attractiveness and expression are processed in similar ways. This question has become an important research objective given the increased interest in investigating the relationship between facial attractiveness and romantic love.

It is speculated that perception of attractiveness and expression share similar processing, given that both attractiveness and expression are derived from facial characteristics (e.g., size, position and movement of eyes, nose and mouth) and that both are capable of eliciting affective experiences in the observers. Besides, previous functional magnetic resonance imaging (fMRI) studies have shown that a number of occipital, limbic, temporal, parietal, and prefrontal brain regions that responded to the manipulation of attractiveness (O'Doherty et al., 2003; Ishai, 2007; Winston et al., 2007; Chatterjee et al., 2009) responded to the manipulation of expression (Vuilleumier and Pourtois, 2007; Fusar-Poli et al., 2009). Moreover, O'Doherty et al. (2003) found that the increased activation elicited by faces of high attractiveness in the orbitofrontal cortex (OFC), a reward-related brain region, was enhanced by a smile, suggesting that some common neural processing (e.g., reward) is shared by perceptions of attractiveness and expression. The aforementioned speculation is still controversial. Previous studies have proven that the processing of face perception is hierarchical; for reviews, please see Eimer and Holmes (2007) and Olofsson et al. (2008). It is possible that attractiveness and expression are processed separately and then are processed as a whole, even if similar brain areas are involved for processing the two types of facial information. However, the fMRI's poor temporal resolution (i.e., 2–3 s) makes it difficult to delineate the time course of face perception's quick neural processing.

The event-related potential (ERP) methodology has a high temporal resolution (i.e., a few milliseconds) and has been widely used to examine the neural correlates of face perception in the temporal domain. Previous ERP studies have revealed a few correlates of perceiving either attractiveness or expression. Firstly, the P2 component is a positive-going deflection at the frontal or parietal sites, peaking at around 200 ms; it is supposed to reflect the comparison between sensory input and stored memory (Luck and Hillyard, 1994) and initial "attention capture" of (physically) distinctive faces (van Hooff et al., 2011). The role of P2 in perceiving facial attractiveness has been reported. An early study by Halit et al. (2000) showed that stretching the distance between pupil, nose and lip made a face less attractive, compared to its original image, and this alteration elicited larger P2 for attractive (intact) faces than unattractive (stretched) faces. van Hooff et al. (2011) found that both attractive and unattractive faces elicited larger P2 peak amplitudes at Pz channel within 120–220 ms than faces with medium ratings of attractiveness. Zhang and Deng (2012) found larger P2 within 150–230 ms for attractive than unattractive faces at CPz and Pz channels. On the other hand, previous studies have shown that P2 responds to the emotional content of stimuli, although the polarity of contrast varied across studies. For example, Spreckelmeyer et al. (2006) showed that P2 was more pronounced for happy (vs. neutral and sad) pictures and for pictures paired with happy (vs. neutral and sad) voices. In contrast, Ofsson and Polich (2007) found that unpleasant pictures yielded larger P2 than did neutral and pleasant pictures.

Secondly, previous studies have also reported that a late component, late posterior positivity (LPP), responds to face stimuli. LPP typically appears in posterior sites after at least 350 ms and lasts for several hundred milliseconds, and it is supposed to reflect the facilitated attention allocation to motivationally relevant, emotional stimuli (Foti et al., 2009) and task-related evaluative processes (Johnston and Oliver-Rodriguez, 1997; Cuthbert et al., 2000; Werheid et al., 2007). Attractive faces were often found to elicit larger LPP than unattractive faces (Johnston and Oliver-Rodriguez, 1997; Werheid et al., 2007; van Hooff et al., 2011; Zhang and Deng, 2012), even when the subjects were instructed to fake their responses (Dong et al., 2010). However, a U-shaped relationship between the LPP amplitudes and the mean attractiveness ratings was also reported, reflected by larger LPP for attractive and unattractive faces than for faces of medium attractiveness (Schacht et al., 2008; Marzi and Viggiano, 2010). On the other hand, detected LPP was larger for fearful than for happy faces, and for happy than for neutral faces, in one study (Luo et al., 2010); larger LPP was also found for happy and neutral schematic expressions than for sad schematic faces in another study (Liu et al., 2013).

The mixed ERP findings listed above might be due to the varied task paradigms, visual stimuli and participants employed across studies. For example, some previous studies manipulated attractiveness while controlling expression, but other studies manipulated expression while controlling attractiveness. Here, we examined within the same group of participants the neural correlates of perceiving either attractive or unattractive faces with either happy or sad expressions. If attractiveness and expression are processed in the same way, we hypothesized that we would detect their interaction effect in P2 and LPP. Otherwise, if they are processed separately first and then integrated for processing, we hypothesized that we would detect the effects of attractiveness and/or expression in P2—and their interaction in LPP.

MATERIALS AND METHODS

Participants

Twenty university students (10 female and 10 male; mean age = 23.9 years, standard deviation [*SD*] = 7.5 years) were recruited from The Hong Kong Polytechnic University. All were right-handed (Oldfield, 1971), with normal or corrected-to-normal vision. None reported a history of physical, neurological, or mental disorders. All participants provided written informed consent. Ethics approval of this study was obtained from the local Institutional Review Board.

Stimuli

Photos of real human faces have often been utilized in previous studies on face perception. They are of high ecological validity, but their confounding factors (e.g., hair color/style, glasses, skin color/texture and sizes/positions of eyes, nose, mouth, and ears) are difficult to control for. Here, we employed fabricated facial stimuli, which were adapted from a few standard face templates, to control the variables of no interest. Facial stimuli were fabricated in two phases. The first phase was to generate face templates with varied levels of attractiveness, while the second phase was to integrate the different levels of facial expressions for forming the final stimuli. In the first phase, 32 Chinese faces (16 females and 16 males) with varied levels of attractiveness were generated with FaceGen software (FaceGen Modeler v3.4). All the faces were of front view with eyes gazing forward. The skin color, hair color, and illumination were also adjusted to the same level across stimuli. The validity of these 32 stimuli was verified by asking a different group of 20 participants to assign ratings reflecting the levels of attractiveness. Faces with the highest (attractive, or A1) and the lowest (unattractive, or UA1) mean ratings, and those with ratings in the 66th percentile (less attractive, or A2) and 33rd percentile (less unattractive, or UA2), were chosen. This resulted in 4 male and 4 female facial templates. In the second phase, happy (H1), less happy (H2), less sad (S2), and sad (S1) expressions were modeled to each of the facial templates according to the criteria described by Ekman (2003), which include raising (or lowering) the tails of both eyes and the edges of the mouth for a happier (or sadder) expression.

This produced 32 facial stimuli (8 stimuli × 4 expressions, see **Figure 1**) for use in the main study.

Task and Procedure

The participant sat in front of a desktop computer, which was situated inside a sound-proof chamber. At the beginning of each trial, a white cross was presented at random intervals (1000–1600 ms), and a facial stimulus was presented on the computer screen for 1200 ms. Upon presentation of the stimulus, the participant was asked to attend to the attractiveness of the face in the Attraction condition and to the expression of the face in the Emotion condition. The participant was to judge the Level of Attractiveness in the Attraction condition or the Level of Expression in the Emotion condition. In most of the trials, the participants were asked to keep the judgments on each face to themselves. Participants were not required to indicate their judgments by making a physical response. This was to enable participants to pay attention to the perception and judgment of the faces and to avoid fatigue from the physical response. The participant, however, was required to make a physical response in each catch trial, which appeared once every 6 to 10 trials within a block. Instead of keeping the judgment to oneself, the participant was to undergo judgment of the face presented and respond using the right hand to press one of two buttons on a keyboard placed in front of the participant. The participant was instructed to regard both A1 and A2 faces as "attractive" and both UA2 and UA1 faces as "unattractive." By the same token, H1 and H2 faces were regarded as "happy," and S1 and S2 faces were regarded as "sad." The right index finger was to press on the left button (indicating "attractive" or "happy"), and the right middle finger was to press on the right button (indicating "unattractive" or "sad"). The correspondence of the buttons to the responses was counterbalanced across the participants.

Stim2 software (Neuroscan Company) was employed to present the facial stimuli and to collect the responses. The 32 facial stimuli were presented twice in a randomized order in each block. There were a total of 16 blocks, eight for each of the Attraction and Emotion conditions. These gave a total of 1024 trials. Each block lasted for about 5 min, with a 30-s break between consecutive blocks. The order of the Attraction and Emotion conditions was interleaved for each participant and counterbalanced across the participants. Each participant was

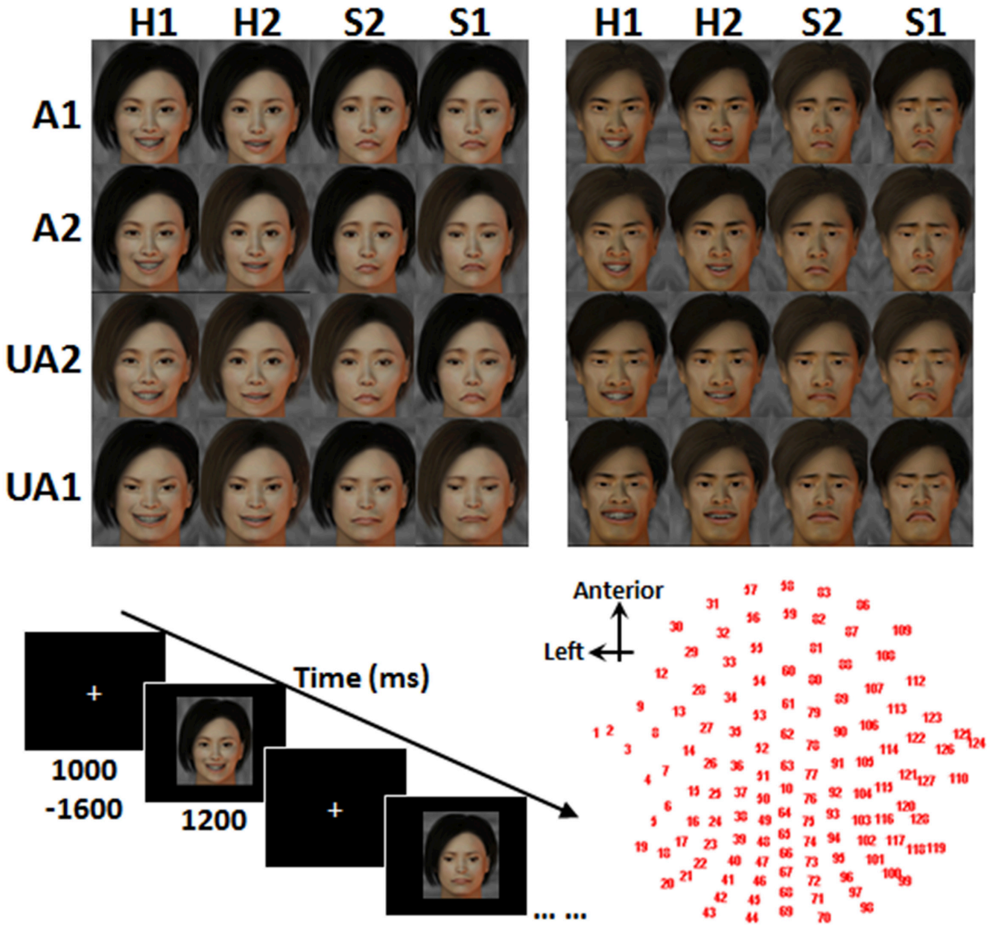

FIGURE 1 | Face stimuli, task paradigm and EEG channel locations. A1, attractive; A2, less attractive; UA2, less unattractive; UA1, unattractive; H1, happy; H2, less happy; S2, less sad; S1, sad.

informed about the condition and reminded of the response set prior to beginning each block. Before commencing the experimental task, the participant completed 10 training trials in which the stimuli were different from those used in the formal task.

Behavioral Responses

For the behavioral data analyses, the faces were classified into 4 categories, i.e., the combinations of attractive (both A1 and A2)/unattractive (both UA1 and UA2) and happy (both H1 and H2)/sad (both S1 and S2) faces. Two 2 (attractiveness: attractive vs. unattractive) by 2 (expression: happy vs. sad) repeated measures ANOVA were conducted under the Attraction condition and the Emotion condition, respectively. *Post-hoc* analyses with Bonferroni correction were carried out if there is significant interaction effect.

ERP Data Recording and Preprocessing

Electroencephalogram (EEG) signals were recorded by a 128-channel fabric cap (Neuroscan company) embedded with Ag-AgCl electrodes in which impedances were kept below 5 kΩ. All channel recordings were referenced to a channel at the left mastoid. The EEG signals were amplified using a 0.01–200 Hz band-pass filter and continuously sampled at 1000 Hz. Vertical eye movement was recorded by two electrodes placed on the top and bottom parts of the left eye. Horizontal eye movement was monitored by two electrodes at the outer canthi of the two eyes.

The EEG data were preprocessed with Scan 4.3 software (Neuroscan Company). The signals were re-referenced to a computed average of channels over the whole scalp and filtered by 0.1–30 Hz band-pass using a zero phase-shift digital filter. Eye-blink artifacts were mathematically corrected (Gratton et al., 1983). Continuous signals were cut into −200 to 1000 ms epochs, with time 0 ms as the reference for the onset of the face stimulus. Baseline correction and artifact rejection were performed so that any signals exceeding $\pm$ 100 μV in any given epoch were discarded. The ERPs of each event for each participant were then averaged.

ERP Data Statistical Analysis

A two-pronged approach was employed for the ERP data analyses: (a) the whole scalp × time space analysis which provides conservative outputs but has the potential to identify unexpected findings, and (b) the region of interest (ROI) analysis which is more sensitive to task effects within sites and time windows selected a priori based on the literature. Here, both analyses were conducted by the statistical parametric mapping (SPM) method which does statistical comparisons voxel-by-voxel. A voxel here is a unit combining both spatial and temporal information (Litvak et al., 2011).

Statistical analyses were conducted using SPM12 software (Wellcome Department of Cognitive Neurology, London, UK). The ERPs were down-sampled to 200 Hz and were then converted into three-dimensional images through interpolating the ERP amplitude at each channel site per time point. The x and y dimensions of an image reflect "left-right" and "anterior-posterior," respectively, on the horizontal projection of a scalp, and the z dimension represents the timeline. The images were smoothed by a full width at half-maximum (FWHM) Gaussian filter of 9 mm, 9 mm, and 20 ms (Sun et al., 2012, 2015). These images were entered into a Three-way analysis of variance (ANOVA) model in SPM12. The three factors were condition (two levels: Attraction and Emotion), Level of Attractiveness (four levels: A1, A2, UA2, and UA1) and Level of Expression (four levels: H1, H2, S2, and S1).

Voxel-by-voxel analyses within a large scalp × time space have to correct a large number of comparisons, and may decrease the statistical sensitivity to the task effects. We thus tried to reduce the number of voxels for comparisons. Firstly, an inclusive mask covering the whole scalp and the time range from 80 to 980 ms was employed to restrict the space of the analysis. This time interval has been commonly adopted in previous ERP studies on face perception. Secondly, some previous studies have reported very early ERP components responsive to attractiveness or expression. Here, to investigate the potential neural correlates before the peak of P2, a separate ANOVA was conducted for signals captured within the 100–200 ms time window.

The significant ANOVA results for clusters of voxels were height-thresholded at $p < 0.001$ (F-tests, two-tailed) and that survived peak- or cluster-level familywise error (FWE) correction ($p < 0.05$) within the space of analysis. Furthermore, the clusters showing significant main or interaction effects were employed as mask images to restrict the space of *post-hoc* analyses. In this study, the *post-hoc* analyses on the Level of Attractiveness/Level of Expression effect had six pair-wise effects (i.e., $[4 - 1] \times 2$, since each had two contrast directions); while the number of *post-hoc* analyses on the Level of Attractiveness × Level of Expression effect was multiplied fourfold. The peak-level FWE *corrected* p-values after Bonferroni adjustments were $0.05/12 = 0.004$ or $0.05/48 = 0.001$, depending on the effects generated from the Three-way ANOVA model. To avoid both type I (due to multiple comparisons) and type II (due to too-stringent thresholds) errors, for simplicity, the statistical significance set for the *post-hoc* analyses was height-thresholded at $p < 0.05$ (T-tests, one-tailed) and survived peak-level FWE $p < 0.004$ in the clusters of interest.

The dissociation in the early processing was tested within the 100–200 ms space (scalp × time) for the Level of Attractiveness effect (height-thresholded at $p < 0.001$) outside a mask showing the Level of Expression effect (height-thresholded at $p < 0.05$). In other words, the effect of Expression was removed when testing for the effect of Attractiveness. The same procedure was repeated for testing Level of Expression effect outside a mask showing Level of Attractiveness effect. A lenient threshold of $p < 0.05$ was adopted, which is common in testing the dissociation effect in other neuroimaging studies (Pochon et al., 2002; Voon et al., 2014).

ERP Source Reconstruction Analysis

The sources of ERP signals were reconstructed and analyzed by the group inversion (imaging method) module in the SPM12 software. The electrode positions over the scalp of each participant were aligned with the standard template devised in SPM12. The ERP data of each event for each participant was inverted using the multiple sparse priors approach (Friston et al., 2008). The process modeled the scalp EEG signals as the activities resulting from numbers of dipolar sources distributed over the cortical sheet with fixed locations and orientations but varied intensities across the participants (Litvak and Friston, 2008). The intensity of the identified sources was converted into the brightness of a 3D image per task event and time window of interest for each participant. The 3D images were spatially smoothed by an 8-mm FWHM and then overlaid onto a standard MNI (Montreal Neurological Institute) brain template. The images derived in the same time window were tested by a Three-way ANOVA model similar to that used for the scalp ERP analyses. Significant main and interaction effects were reported. The statistical significance set for the source analyses was $p < 0.05$ with cluster size > 150 voxels. A large cluster size was used to minimize false positive errors.

RESULTS

Behavioral Findings

The accuracy rates of the behavioral responses were shown in Supplementary Table 1. Besides the significant main effect of attractiveness and the main effect of expression under both Attraction and Emotion conditions ($Fs > 9.553$, $ps < 0.006$), the more interesting findings are that the interaction between attractiveness and expression was significant under both Attraction [$F_{(1,\ 19)} = 101.761$, $p < 0.001$] and Emotion [$F_{(1,\ 19)} = 27.193$, $p < 0.001$] conditions. *Post-hoc* analyses showed that, under the Attraction condition, the accuracy rates of happy expression were significantly higher than those of sad expression [$t_{(19)} = 12.155$, $p < 0.001$] when presenting attractive faces, whereas the accuracy rates of sad expression were significantly higher than those of happy expression [$t_{(19)} = 6.720$, $p < 0.001$] when showing unattractive faces. On the other hand, under the Emotion condition, the accuracy rates of attractive faces were not significantly different from those of unattractive faces [$t_{(19)} = -1.955$, $p = 0.130$] when the expression was happy, whereas the accuracy rates of unattractive faces were significantly higher than those of attractive faces [$t_{(19)} = 9.308$, $p < 0.001$] when the expression was sad. The findings suggested that the judgment of attractiveness (expression) is modulated by facial expression (attractiveness) even when the latter facial characteristic is of no interest.

ERP Findings

The statistical results are shown in **Tables 1**, **2**. The Condition effect was found to be significant only in within the 160–200 ms period, in a cluster in the left occipital region where Attraction condition was associated with more positive amplitudes than the Emotion condition.

The waveforms and 2D topographies for the Level of Attractiveness effect are presented in **Figure 2**. The Level of Attractiveness effect was found to be significant in three voxel clusters within the 80–980 ms time window. The first cluster was in the left occipito-temporal region within the 220–260 ms period. The UA1 faces elicited more negative-going amplitudes than did the A2 faces. The second cluster was in the medial centro-parietal region within the 510–610 ms period. The results of this cluster will be elaborated later under the results of the interaction between Level of Attractiveness and Level of Expression. The third cluster was at the right temporal region

TABLE 1 | SPM ANOVA results on the ERP amplitudes.

t-begin	*t*-peak	*t*-end	Cluster	*Z*	Channel	Area
MAIN EFFECT OF LEVEL OF ATTRACTIVENESS						
150[a]	175	200	827	4.958	20	L OT
155[a]	190	200	476	4.939	99	R OT
220	240	260	582	4.461	20	L OT
510	535	610	412	4.221	66	M CP
825	845	900	430	3.833	120	R T
MAIN EFFECT OF LEVEL OF EXPRESSION						
150	190	305	2349	6.622	72	M P
365	580	780	12713	6.345	75	M CP
430	570	680	2330	5.114	123	R F
150	165	205	545	4.627	52	M C
INTERACTION: LEVEL OF ATTRACTIVENESS × LEVEL OF EXPRESSION						
450	580	725	2191	5.039	75	M CP
MAIN EFFECT OF CONDITION						
160[a]	180	200	308	3.874	45	L O
INTERACTIONS INVOLVING CONDITION						
NS						

Height-thresholded at $p < 0.001$ and survived cluster- or peak-level FWE correction ($p < 0.05$) on the whole scalp and within the time window 80–980 ms.

[a] denotes significance detected within 100–200 ms only. The time of the beginning, peak significance and end of the cluster are represented by t-begin, t-peak and t-end, respectively. Cluster refers to the number of voxels in the cluster. Z is the Z-value. Channel denotes the channel nearest to the peak significance. Area denotes the spatial distribution on the scalp. NS, no significance; L, left; M, medial; R, right; F, frontal; C, central; CP, central-parietal; P, parietal; T, temporal; OT, occipital-temporal; O, occipital.

within the 825–900 ms period. *Post-hoc* analyses showed that UA1 faces elicited more negative-going amplitudes than any other faces.

Within the special time window of 100–200 ms, the Level of Attractiveness effect was found to be most significant in two voxel clusters: the left and right occipito-temporal regions within 150–200 ms. The effects were in fact most prominent at the rising edge of P2, and were thus defined as P2-lateral (P2l).

The waveforms and 2D topographies for Level of Expression effect are presented in **Figure 3**. The Level of Expression

TABLE 2 | *Post-hoc* analyses within the clusters showing significant effects shown in Table 1.

	Main effect of Level of Attractiveness					
	A2	**UA2**	**UA1**	**A2**	**UA2**	**UA1**
	150–200 ms, L OT area			**155–200 ms, R OT area**		
A1	NaN	0.050	<0.001*	NaN	0.191	<0.001*
A2	–	0.312	<0.001*	–	0.341[a]	<0.001*
UA2	–	–	0.014	–	–	0.001*
	220–260 ms, L OT area			**825–900 ms, R T area**		
A1	0.403[a]	0.202	0.005	0.168[a]	NaN	0.001*
A2	–	0.012	<0.001*	–	NaN	<0.001*
UA2	–	–	0.114	–	–	0.001*
	Main effect of Level of Expression					
	H2	**S2**	**S1**	**H2**	**S2**	**S1**
	150–205 ms, M C area			**150–305 ms, M P area**		
H1	0.001[a]*	<0.001[a]*	<0.001[a]*	<0.001*	<0.001*	<0.001*
H2	–	0.220[a]	0.047[a]	–	NaN	0.013
S2	–	–	0.136[a]	–	–	0.140
	430–680 ms, R F area			**365–450 ms, M CP area**		
H1	0.096	0.009[a]	0.007[a]	0.011	<0.001*	<0.001*
H2	–	<0.001[a]*	<0.001[a]*	–	<0.001*	0.007
S2	–	–	0.025	–	–	0.102[a]
	725–780 ms, M CP area					
H1	0.016[a]	0.051	0.003*			
H2	–	<0.001*	<0.001*			
S2	–	–	0.344			
	Level of Attractiveness × Level of Expression, 450–725 ms, M CP area					
	A2	**UA2**	**UA1**	**A2**	**UA2**	**UA1**
	H1			**H2**		
A1	0.740	0.002*	0.005	0.805	0.547	0.137
A2	–	0.005	0.077	–	0.316	0.109
UA2	–	–	0.587[a]	–	–	0.303
	S2			**S1**		
A1	0.306	0.001*	0.562	0.408	0.619[a]	0.001[a]*
A2	–	0.026	0.041[a]	–	0.093[a]	<0.001[a]*
UA2	–	–	0.006[a]	–	–	0.001[a]*

Values shown in the table were p-values of T-tests (peak-level FWE corrected within the cluster of interest defined in ANOVA) between variables in rows and variables in columns. The p-values with (without) a superscript character (a) refer to variables in columns that are smaller (greater) than variables in rows. An asterisk (*) denotes that the p-value survived a Bonferroni correction for multiple comparisons in the post-hoc analyses. A1, attractive; A2, less attractive; UA2, less unattractive; UA1, unattractive; H1, happy; H2, less happy; S2, less sad; S1, sad.

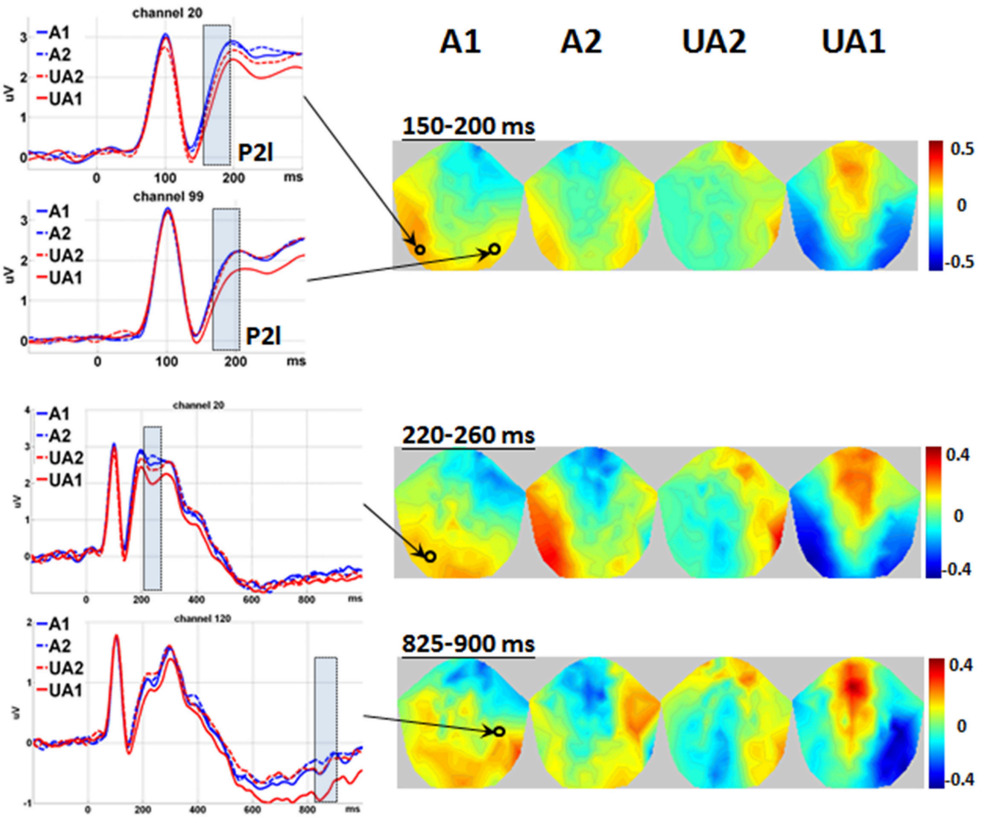

FIGURE 2 | Main effect of level of attractiveness. Waveforms are shown in the representative channels 20 (left occipital-temporal), 99 (right occipital-temporal), and 120 (right temporal). The waveforms of P2l are only shown from −100 to 300 ms to clarify the details of each level of Level of Attractiveness. The 2D topographies are shown for the amplitudes averaged within the intervals 150–200, 220–260, and 825–900 ms, respectively. To clarify the difference between different levels of Attractiveness, mean amplitudes averaged across all conditions were removed from the 2D topographies. The shadowed bars represent the time windows' detecting significance, the small circles locate the representative channels, and the color bar denotes the range of amplitudes (μV). A1, attractive; A2, less attractive; UA2, less unattractive; UA1, unattractive.

effect was also found to be significant in voxel clusters within the 80–980 ms time window. To avoid being confused by the interaction between Level of Attractiveness and Level of Expression in the 450–725 ms range and distributed at the medial central-parietal areas (which corresponded to the LPP), the cluster showing a significant Level of Expression effect within the 365–780 ms period was further separated into two clusters covering 365–450 ms and 725–780 ms periods. The first cluster was in the medial centro-parietal region, which showed a positive-going deflection at the 365–450 ms period. This suggested the elicitation of the LPP, of which H1 faces were more positive-going than either S1 or S2 faces, and H2 faces were more positive-going than the S2 faces. Within the cluster at the 725–780 ms interval, H1 faces were more positive-going than S1 faces, and H2 faces were more positive-going than either S1 or S2 faces. Another cluster showing a significant Level of Expression effect was found in the frontal region, which showed a negative-going deflection within the 430–680 ms range. The H2 faces were more negative-going than either S1 or S2 faces.

Within the special time window of 100–200 ms, the Level of Expression effect was further found to be significant in two voxel clusters. For the first cluster, it was in the medial parietal region, eliciting a positive-going deflection around 190 ms. This corresponded closely to the elicitation of the P2 component, and was defined as P2-medial (P2m) to differentiate it from the P2l associated with attractiveness. The H1 faces were found to have more positive-going P2m than all other faces. Its negative-going counterpart was detected in the medial central region. Similarly, all other faces were more negative-going than the H1 faces. It is noteworthy that the effects of Level of Expression and Level of Attractiveness had similar times of onset (i.e., 150 ms) but different spatial distributions. The Level of Expression was found to be most significant in the medial parietal region (for P2m), and the Level of Attractiveness was most significant in the bilateral occipito-temporal regions (for P2l).

Further analysis supported the double dissociation between the Level of Attractiveness and Level of Expression effects within the 100–200 ms time window (**Figure 4**). The Level of Attractiveness effect was found to peak in the left occipital-temporal sites at 175 ms ($Z = 4.928$, cluster size $= 492$ voxels) after excluding the Level of Expression effect. In contrast, after excluding the Level of Attractiveness effect, the Level of

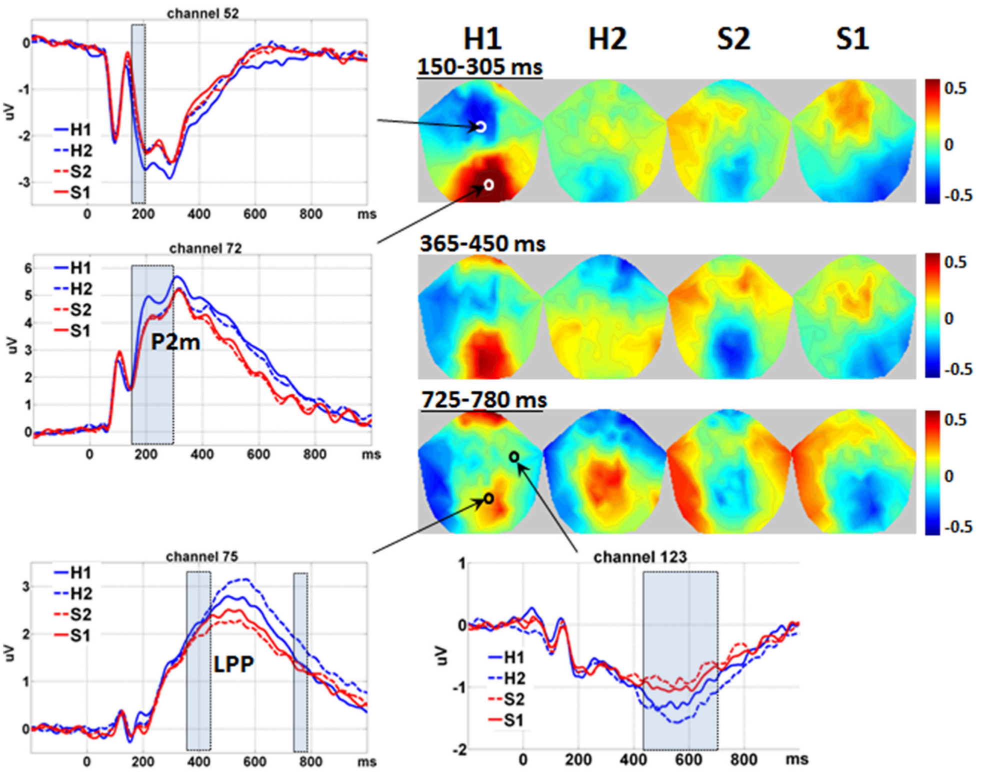

FIGURE 3 | Main effect of level of expression. Waveforms are shown in the representative channels 52 (medial central), 72 (medial parietal), 75 (medial central-parietal), and 123 (right frontal) according to **Table 1**. The shadowed bars represent the time windows' detecting significance. Please notice that the interval of 450–725 ms is not covered to avoid overlap with the interaction effect between Level of Attractiveness and Level of Expression. For the same reason, the 2D topographies are shown for the amplitudes averaged within the intervals 150–305 ms (150–205 ms is not shown for simplicity), 365–450 ms and 725–780 ms, respectively. To clarify the difference between different levels of Expression, mean amplitudes averaged across all conditions were removed from the 2D topographies. The small circles locate the representative channels, and the color bar denotes the range of amplitudes (μV). H1, happy; H2, less happy; S2, less sad; S1, sad.

Expression effect was found to peak in the medial parietal sites at 190 ms ($Z = 7.151$, cluster size = 710 voxels) and in the medial fronto-central sites at 165 ms ($Z = 4.848$, cluster size = 176 voxels).

Significant interactions were found between the Level of Attractiveness and Level of Expression effects in the voxel cluster in the medial centro-parietal region within the 450–725 ms time window (**Figure 5**). These corresponded to the LPP, in which A1 faces were found to elicit more positive amplitudes than the UA2 faces when the expression was either H1 or S2. In contrast, the UA1 faces elicited more positive amplitudes than all other faces when the expression was S1.

Source Analysis Findings

For the Level of Attractiveness effect, significant activities were detected in sites that coincided with locations in the bilateral parahippocampal gyri within the 150–200 ms and 220–260 ms periods (**Figure 6**). Another significant site was identified in the right fusiform gyrus within the 825–900 ms period. For the Level of Expression effect, significant activities were detected at the site that coincided with the bilateral middle temporal gyri within the 150–305 ms and 365–450 ms periods. A few more sites were identified, with one detected in the right fusiform gyrus within the 365–450 ms period and another in the bilateral fusiform gyri and the left temporal gyri within the 725–780 ms period. For the interaction between Level of Attractiveness and Level of Expression, significant activities were detected in the site that coincided with the bilateral temporal poles within the 450–725 ms period.

DISCUSSION

The results suggested that the Level of Attractiveness and Level of Expression were reflected by two early ERP components, P2l and P2m, respectively. Significant interaction effects were found in a late ERP component, LPP. These findings supported the hypothesis that facial attractiveness and expression are likely to be processed separately in the early phase and then integrated for processing in the late phase. To our knowledge, this study is the first to dissociate the neural processes of perceiving attractiveness and emotional expression, filling the gap in the classical model of face perception (Bruce and Young, 1986; Haxby et al., 2000).

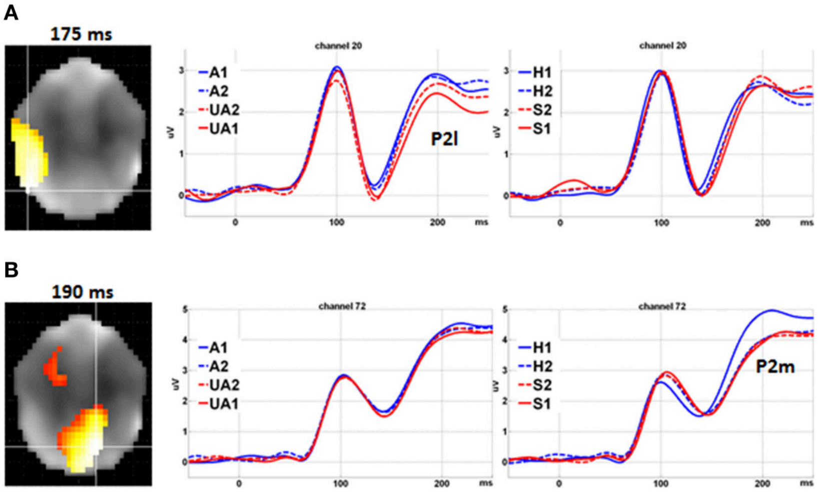

FIGURE 4 | Double dissociation between level of attractiveness and level of expression. (A) Main effect of Level of Attractiveness after excluding the effects of Level of Expression. Waveforms in channel 20 at left occipital-temporal sites showed clear differences for different levels of Attractiveness (reflected by P2l) but not for different levels of Expression. **(B)** Main effect of Level of Expression after excluding the effects of Level of Attractiveness. Waveforms in channel 72 at medial parietal sites showed clear differences among different levels of Expression (reflected by P2m) but not for different levels of Attractiveness. A1, attractive; A2, less attractive; UA2, less unattractive; UA1, unattractive; H1, happy; H2, less happy; S2, less sad; S1, sad.

Early Processing Before 350 ms

No interaction effects were revealed on the Level of Attractiveness and Level of Expression in the early stage of face perception. This result suggested that facial attractiveness and facial expression are likely to be processed independently soon after the subjects viewed the face stimuli. This was supported by the different scalp and temporal distributions and amplitudes elicited by the different levels for the attractiveness and expression conditions. First, the amplitudes of the Level of Attractiveness effect were the most significant at the bilateral occipital-temporal sites (P2l), while the Level of Expression effect reached its peak significance at the medial parietal (P2m) and medial central sites. Second, although both effects began from 150 ms after the face onset, the Level of Attractiveness effect ended at 200 ms while the Level of Expression effect ended at 305 ms. Third, significant P2l deflection was observed between the faces with the most negative valence in Level of Attractiveness (i.e., UA1 or unattractive faces) and all other faces, whereas significant P2m deflection was detected between the faces with the most positive valence in Level of Expression (i.e., H1 or happy faces) and all other faces. Using the "exclusive mask" method, significant Level of Attractiveness effects at the left occipital-temporal sites (P2l) were identified after excluding the Level of Expression effect. In contrast, significant Level of Expression effects were identified at the medial parietal and medial frontal-central sites (P2m) after excluding the Level of Attractiveness effect. These converging findings showed a double dissociation between the two effects within the 100–200 ms range. They support our hypothesis that processing of facial attractiveness and facial emotional expression are distinct during the early stage of face perception. Given that P2 has been supposed to reflect the comparison between sensory input and stored memory (Luck and Hillyard, 1994) and initial "attention capture" of (physically) distinctive faces (van Hooff et al., 2011), our findings suggest that faces at the early stage of processing are compared with stored prototypes and/or are allocated with attentions in the dimensions of attractiveness and expression in parallel. This idea is consistent with the opinion that varied aspects of the face may be extracted in parallel to build a multi-dimensional space (Freeman et al., 2010). Previous studies reported that P2 was modified by facial attractiveness (Halit et al., 2000; van Hooff et al., 2011; Zhang and Deng, 2012) or facial expression (Spreckelmeyer et al., 2006; Ofsson and Polich, 2007). Their findings are different from those revealed in this study. All of these studies did not concurrently manipulate both effects, which perhaps introduced confounding effects in their study design. In our study, facial attractiveness and expression were manipulated in the experimental task. The difference in the task designs is likely to contribute to the difference in interpretation of the functionality of P2.

The results of the source reconstruction offer further insight into the neural processing of facial attractiveness and emotional expression. Bilateral parahippocampal gyri were identified as the key neural substrate associated with the attractiveness effects. This contrasted to the bilateral middle temporal gyri associated with the facial expression effects. The parahippocampal gyri are adjacent to the fusiform gyri which have been found to respond stronger to attractive (vs. neutral) faces (Chatterjee et al., 2009). Given that our source results were only derived from the scalp ERP data and might be biased in spatial localization, the findings in parahippocampal gyri could have been originated from the fusiform gyri. On the other hand, the middle temporal gyrus has often been reported in studies on emotion (Sabatinelli et al., 2011), although there is no direct evidence supporting the relationship between this area and P2.

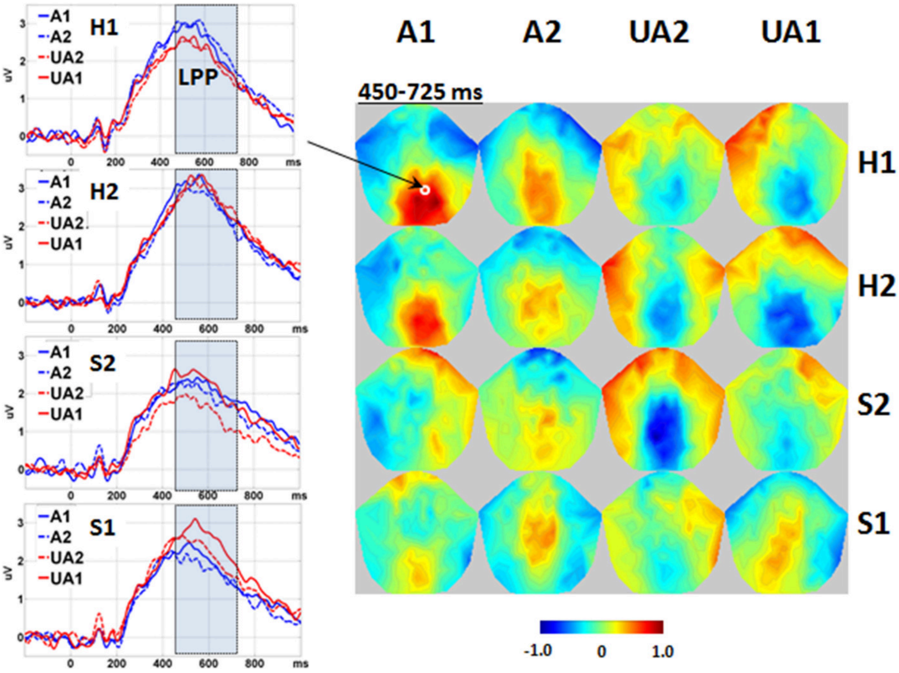

FIGURE 5 | Interaction between level of attractiveness and level of expression. Waveforms are shown in the representative channel 75 (medial central-parietal). The 2D topographies are shown for the amplitudes averaged within the interval 450–725 ms. To clarify the difference between conditions, mean amplitudes averaged across all conditions were removed from the 2D topographies. The shadowed bars represent the time windows' detecting significance, the small circles locate the representative channels, and the color bar denotes the range of amplitudes (μV). A1, attractive; A2, less attractive; UA2, less unattractive; UA1, unattractive; H1, happy; H2, less happy; S2, less sad; S1, sad.

These results suggested that the brain areas involved are different for the two types of face information in the early stage of face perception.

It is noteworthy that besides P2l and P2m, this study identified a third component elicited within the 220–260 ms time-window at the left occipital-temporal sites associating with the Level of Attractiveness but not the Level of Expression effect. The results indicated that the less attractive faces (A2) elicited more positive amplitudes than the unattractive faces (UA1). Burkhardt et al. (2010) reported a positive deflection peaked at around 250 ms, identified as P250, at the bilateral temporal-occipital sites. The amplitude was found decreased with the increase in the amount of distortion (compressive or expansive) of a face. Burkhardt et al.'s study has two implications. First, the component associated with the facial attractiveness effects could be P250. Second, unattractive faces could have been perceived by subjects as distorted representation of average faces, of which the latter were regarded as norm or mental (Langlois and Roggman, 1990; Rhodes et al., 1999). Another possibility of this third component associating with facial attractiveness is an early posterior negativity (EPN) elicited within the 220–260 ms. Previous studies suggested that EPN was associated with visual attention to emotional stimuli (Junghöfer et al., 2001; Schupp et al., 2007). However, other studies reported more-negative EPN for attractive than unattractive faces (Werheid et al., 2007) or for highly attractive than for medium- or low-attractive faces (Marzi and Viggiano, 2010). These findings are in contrary to results of this study. Future studies are called for to verify the association of P250 or EPN with early processing of the facial attractiveness effects.

Late Processing After 350 ms

Significant interactions were revealed between the Level of Attractiveness and Level of Expression effects. Within the 450–725 ms range, the unattractive sad faces (UA1 in S1 condition) were found to elicit more positive LPP than all the other sad faces; on the contrary, attractive happy faces (A1 in H1 condition) also elicited more positive LPP than less unattractive happy faces. It appears that the LPP was modulated and enhanced by both the attractiveness and expression effects along the same direction of valence. The strongest effects were found in negative valences, i.e., unattractive faces with sad expression. Previous studies suggested that LPP reflects late neural process of allocating attentional resources on stimuli of high intrinsic motivational properties (Johnston and Oliver-Rodriguez, 1997; Cuthbert et al., 2000; Werheid et al., 2007; Foti et al., 2009). In other words, late processing of face perception is likely to tap on an increase in attentional resource intensified by unattractive faces with sad expressions. This observation coincides with the "negativity bias" in which unpleasant stimuli were found to produce stronger emotional effects than pleasant stimuli (Crawford and Cacioppo, 2002). In real life situation, people

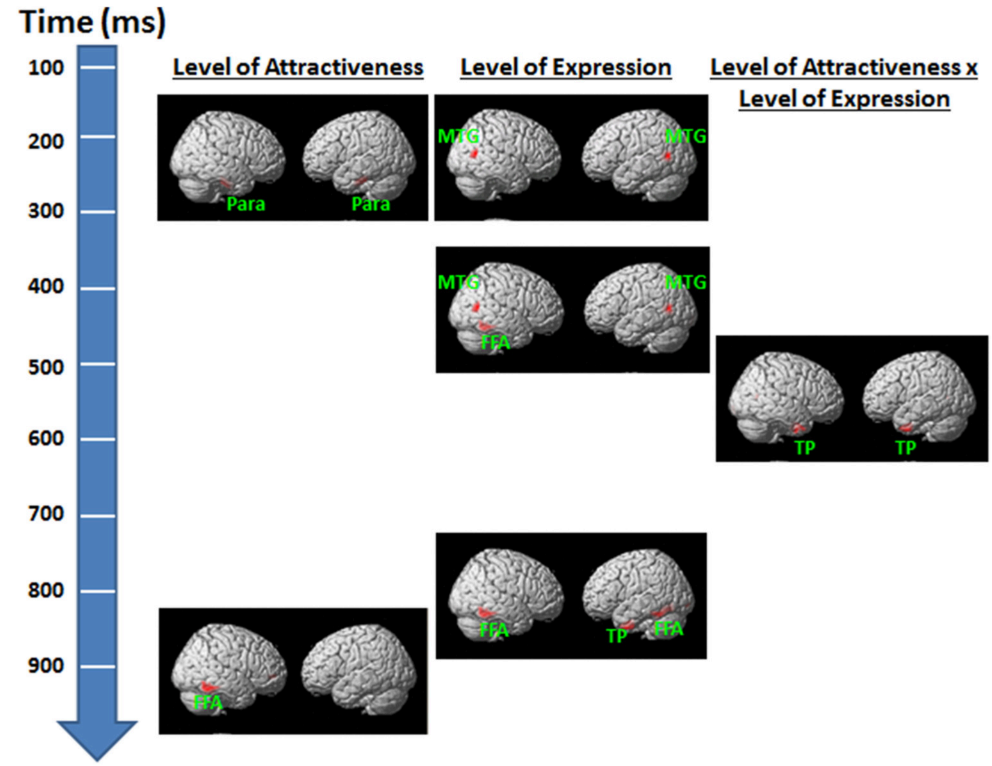

FIGURE 6 | Source reconstruction results for the effects of level of attractiveness and level of expression and their interaction in each time window of interest. For observation purposes, results are height-thresholded at $p < 0.05$ with cluster size > 150 voxels. FFA, fusiform area; MTG, middle temporal gyrus; Para, parahippocampal gyrus; TP, temporal pole.

would readily attend to smiling face of a pretty celebrity which can be easily forgotten. In contrast, people would be hesitated to look at sad face of an unfortunate victim which is vividly remembered for a prolonged period of time.

Some previous studies have detected U-shaped pattern of LPP for the effect of attractiveness (Schacht et al., 2008; Marzi and Viggiano, 2010). That is, larger LPP is elicited by either attractive or unattractive faces than faces of medium attractiveness. Here, we also found in some cases that faces with extreme rating on attractiveness elicited larger LPP than those with relatively neutral ratings. In another words, when the expression was either happy (H1) or less sad (S2), attractive faces (A1) elicited larger LPP than relatively more neutral faces, i.e., less unattractive faces (UA2). The findings suggested that the U-shaped pattern of LPP is modulated by both attractiveness and expression.

It should be noted that an interval showing significant effect of Level of Expression (365–450 ms) was found just before the interval showing the abovementioned interaction effect (450–725 ms). Larger LPP (rising edge) was found to be elicited more by happy (H1) than by less sad (S2) or sad (S1) faces, and more by less happy (H2) than by less sad (S2) faces. This finding suggested that positive and negative expressions would have been discriminated prior to interacting with attractiveness. This processing could have facilitated the integrative processing of attractiveness and expression during the 450–725 ms time-window.

The results of source analyses indicated that the right fusiform gyrus was identified to associate with the significant LPP amplitudes elicited by the facial expression effect within the 365–450 ms. This result is consistent with previous findings that the fusiform gyrus mediated perception of human faces (Haxby et al., 2002; Gobbini and Haxby, 2007), particularly for faces with emotional (rather than neutral) expressions (Sabatinelli et al., 2011). On the other hand, the bilateral temporal poles were identified to associate with the significant LPP amplitudes elicited by both the facial attractiveness and facial expression effects. The temporal poles were found to mediate binding of complex perceptual inputs to visceral emotional responses (Olson et al., 2007). The source analyses results further corroborate the finding that the late process of LPP within the 450–725 ms range reflects complex attention allocation and/or appraisal processing integrating the facial attractiveness and emotion effects.

We found that the interval showing significant interaction between Level of Attractiveness and Level of Expression (450–725 ms) was located within a long time window showing main effect of level of Expression (365–780 ms). Similar to the main effect of Level of Expression found at the rising edge of LPP (365–450 ms), larger LPP (descending edge, 725–780 ms) was elicited by happy (H1) than by sad (S1) faces, and more by less happy (H2) than by less sad (S2) faces or sad faces. In line with the thought that LPP reflects allocation of attention to stimuli of high intrinsic motivational properties (Werheid et al., 2007; Foti et al., 2009), our findings suggested that facial expression changes the attention allocated on the faces, and this modulation further interacts with the processing of facial attractiveness.

We also found, on the other hand, a significant main effect of Level of Attractiveness 825-900 ms. Previous ERP studies on LPP findings of facial attractiveness are often within the time window between 200 and 700 ms (Werheid et al., 2007; Marzi and Viggiano, 2010; van Hooff et al., 2011; Zhang and Deng, 2012). Few studies on attractiveness have reported the findings beyond 800 ms. Thus, the cognitive processes associated with this late component are still unclear. A previous study by Foti et al. (2009) showed that the LPP appears to include three positivities peaking at 353, 841, and 1595 ms, suggesting that LPP consists of several subcomponents. However, the neural processes reflected by the three subcomponents are still unknown. The findings by both us and other teams convergently suggest that our understanding of the late ERP components is still limited. Future studies should investigate the cognitive processes associated with the late components.

The behavioral responses showed dramatic changes of the classification of attractiveness (expression) when the Level of Expression (Attractiveness) varied. The response patterns may reflect the behavioral outputs of the interactions between Level of Attractiveness and Level of Expression. In this study, we fabricated the face stimuli in the way that the variation of Level of Attractiveness and the variation of Level of Expression are independent from each other. The selected face stimuli thus allow us to investigate the neural correlates of either facial attractiveness or expression without being confounded by participants' subjective judgment. Future studies should further address the question that how the judgment of either attractiveness or expression is influenced by task requirement.

Findings in this study are consistent with studies on romantic love. For example, enhanced LPP was found to be elicited by beloved-related (vs. friend-related) face images (Langeslag et al., 2007) and words/phrases (Langeslag et al., 2015), suggesting that attention is enhanced for beloved-related information. A recent study using magnetoencephalography (MEG) also reported results comparable to the LPP effect (Tiedt et al., 2014). In line with our findings and the aforementioned discussions, facial attractiveness and facial expression may affect the processing of beloved-related information by influencing the attention given to it. This effect may be reflected by late-latency components, including LPP. This hypothesis should be tested in future studies on the neural processing of romantic love.

CONCLUSION

This study delineated the time course of neural processing for perceiving facial attractiveness and facial expression. In early processing, facial attractiveness (reflected by P2l), and facial expression (reflected by P2m) are likely to be processed separately for discrimination between stimuli during the early stage of face perception. In later processing, more attentional resources (reflected by LPP) would be allocated to the faces with the most positive or most negative valences in either attractiveness or expression. Finally, the faces are processed separately (reflected by slow waves). These findings contribute to advancing the theoretical model of face perception.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fpsyg.2015.01812

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Romantic Love Is Associated with Enhanced Inhibitory Control in an Emotional Stop-Signal Task

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Purpose: This study explored whether romantic lovers differ in emotion-related inhibitory control capacity from those who are single.

Methods: 88 healthy undergraduate college students participated in the study. Half were currently in love and in a romantic relationship (love group, LG), and half were single and had never been in a romantic relationship (single group, SG). Based on duration of romantic relationship (i.e., love duration), the LG were further divided into two subgroups: "early stage love" and "longer periods of love". All participants completed an emotional Stop Signal Task, consisting of a variety of human face stimuli displaying either sad or neutral affect.

Results: Results found that relative to SG, lovers showed greater inhibitory control [shorter stop-signal reaction time (SSRT)] during negative emotion condition trials. Furthermore, in early stages of love, SSRT for negative emotion condition trials was significantly shorter compared to that in "longer periods of love" or SG individuals, with no significant differences between the two latter groups.

Conclusion: Compared with individuals who were single, early stage lovers showed greater capacity for inhibiting action during presentation of negative emotional stimuli. Within a greater social context, greater inhibitory control capacity during early stages of love may be related to the successful formation of romantic relationships, particularly to the ability to persevere in goal-directed action despite negative emotional contexts such as that of sadness.

Keywords: romantic love, inhibitory control, emotional stop signal task, sadness

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INTRODUCTION

Romantic love manifests from an integration of behaviors, cognitions, and emotions associated with the desire to enter or maintain an intimate relationship with a specific other person (Aron and Aron, 1991; Cacioppo et al., 2012; Diamond and Dickenson, 2012). This involves behavioral, emotional, and cognitive components (Sternberg, 1986; Hazan and Shaver, 1987). Romantic love is highly correlated with relationship intimacy satisfaction, relationship quality and stability (Riehl-Emde et al., 2003; Acevedo and Aron, 2009), and is even a precondition for marriage (Simpson et al., 1986). Within a wider context, the ability to form meaningful and enduring relationships is an important social skill.

Cognitive control, also known as self-control or executive function (Baumeister and Vohs, 2003), is a skill commonly associated with higher order processing, necessary for goal-oriented behavior. Individual differences in cognitive control capacity have been shown to predict a wide range of behaviors, including forgiveness and faithfulness in close relationships, ability to resist from flirting behaviors with a confederate, and mastery over the desire to meet an attractive person (Pronk et al., 2010, 2011). These findings suggest that the formation of romantic relationships may benefit from optimal cognitive control abilities.

Negative emotions can disrupt cognitive control capacity, such as the ability to inhibit action via top-down mechanisms (Goldstein et al., 2007; Verbruggen and De Houwer, 2007; Kalanthroff et al., 2013; Rebetez et al., 2015). On the other hand, romantic love has been shown to provide resiliency against the adverse impact that negative emotion can have on individuals. For example, a study found that autonomic reactivity (indexed by Respiratory Sinus Arrhythmia) in single individuals decreased during the presentation of negative emotions, indicating a physiological stress response (Schneiderman et al., 2011). No such decrease was found amongst new lovers who began a romantic relationship 2.5 months prior to the experiment, pointing towards enhanced vagal regulation during periods of falling in love (Schneiderman et al., 2011). Furthermore, Studies have even demonstrated pain relief from simply viewing pictures of a romantic partner (Nilakantan et al., 2014). Given the social and biophysiological implications, it is thus important to examine the interaction between emotion and cognitive control within the context of romantic love.

Sadness is a subjective experience that may arise from unpleasant situations and inner feelings of loss or lack of expected gains (Ellsworth and Smith, 1988). In fact, it is reported as one of the most widespread forms of emotional distress. Generally, sadness is thought to motivate vigilant and detail-oriented processing of information, possibly in order to reestablish a sense of control over a situation (Schwarz and Clore, 1996; Bodenhausen et al., 2000; Gasper, 2004). Importantly, although many may differentiate sadness from other negative emotions, to some extent, sadness itself is a negative stimulus that influences attention and results in many similar effects as other negative emotions (Joormann and Gotlib, 2007).

The stop signal task is canonically a behavioral task that is used to examine the ability to control and inhibit ongoing action, called "response inhibition" (Logan and Cowan, 1984; Aron and Poldrack, 2006). In this task, stimuli are presented in regular succession for speeded discrimination responses, but they occasionally appear with unpredictable stop signals that require withholding responses to the target in mid-action (i.e., require inhibition of prepotent motor action). A measure of the stop signal task, the stop signal reaction time (SSRT) is one of the most often used indices of inhibition, where the shorter the SSRT, the greater the hypothesized inhibitory control (Logan and Cowan, 1984). Similarly, the *emotional* stop signal task (eSST) has emerged as a good paradigm for studying the interaction between emotion and inhibitory control that also provides the SSRT metric for analysis and interpretation.

The eSST is an emotion-focused version of the stop-signal task that helps assess how task-related or task-independent emotional signals modulate inhibitory motor control during performance of a behavior (Hare et al., 2005; Pawliczek et al., 2013). In the eSST, emotional pictures are intermixed with neutral stimuli/non-emotional pictures. Interestingly, emotion recognition and emotion regulation are important components of the quality of inter-communication experienced between partners of a romantic relationship (Roisman, 2007). In fact, it has been found that they can help predict marital dissatisfaction and even divorce (Levenson and Gottman, 1985; Gottman and Levenson, 1992). Various studies have also found that negative emotional stimuli can harm inhibitory control capacity, with longer SSRT seen for negative emotion condition trials (Verbruggen and De Houwer, 2007; Kalanthroff et al., 2013). This "negativity effect", is thought to be attributed to the greater attention and deeper processing that is allocated to threatening information/stimuli (Fox et al., 2002; Vuilleumier and Huang, 2009). In neuropsychiatric disease, negative emotional stimuli have been shown to disrupt inhibitory function in conditions such as anxiety (Sehlmeyer et al., 2010), depression (Gotlib and McCann, 1984; Johnstone et al., 2007; Joormann and Gotlib, 2010) and post-traumatic stress disorder (Frewen and Lanius, 2006).

In the current study, an eSST that incorporates sadness as the emotional experimental stimulus was used to explore the interaction between emotion and response inhibition in romantic lovers, relative to not-in-love single individuals. Interestingly, this kind of interaction may be shown in varying degrees depending on the stage of love one is in, as different stages of love are hypothesized to have different underlying psychological and physiological characteristics. The first phase of an intimate relationship is "being in love" (i.e., early stage of love), and it is characterized by increased commitment, high passion, and a rapid rise in intimacy (García, 1998). This stage plays a key role in the successful formation of pair bonding, and can last from half a year to a year (Marazziti and Canale, 2004). The general features of early stage love may include an altered mood and mental state, as well as excitation and stress caused from insecurity (Stárka, 2007; Berscheid, 2010). These characteristics in new lovers may lead to changes in biomechanisms (Marazziti and Canale, 2004), and may elicit the need for greater cognitive effort when dealing with the risk of a breakdown in a new and still fragile relationship. After several months up to about a year (Marazziti and Canale, 2004; Stárka, 2007), the initial phase of excitation, euphoria and stress, evolves into a "longer period of love", driven by feelings of balance, safety, and tranquility (Stárka, 2007). It is also composed of features related to passionate love, but in contrast to early stage love, here commitment and intimacy increase steadily and gain more importance (García, 1998). Thus, it is suggested that early stage love may ameliorate the interference of negative emotions on inhibitory control ability, leading to greater inhibition even during emotionally negative conditions, a process theorized to help form romantic relationships. Correspondingly, once having entered later stages of love, decreased stress (Esch and Stefano, 2005), safety and calmness (Stárka, 2007), as well as a relatively stable relationship, may cause a psychophysiological shift where greater inhibitory control capacity becomes less of a necessity.

To better understand this phenomenon and stratify emotional inhibitory control capacity as a function of duration of love, in the current study we employed an emotional stop-signal task. We first ran an exploratory analysis to determine whether there is a significant difference in inhibitory control for emotional condition trials between love and control groups. Then, we performed further analyses to explore possible differences between early stage (ELG) and longer periods of love (LLG). We hypothesized that relative to a control group of single individuals, early stage lovers would demonstrate greater inhibitory control capacity (shorter SSRT), particularly for negative emotion condition trials. On the other hand, an enhanced inhibitory effect was not predicted for romantic lovers in LLG.

MATERIALS AND METHODS

Ethics Statement

This study was approved by the review board and Ethics Committee of Southwest University. Written informed consent was obtained from all participants. All participants were informed that their participation was completely voluntary and that they may withdraw from the study at any time. All participants were over 18 years of age.

Participants

Eighty-eight students from Southwest University (SWU, Chongqing, China) participated in the study for monetary compensation. They were interviewed at the beginning of the study procedure regarding previous romantic relationships and demographic characteristics. All participants were divided into two groups according to their previous romantic relationship: (1) an "in-love" group (LG; $N = 44$, 21 males) consisting of individuals currently intensely in love [duration of love ranged from 1 to 18 months (8.8 ± 5.0)] – all LG were not married and had no children; and (2) a "single" group (SG; $N = 44$, 19 males), consisting of individuals who had never been in a romantic relationship with anyone before. Based on the distribution of the duration of love, we divided the LG into two subgroups: early stage love (ELG, from 1 to 8 months, $N = 23$), and longer periods of love group (LLG, from 9 to 18 months, $N = 20$).

Age of participants ranged from 18 to 25 years old – LG (21.39 ± 2.1) and SG (21.45 ± 2.2). All participants had normal or corrected-to-normal vision, were right-handed, had no history of attention deficit or learning disabilities, and all were naive as to the purpose of the experiment. Five participants were excluded from further analyses due to high error rate on no-stop-signal trials [more than 3 standard deviations (SD) from the mean], leaving the sample with 83 participants in total for analyses: LG ($N = 43$, 21 males) and SG ($N = 40$, 15 males).

Questionnaires

Passionate Love Scale

The Passionate Love Scale (PLS) (Hatfield and Sprecher, 1986) was used to measure the status of passionate/romantic love in the LG. The PLS has been previously used in samples of Chinese college students (Yin et al., 2013; Song et al., 2015).

Equipment

Participants sat in a soundproof experiment room with their eyes approximately 100 cm from a 17-in monitor. The screen resolution was 72 pixels per inch, and the viewing angle was $5.7 \times 4.6°$. A keyboard was placed on the table between the participant and the screen, and participants were tested one by one. All experiment programs were compiled and executed using E-Prime software (Schneider et al., 2002).

Stimuli

Stimuli consisted of face pictures from the Chinese Affective Picture System (Bai et al., 2006) of males and females displaying either sad or neutral affect. Each emotion category had 40 pictures, half of them males, and the remaining half females. The picture system provided rated valance and arousal values for each stimulus. For valence rating [mean: sad = 3.11 ($SD = 0.63$), neutral = 4.33 ($SD = 0.45$)], sad face pictures were rated more negatively relative to neutral pictures [$t_{(78)} = -9.96$, $p < 0.001$]; for arousal rating [mean: sad = 5.37 ($SD = 1.34$), neutral = 4 ($SD = 1.12$)], sad face pictures were rated as more arousing relative to neutral pictures [$t_{(78)} = 4.95$, $p < 0.001$]. All stimuli were similar to the others in size, background, brightness, contrast grade, spatial frequency, and other physical properties.

Emotional Stop Signal Task

We used an emotional version of the stop-signal task (Sagaspe et al., 2011). The task included 20 practice trials, which were not further analyzed. Participants were told that the practice trials would be identical to the experimental blocks, except that the experimental blocks would be longer, and would not include feedback.

Each Go trial began with a fixation cross (the duration was jittered from 600 to 1500 ms), immediately followed by a face stimulus for 1000 ms. Participants were required to discriminate the emotion of the face and answer by pressing the correct keyboard button (for sad emotion: using their right index finger to press "1"; for neutral emotion: using their right middle finger to press "2"; experimental keyboard button rules were counterbalanced) as quickly and as accurately as possible during the 1000 ms presentation (**Figure 1A**). All participants were right-handed and used their right hand to respond.

In Stop trials, a red 'x' mark ('×') appeared after a face picture and participants were instructed to inhibit their response if they saw the "×" picture after a face picture (**Figure 1B**). The interval between the face onset and the "×" picture (the stop signal delay; SSD) was adjusted online as a function of the subject's performance on their previous stop-trial with the same facial expression. SSD was initially set at 250 ms. Each time a participant failed to inhibit their response in presence of a stop signal, the SSD decreased by 50 ms. On the other hand, when inhibition was successful, the SSD increased by 50 ms. Thus, stopping difficulty was kept under experimental control on a trial-by-trial basis, eventually obtaining a probability of successful stopping of 50% for both neutral and emotional trials (Levitt, 1971).

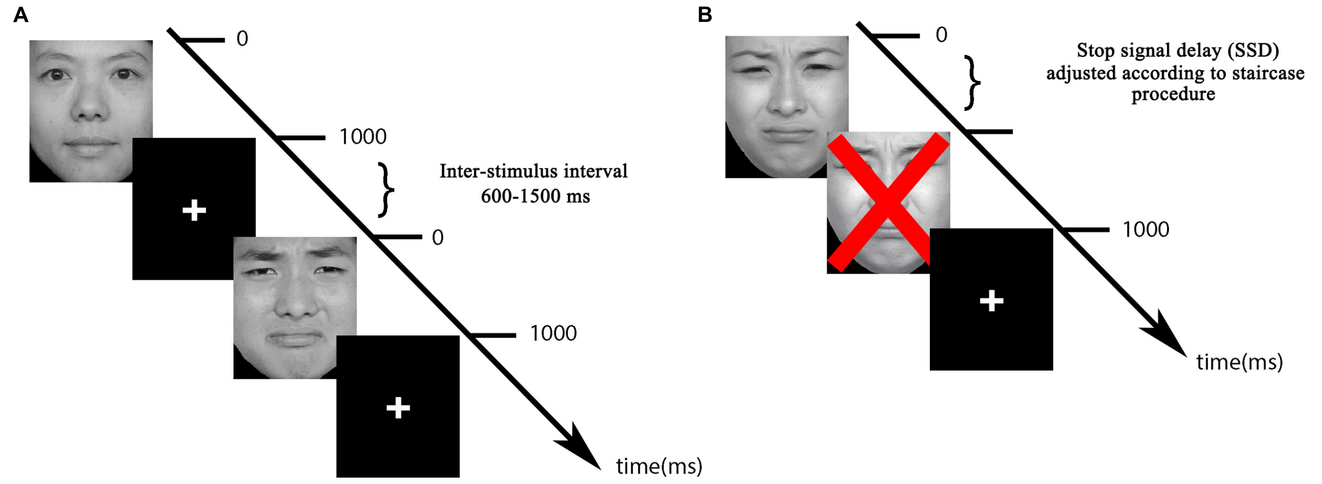

FIGURE 1 | Task trials depicting one neutral, one sad Go trial (A), and one sad Stop trial (B).

Taken together, there was only a 25% probability chance of a "×" picture appearing after a face picture, and the participants did not know when to restrain their reaction. Because they may be tempted to wait for the emergence of an "×", we instructed to the participants to press the correct key as fast and as accurately as possible, and we emphasized to not wait for a potential stop signal. After practice, there were a total of six blocks of 80 trials each. Each block comprised of 60 Go trials and 20 Stop trials. Half of the trials displayed sad faces, and the other half displayed neutral faces. The experimental trials were delivered in a pseudorandom order, with a maximum of two Stop trials in a row.

Accuracy on Stop trials as well as mean RT was calculated automatically after each block as feedback for the experimenter to verify compliance with the task. After each block, participants were again reminded that both speed and accuracy in each trial were important.

Data Analysis

Reaction times (RTs) for correct responses during the 1000 ms presentation of the stimuli are reported. The most important indicator describing stopping efficacy that uses RT and is typically derived from a Stop Signal Task is the SSRT. This metric shows the time taken after a stop signal is presented for inhibition to be completed (Logan, 1994). As some participants may strategically slow down their responses over the course of the experiment in order to make inhibiting easier, we adopted the integration approach (Logan and Cowan, 1984; Boehler et al., 2012) instead of the mean approach (Logan, 1994). By taking deviations from an even ratio of successful and unsuccessful Stop-trials into account, this approach is more robust against variations. Go-trial reaction times (goRTs) were rank-ordered, and the RT value at the percentile that corresponded to the percentage of unsuccessful Stop-trials was determined on a subject-per-subject basis (Boehler et al., 2012). Then, the SSRT was calculated as goRT minus average SSD.

Any goRT less than 300 ms (~1%) in the current study was removed from the analysis. Repeated-measures ANOVAs were performed, with Emotion condition (neutral vs. sad) modeled as a within-subjects factor, and Group (LG vs. SG) as a between-subjects factor. The correct percentage of Go trials were also recorded, as well as unsuccessful rate of stopping and SSRT. In order to further explore differences in inhibitory control across early stage love (from 1 to 8 months, 23 participants), LLG (from 9 to 18 months, 20 participants), and those in the single group (23 participants randomly selected from all 40 single individuals), SSRTs of sad emotion condition trials were further analyzed using one-way ANOVA with Tukey's Honest Significant Difference (HSD) as *post hoc* analyses.

RESULTS

The mean PLS score in LG was 96.7 ± 11.19.

For goRT, percentage of correct Go trials and unsuccessful stopping rate showed no significant main effect or interaction ($Fs < 1$) (**Table 1**).

For SSRT, there was a significant main effect of emotion condition [$F_{(1,81)} = 27.731$, $p < 0.001$, $\eta^2 = 0.255$], with longer SSRT (indicating poorer response inhibition) in the sad compared to the neutral condition trials. No significant main effect of group was observed [$F_{(1,81)} = 2.022$, $p > 0.05$] (**Table 1**). A significant interaction between emotion condition and group was found [$F_{(1,81)} = 6.445$, $p = 0.013$, $\eta^2 = 0.074$]. A simple main effect analysis showed that the SSRT for sad stimuli was significantly shorter in LG than in SG [$F_{(1,81)} = 4.988$, $p = 0.028$, $\eta^2 = 0.058$], but that SSRT for neutral stimuli was not significantly different between LG and SG [$F_{(1,81)} = 0.227$, $p > 0.05$, $\eta^2 = 0.003$]. Concurrently, while in SG the SSRT for sad stimuli was significantly longer than the SSRT for neutral trials [$F_{(1,81)} = 29.394$, $p < 0.001$, $\eta^2 = 0.266$] (**Figure 2**), in LG SSRT was similar between sad and neutral trials [$F_{(1,81)} = 3.678$, $p > 0.05$, $\eta^2 = 0.045$].

TABLE 1 | Behavioral performance on the emotional stop signal task (eSST) for LG and SG individuals.

		LG ($N = 43$)		SG ($N = 40$)		ME (*p*) (group)	ME (*p*) (emotion)	Interaction (*p*)
		Mean	***SD***	**Mean**	***SD***			
goRT (ms)	Sad	580.10	66.07	575.25	55.61	0.674	0.618	0.868
	Neutral	579.10	60.50	573.29	52.52			
Percentage go success	Sad	0.88	0.08	0.89	0.07	0.704	0.683	0.54
	Neutral	0.89	0.07	0.89	0.07			
Percentage stop error	Sad	0.41	0.05	0.42	0.06	0.559	0.749	0.189
	Neutral	0.41	0.05	0.41	0.05			
SSRT (ms)	Sad	211.16	33.86	228.42	36.55	0.159	**<0.001**	**0.013**
	Neutral	203.93	37.10	207.74	35.72			

LG, love group; SG, single group; SD, standard deviation; RT, reaction time; SSRT, stop signal reaction time; ME, main effect; ms, milliseconds; group = LG, SG; emotion = sad, neutral. Significant effects are marked in bold.

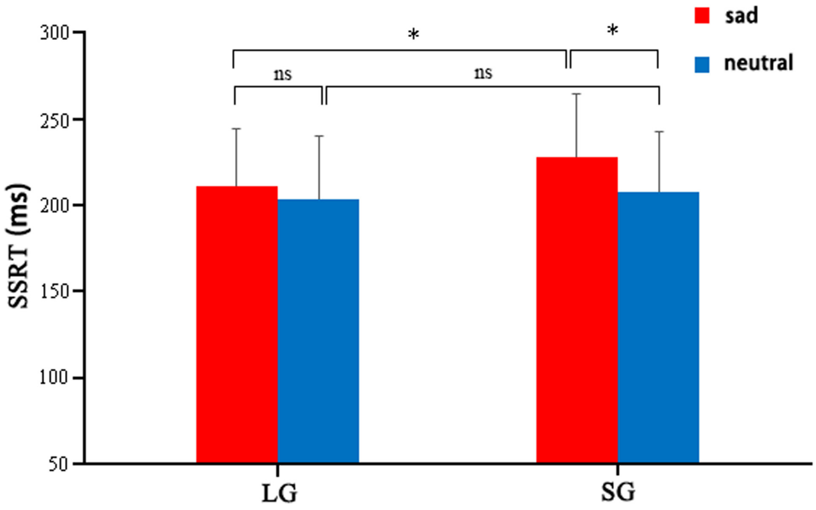

FIGURE 2 | Emotional Stop Signal Task (eSST) performance between LG and SG, by emotion condition (neutral, sad). eSST, emotional Stop Signal Task; SSRT, stop signal reaction time; LG, love group; SG, single group. *$p < 0.05$; ns, not significant.

Differences across Early Stage Love, Longer Periods of Love, and SG for SSRT of Sad Emotion Condition Trials

Significant differences in the SSRT of sad emotion was found across these three groups: early stage love (199.84 ± 37.85), longer period love (224.17 ± 23.29), and SG (228.52 ± 35.09), $F_{(2,65)} = 4.96$, $p < 0.01$. In *post hoc* analyses, significant differences for SSRT of sad condition trials were observed between early stage love compared with both individuals in LLG ($p = 0.049$) and SG ($p = 0.013$), but no significant differences between the LLG and SG were found ($p > 0.05$) (**Figure 3**). Similar results were found when including participants' PLS scores as a covariate to the group of lovers.

DISCUSSION

To our knowledge, this is the first study investigating the possible effects of romantic love on negative emotion-related inhibitory control capacity. We found that sad face stimuli in the negative emotion condition of the eSST can interfere with inhibitory control mechanisms, as demonstrated by the longer SSRT relative to the SSRT of the neutral condition. Furthermore, romantic love may attenuate the inhibitory control impairment effect associated with unpleasant emotion priming. Compared to the single group, in lovers, we found enhanced inhibitory control during the presentation of sad stimuli. Furthermore, the lovers in the early stage had better inhibitory control performance for negative emotion condition trials than those in LLG. These findings suggest that individuals in early stages of romantic love could benefit from enhanced self-control ability, allowing for relationships to form and mature.

The Influence of Sad Emotion on Cognitive Control

We found prolonged SSRT for sad (negative) emotion stimuli trials compared to neutral stimuli trials, consistent with several previous studies using an eSST (Verbruggen and De Houwer,

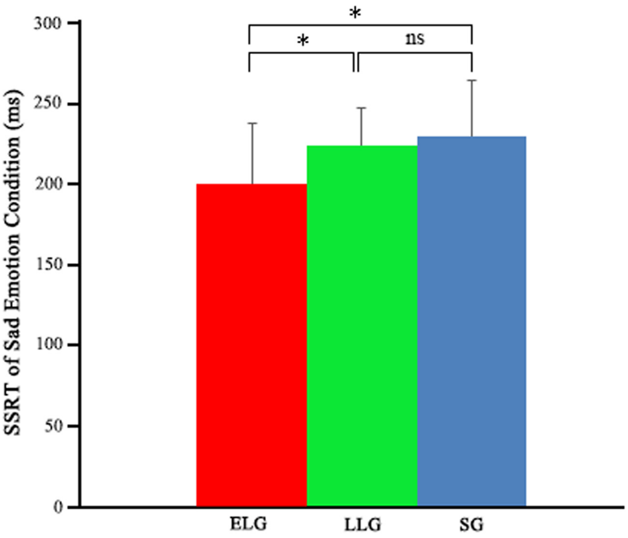

FIGURE 3 | Emotional Stop Signal Task performance (sad condition) between ELG, LLG, and SG. eSST, emotional Stop Signal Task; SSRT, stop signal reaction time; ELG, early stage lovers; LLG, longer period lovers; SG, single group. *$p < 0.05$; ns, not significant.

2007; Herbert and Sütterlin, 2011; Kalanthroff et al., 2013), and a go/no-go task (Goldstein et al., 2007). Essentially, the ability for stopping via top–down control mechanisms was impaired on average during the presentation of a negative stimulus.

Numerous studies suggest that emotionally salient cues (for example, threatening stimuli or angry faces) can intensely impact attention (Lerner et al., 2012; Pourtois et al., 2013; Carretié, 2014), that being the capacity to selectively respond to pertinent aspects of the environment while suppressing potential sources of distraction and competing courses of action (Desimone and Duncan, 1995; Miller and Cohen, 2001). Furthermore, emotion and cognition have been classically viewed as rival forces (Damasio, 2005; Okon-Singer et al., 2007). Specifically, a threatening stimulus consumes processing resources that are needed for successful inhibitory performance (Pessoa, 2009; Pessoa et al., 2012). From these perspectives, threat-related emotional stimuli may disturb cognitive processes.

Although sadness differs from other negative emotions (for example, anger) with lower arousal levels, it is arguably more far-ranging, and longer lasting in daily life relative to other emotional states (Ellsworth and Smith, 1988). To some extent, it is also a negative stimulus that influences our attention (Joormann and Gotlib, 2007). Some early research studies suggest that sadness reduces the efficiency of attention-related tasks, and may constrict the attention range (Potts et al., 1989). Still others have shown sadness to be related to higher physiological impulsivity (Camras and Allison, 1989), as well as a tendency to overly focus on the self and one's self image (Wang et al., 2005). Several cerebral limbic and paralimbic systems have been identified when coping with sadness, including the ventral medial preFrontal Cortex (vmPFC) (Suslow et al., 2013), Anterior Cingulate Cortex (ACC) (Habel et al., 2005), Insula (Liotti et al., 2000), and Amygdala (Aldhafeeri et al., 2012). However, few studies have examined the specific influence of sadness on response inhibition via an eSST. As the neural mechanisms also remain unclear, these should be addressed in future studies as it was not the main focus of the present study.

Romantic Love Can Modulate the Influence of Negative Emotion on Inhibitory Control

This study provides the first evidence that romantic love may modulate the interference of negative emotion on inhibitory control. Our results also offer a further extension to earlier work about intimate relationships and self-control. In particular, we demonstrate that individuals in the early stage of love (ELG) group showed greater response control during the sad emotion condition trials. However, relative to ELG, this improvement in inhibitory control was absent in those who were in the LLG.

The disparate results between ELG and LLG are consistent with characteristics of the two stages of love. For example, during the initial stages of love, it is important to efficiently inhibit any harmful or impulsive behavior arising from negative emotion in order to form an intimate relationship with the special partner – a lack of constructive reaction to negative emotions may halt or stand in the way of successful formation of the intimate relationship. Interestingly, early stage lovers also seem to experience significant pain relief when looking at a picture of their partner (Nilakantan et al., 2014), a potentially beneficial survival mechanism that goes hand in hand with enhanced cognitive control mediated by romantic love. Previous studies have found that those in longer partnerships (8–17 months), rather than the early stage (1–8 months), showed greater activity in the ventral pallidum (Aron et al., 2005). The ventral pallidum has been implicated in attachment in prairie voles (Lim and Young, 2004; Lim et al., 2004). Thus, after several months of stressful interplay, the lovers enter into a calm and safe state (García, 1998). The experience of attachment starts to accompany feelings of romantic love (Fisher, 2004; Acevedo et al., 2012) and the commitment aspect of love becomes more important during longer-term stages. By this stage, they have formed a relatively stable close relationship with their partner(s) and the need for greater cognitive control to integrate negative emotions diminishes.

Improved cognitive control in romantic lovers is in general in line with with several studies showing that romantic love can be beneficial for cognitive control (Bianchi-Demicheli et al., 2006; Nilakantan et al., 2014; Wlodarski and Dunbar, 2014). For example, studies including participants from early to longer stages of love (but without the additional analyses differentiating between the two phases), suggest that presentation of a love-related stimulus can also prime love-relevant networks and enhance subsequent performance on conceptually related mentalizing tasks (Wlodarski and Dunbar, 2014). Even the subliminal presentation of a romantic partner's name, in contrast with a friend's name, can facilitate cognitive performance on a lexical-decision task (Bianchi-Demicheli et al., 2006; Ortigue et al., 2007).

Furthermore, the potentially enhanced social inhibition capacity in lovers may be related to increased parasympathetic activity as measured by the Respiratory Sinus Arrhythmia response to negative stimuli. This response works to prevent autonomic stress and facilitates emotion regulation in the early stages of love (Schneiderman et al., 2011). Overall, properly adjusting current action in order to make better suitable behavioral responses to lovers, friends or even strangers, is dependent upon the proper recognition of others' explicit negative demeanor (such as sadness).

The neural mechanisms for the greater cognitive function found in lovers may be related to increased functional connectivity (FC) in frontal areas. Our previous study (Song et al., 2015) for example, found that the FC between the temporo-parietal junction, ventromedial prefrontal cortex, and dorso-medial prefrontal cortex were increased in lovers. These brain networks are known to subserve social cognition. Additionally, some of these regions and networks have been consistently suggested to be associated with 'theory of mind' tasks (the ability to determine other people's emotions and intentions) (Gallagher and Frith, 2003), facial expression recognition (Winston et al., 2002), and have been reported in several functional Magnetic Resonance Imaging (fMRI) studies of lovers (Aron et al., 2005; Xu et al., 2011; Acevedo et al., 2012).

The enhanced cognitive function in lovers may also be the result of neural biochemical mechanisms. Studies show a critical role for oxytocin (OT) in promoting pair-bonding formation, and OT has been shown to modulate social interaction and sexual satiety in prairie voles (Carter, 1992; Williams et al., 1992; Witt et al., 1992). Importantly, significantly elevated plasma OT has been found during the early stages of human romantic relationships (Schneiderman et al., 2012).

Furthermore, in order to solve stressful situations (Marazziti and Canale, 2004), cortisol levels elevate, and testosterone levels and follicle stimulating hormone are down regulated in early romantic love (de Boer et al., 2012). This early phase is also characterized by low serotonin levels (Marazziti et al., 1999) and high nerve growth factor (Emanuele et al., 2006). However, during later stages of love, levels of several neuroendocrine substances found to be changed in early romantic love, return back to normal levels (de Boer et al., 2012). For example, platelet serotonin transporter (Marazziti et al., 1999) and nerve growth factor (Emanuele et al., 2006), return to normal levels, and stress is decreased (Esch and Stefano, 2005). Because of the potential use of these substances as biomarkers for love (including duration of love) and their potential psychophysiological effects, in future studies we aim to collect and explore these biochemicals across early stage and the late stages of love.

On a related note, the current study has some implications for addiction. For example, romantic lovers can show impulsive behaviors that are similarly found in addiction (e.g., obsessive thinking about the person, increased energy, as well as emotional dependency on and craving for emotional union with the beloved) (Aron et al., 2005), and these behaviors are sometimes even viewed as a form of natural reward addiction (Fisher et al., 2016). Furthermore, both romantic love and drug addiction display functional enhancement of reward and emotion regulation networks (Breiter et al., 1997; Aron et al., 2005; Ortigue et al., 2007; Volkow et al., 2007; Frascella et al., 2010; Xu et al., 2011). However, the current findings and our previous fMRI study results suggest that romantic love displays special functional enhancement in social cognition networks (Song et al., 2015), while drug addiction displays special dysfunctions of cognitive control networks (Goldstein and Volkow, 2011). Thus, cognitive control seems to be the key difference between romantic love and addiction. In turn, we see that greater inhibitory capacity in early stages of love may thus not only help form close relationships with others, but also help to develop and mature those relationships in a healthy manner, in contrast with drug and behavioral addiction. Because of these similarities and key differences, a better understanding of how romantic love improves cognitive control during early development of love could help inspire new treatments for drug addiction.

Limitations and Future Directions

Despite the novel results of the study, there are several limitations to be acknowledged. First, only sad and neutral emotion stimuli were used in the current study, and thus, findings may not be arbitrarily generalized to other negative emotions (e.g., fear and/or anger). Thus, cognitive control capacity in other emotional contexts needs to be explored in future studies. Second, duration of love within the sample only ranged from 1 month to 18 months, and all participants were not married and had no children. Thus, the current results do not allow us to make any assumptions about longer-term durations of romantic love (e.g., several years). Because of this, it is also unknown if the early stage of a new marriage or that of having a child would show similar enhancement of inhibitory control, which could serve as an interesting topic for future research studies. Third, longitudinal studies would be very helpful in disentangling how and why inhibitory control changes across the development and maturation of romantic relationships, perhaps providing more causal findings than what is possible with cross-sectional studies such as the present one.

CONCLUSION

To conclude, in the current study we found that early stage lovers, compared to later stage lovers and single individuals, had greater inhibitory control performance during negative emotion condition trials of an eSST. Greater inhibitory control capacity in those who are in love may help form and maintain romantic relationships in the fragile initial stages. These results shed light on the possible benefits of being "in love" on cognitive control and inhibition capacity, and demonstrate the possibility of applying an approach without using love-relevant cues (e.g., pictures of romantic partners) for investigating the influence of romantic love on cognition.

AUTHOR CONTRIBUTIONS

SS is responsible for the original experimental design, data analysis and article writing. ZZ is responsible for the experimental process, data collection, and article writing. HS is responsible for experimental design and data analysis. YW is responsible for behavioral questionnaire data and experimental procedure plan. FdU is responsible for manuscript writing, copy editing, and content editing. HW is responsible for chart and graph arrangement, including **Table 1** and **Figures 1** to **3**, arrangement of data, and proofreading of the manuscript. HC is responsible for experimental design and guidance throughout.

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A Role of DLPFC in the Learning Process of Human Mate Copying

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In the current study, we conducted a behavioral experiment to test the mate coping effect and a functional magnetic resonance imaging (fMRI) experiment to test the neural basis involved in the social learning process of mate copying. In the behavioral experiment, participants were asked to rate the attractiveness of isolated opposite-sex (potential mates) facial photographs, then shown the targets associating with a neutral-faced model with textual cues indicating the models' attitude (interested vs. not-interested) toward the potential mates, and then asked to re-evaluate the potential mates' attractiveness. Using a similar procedure as the behavioral experiment, participants were scanned while observing the compound images in the fMRI experiment. The mate copying effect was confirmed in the behavioral experiment – greater increase in attractiveness ratings was observed for opposite-sex photographs in the interested than in the not-interested condition. The fMRI results showed that the dorsolateral prefrontal gyrus (DLPFC) was significantly active in the comparison of interested > not-interested condition, suggesting that a cognitive integration and selection function may be involved when participants process information from conditions related to mate copying.

Keywords: mate copying, social learning, cognitive execution, fMRI, DLPFC

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INTRODUCTION

When it comes to assessing the attractiveness of men, women can be influenced by other women relatively easily. For example, in a study by Eva and Wood (2006), in which 38 women rated physical attractiveness of men in photographs, men who were identified as married were generally rated as more physically attractive than men who were identified as single. Women rated men as being more desirable if the men were pictured with other women rather than pictured alone or with other men (Hill and Buss, 2008). This social transmission of mate preferences has been broadly referred to as mate copying or mate-choice copying and has been described in humans in recent years (Eva and Wood, 2006; Jones et al., 2007; Waynforth, 2007; Little et al., 2008; Place et al., 2010; Yorzinski and Platt, 2010; Bowers et al., 2011).

The attitude of the same-sex partner (the model) toward a potential mate (the target) has been shown to influence observers' assessment intensively (Jones et al., 2007; Place et al., 2010; Yorzinski and Platt, 2010). For example, Jones et al. (2007) performed a study in which the participants viewed the same males associating with either a female with smiling face (showing interest) or a female with a neutral expression (not showing interest). They found that observing a paired female showing interest in the male enhanced observers' preference for that male to a greater extent than did observing a paired female with an uninterested expression. Although it has been observed more in women, mate copying effect has also been systematically observed in men (Place et al., 2010; Yorzinski and Platt, 2010). For example, both men and women were observed to express more interest in engaging in a relationship with a potential mate if that mate was paired with a partner with smiling face (Yorzinski and Platt, 2010).

Mate copying has been hypothesized to save time and cognitive effort through social learning otherwise needed to evaluate the quality of potential mates (Dugatkin, 1992; Pruett-Jones, 1992; Westneat et al., 2000). However, individual-based copying also carries a possibly costly consequence: It places mate seekers especially in the thick of competition (Brennan et al., 2008), specifically when the mates have already been chosen by others. In many species, competition often leads to intra-sexual conflict which can induce serious survival costs (Bowers et al., 2011). Therefore, some researchers have suggested that mate copying is a strategic use of public information via social learning (Richerson and Boyd, 2005; Little et al., 2008, 2010). That is, mate copying may be not just a blind copying, but a process involving copiers' recon on trade-offs between personal and public information use (Laland, 2004; Kendal et al., 2005), and how and when the public information will be most useful (Little et al., 2010). Indeed, once social learning evolved, it would pay to be selective about whom to learn from and what cues to learn because some models will be more successful than others (Henrich and Gil-White, 2001). Previous studies have shown this 'selection bias' in mate copying. For example, men and women were influenced in their judgment of attractiveness of potential mates by the apparent choice of attractive members of the same sex (Sigall and Landy, 1973; Yorzinski and Platt, 2010; Little et al., 2011). Another study using images that were presented with a fictitious partner has shown that both men and women find a face paired with an attractive partner to be more attractive than one paired with an unattractive partner for a long-term but not a short-term relationship (Little et al., 2008). In non-human species, bias has been observed in fish that while younger female guppies copy the choice of older females, the latter do not copy the choice of the former (Dugatkin and Godin, 1993).

In addition, copying effects can be trait-based and more general, where individuals learn about the traits of those chosen and find those traits more attractive in other individuals (White and Galef, 2000; Godin et al., 2005; Swaddle et al., 2005). This generalization has also been shown quite complicated. For example, while the generalized change of attractiveness ratings has been found with manipulations of eye-spacing (Little et al., 2010), the other studies indicate that both males and females fail to exhibit trait-based mate copying for facial traits, yet exhibit it for hair and clothing traits (Bowers et al., 2011) and shirt color trait (Place et al., 2010).

In a summary, in the learning process of mate copying, copiers may need to integrate and select information from the observed partners and then make an appropriate response accordingly. This cognitive execution function has been found especially related to the dorsolateral prefrontal cortex (DLPFC) in recent study (Buckholtz and Marois, 2012). For example, the 'integration-and-selection' hypothesis suggests that the role of DLPFC is to guide the selection of a specific response from among possible response options by integrating relevant information with context-specific rules about how to apply this information (Buckholtz and Marois, 2012). Thus, we hypothesized that compared with the condition of models with uninterested attitude toward the target, the DLPFC should be more active in the condition where models are interested in the potential mates because copiers have to integrate information to recon on trade-offs between personal and public information use (Laland, 2004; Kendal et al., 2005) and which information will be most useful to make an adaptive decision.

Accordingly, we conducted a behavioral and a fMRI experiment to test our hypothesis. The behavioral experiment was conducted to test the effect of mate copying by using a similar paradigm of previous research (Little et al., 2008; Place et al., 2010; Yorzinski and Platt, 2010; Bowers et al., 2011). Specifically, participants were first asked to rate the attractiveness of isolated opposite-sex (potential mates) faces, then shown the targets associating with a neutral-faced model (compound images) with textual cues indicating the models' attitudes (interested vs. not-interested) toward the potential mates, and then asked to re-evaluate the potential mates' attractiveness. The effect of mate copying was assessed by calculating the attractiveness ratings assigned to the individual opposite-sex facial photographs before vs. after viewing the compound images in the interested and not-interested conditions. The fMRI experiment was conducted using the similar rating-observation-re-rating procedure. The scanning process was performed while participants viewing the compound images, which has been the key social learning process in mate copying (Richerson and Boyd, 2005; Jones et al., 2007; Little et al., 2008, 2010, 2011; Yorzinski and Platt, 2010; Bowers et al., 2011). The activated brain regions involved in the learning process related to mate copying can be extracted by comparing trials in the interested condition with trials in the not-interested condition. The difference in DLPFC activation was predicted to be captured by the above-mentioned statistical analyses.

MATERIALS AND METHODS

Participants

There were 92 participants (46 of each sex; age range: 18–24 years; mean age ± standard deviation: 21.56 ± 2.12 years) recruited from a university community with flyers and by word of mouth. All were healthy, self-reported heterosexuals with normal or corrected-to-normal vision, and all provided written informed consent. The study protocols were approved by the ethics committee of the university. Participants were randomly assigned to separate behavioral ($N = 60$, 30 of each sex) or scanning ($N = 32$; 16 of each sex) pools at signup. Scanning participants were screened for current psychiatric diagnoses, and right-handedness. Participants were paid and debriefed after they finished the experiment.

Stimuli

Individual Photographs

Stimuli were color photographs of 64 men and 64 women from the local university student population. All photographs captured a neutral expression and showed a frontal view without makeup, accessories, or glasses. They were cropped at the neck and adjusted to 300 × 300 pixels against a white background in Adobe Photoshop. The lighting conditions were adjusted to a consistent standard. The photographs were rated for attractiveness by other participants from the university using a 1–7 Likert scale (1 = very unattractive, 7 = very attractive). The rater group included 30 males and 35 females (age range, 18–27 years). Mean attractiveness scores for male and female faces were 3.06 ± 0.80 and 3.32 ± 0.78, respectively. We included photographs with mid-range attractiveness scores ($M \pm 1$ *SD*) to exclude extremely attractive or unattractive individuals. Neither the participants who rated the photographs nor the individuals in the photographs participated in the behavioral/fMRI experiments.

Compound Images

Photographs were edited in Adobe Photoshop to create dual-image compounds (300 × 400 pixels). Each compound image included one male and one female photograph, which were chosen randomly and arranged side by side against a gray background (**Figure 1**). The side on which the female face was displayed was counterbalanced across the compounds. In total, 64 compound images were used in the experiment.

Textual Cues

All word cues were in Simplified Chinese and placed at the bottom of the compound images. An affirmative sentence “照片中的女性 /男性对照片中的男性/女性 感兴趣” (The woman/man in the picture is interested in the man/woman) was assigned to half of the compounds, and the annulling sentence “照片中的女性 /男性对照片中的男性/女性 不感兴趣” (The woman/man in the picture is not interested in the man/woman) was assigned to the other half of the compounds. For each sex of the participants, they would only be presented with words indicating the same-sex models’ attitude toward the opposite-sex potential mates.

Procedure

A rating-observation-re-rating procedure was performed. The participants performed the whole process at a computer and finished the re-rating process immediately after each compound image in the behavioral experiment, whereas participants performed the observation process in the scanner and completed the rating and re-rating processes immediately before and after scanning, respectively, outside of the scanner in the fMRI experiment. The task was otherwise identical.

Specifically, in the first rating process, each participant was shown the 64 individual opposite-sex photographs one by one, in a random order on a computer monitor and was asked to rate each face for attractiveness using the 1–7 Likert scale (where 1 = very unattractive, 7 = very attractive) on a self-determined pace.

For the behavioral participants, after the initial rating process, each of the 64 compound images was randomly presented for 2700 ms with an inter-stimulus interval (ISI) of 300 ms and the participants were asked to observe them attentively. As soon as the compound image disappeared, the target (the opposite-sex photograph) in the compound was presented and participants were asked to rate the attractiveness using the 1–7 Likert scale in a self-paced speed.

In the fMRI experiment, we scanned the observation process after the initial rating process out of the scanner. After a structural scan, each participant’s assigned series of image compounds was presented and they were asked to observe them attentively. The stimulus presentation, timing, and counterbalancing of the compound images are outlined in **Figure 1**. There were eight blocks. Each block contained eight instances of the same compound type. Each compound image was presented for 2700 ms with an inter-stimulus interval of 300 ms. Images of each type block (interested vs. not interested) were presented in an alternating fashion, with the presentation order of the blocks being counterbalanced across participants. Each block lasted for 24 s with a 24-s rest between blocks, during which a black fixation cross was presented against the gray background. The re-rating process was a repetition of the first one, which was performed immediately after the scanning outside of the scanner.

After finishing the experiment, all participants reported that they were not familiar with any of the individuals pictured.

Data Acquisition

Imaging was performed with a 3.0-T Siemens Trio Tim Scanner (Erlangen, Germany) with a 32-channel head coil. T1-weighted sagittal structural images were acquired first with the following parameters: TR/TE = 2530 ms/2.34 ms, field of view (FOV) = 256 mm × 256 mm, flip angle = 7°, and voxel size = 1 mm × 1 mm × 1 mm, 192 slices. The stimuli were presented via the *in vivo* ESys fMRI system (Gainesville, FL, USA). Functional images were obtained with a gradient echo-planar imaging sequence (TR/TE = 2000 ms/30 ms, FOV = 192 mm × 192 mm, flip angle = 90°, voxel size: 3.13 mm × 3.13 mm × 3.5 mm, 32 slices).

Data Analysis

Behavior

The dependent behavioral variable in the two experiments was the attractiveness rating that the participants assigned to the individual opposite-sex facial photographs. A 2 (pre- *vs.* post-observation) × 2 (interested *vs.* not-interested) repeated measures of ANOVA (rmANOVA) on the attractiveness rating of opposite-sex faces was conducted to obtain the effects of experimental manipulations on mate copying.

Functional Magnetic Resonance Imaging

Imaging data preprocessing was performed using Statistical Parametric Mapping software, version 8 (SPM8; The Wellcome Department of Imaging Neuroscience, London, UK). The first four volumes were discarded to exclude calibration effects. The functional images were realigned to the first image to correct for interscan head movements. Six participants

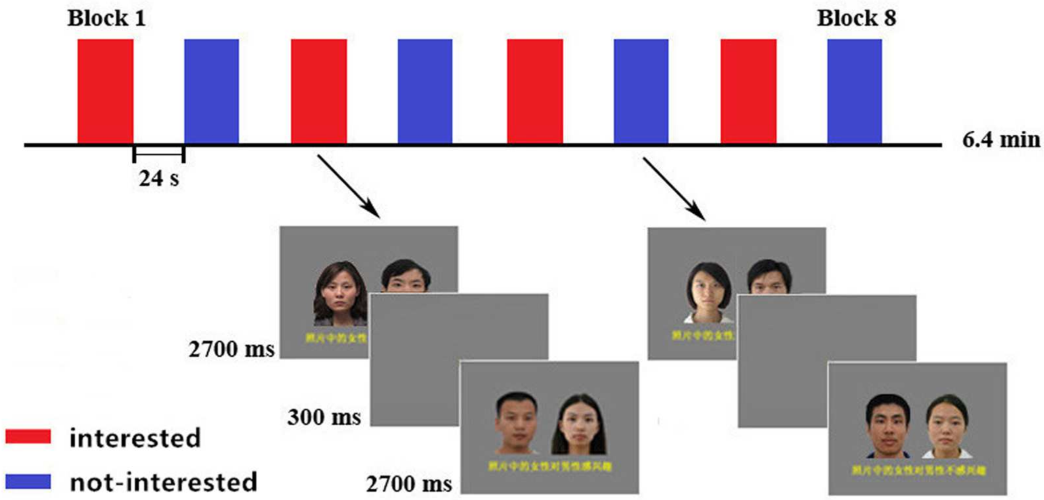

FIGURE 1 | Compound images and Procedure of the fMRI experiment. Block design with four blocks for each condition. Each block contained eight compound images of the same type. Two kinds of blocks were alternated between each other, with the order of the blocks counterbalanced across participants. A black fixation cross appeared in the center of the screen during the 24-s pre-block rest periods.

(four male, two female) who had excessive head movement (translation $\geq$ 2 mm, rotation $\geq$ 2°) were excluded from further analysis. The individual T1-weighted, 3D structural image was co-registered to the mean EPI image generated after realignment. The co-registered structural image was then segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using a unified segmentation algorithm (Ashburner and Friston, 2005). The functional images after the realignment procedure were spatially normalized to the Montreal Neurological Institute (MNI) space (resampled to 2 mm *2 mm *2 mm) using the normalization parameters estimated during unified segmentation and then spatially smoothed with a Gaussian kernel of 8 mm full-width half-maximum (FWHM).

Statistical analyses were performed using a general linear model. The two stimulus types (interested, not-interested) were modeled as a boxcar function convolved with the canonical hemodynamic response. The models additionally included six movement parameters derived from realignment as covariates of no interest. We applied a high-pass filter with a cut-off of 128 s to remove low-frequency signal components. For each subject at the first-level analysis, simple main effects for the interested and not-interested conditions were calculated by applying the '1 0' contrasts. The two first-level individual contrast images were then analyzed at the second group level by employing the random-effects model.

The main effect of models' attitude was calculated by contrasting trials in the interested condition with trials in the not-interested condition (interested > not-interested) and the reverse contrast (not-interested > interested) to identify brain regions involved in the learning process of mate copying. Activations were reported significant with a voxel-level threshold of $p < 0.001$ (uncorrected), and a cluster size of $k > 50$.

RESULTS

Behavioral Results

For the behavioral experiment, a 2 (pre- *vs.* post-observation) × 2 (interested *vs.* not-interested) repeated measures of ANOVA (rmANOVA) on the attractiveness rating of opposite-sex faces revealed significant main effects of pre-to-post ratings ($F_{1,59} = 25.88$, $p < 0.001$, $\eta_p^2 = 0.31$) and attitude ($F_{1,59} = 53.28$, $p < 0.001$, $\eta_p^2 = 0.48$). The effect of interaction was also significant, $F_{1,59} = 25.32$, $p < 0.001$, $\eta_p^2 = 0.30$. Simple effects analysis showed that though the post-attractiveness ratings were significantly higher than the pre-ratings for both conditions (interested: $M_{post} = 3.49$, $SD_{post} = 1.26$; $M_{pre} = 2.54$, $SD_{pre} = 1.02$; $F_{1,59} = 66.10$, $p < 0.001$, $\eta_p^2 = 0.53$; not-interested: $M_{post} = 3.12$, $SD_{post} = 1.24$; $M_{pre} = 2.52$, $SD_{pre} = 1.06$; $F_{1,59} = 31.92$, $p < 0.001$, $\eta_p^2 = 0.35$), the post attractiveness rating in the interested condition was significantly higher than that in the not-interested condition, $F_{1,59} = 34.56$, $p < .001$, $\eta_p^2 = 0.37$ (see **Figure 2**). These combining results confirmed a mate copying effect presented in the interested condition.

For the fMRI experiment, a 2 (pre- *vs.* post-observation) × 2 (interested *vs.* not-interested) repeated measures of ANOVA (rmANOVA) on the attractiveness rating of opposite-sex faces revealed significant main effect of pre-to-post ratings ($F_{1,25} = 4.36$, $p < 0.048$, $\eta_p^2 = 0.15$), but not of the attitude ($F_{1,25} = 1.06$, $p = 0.31$, $\eta_p^2 = 0.04$). The effect of interaction was also not reaching the significant level, $F_{1,25} = 0.085$, $p = 0.77$, $\eta_p^2 = 0.004$ (see **Figure 2**).

fMRI Results

In the comparison of interested > not-interested condition, the bilateral DLPFCs were observed significantly

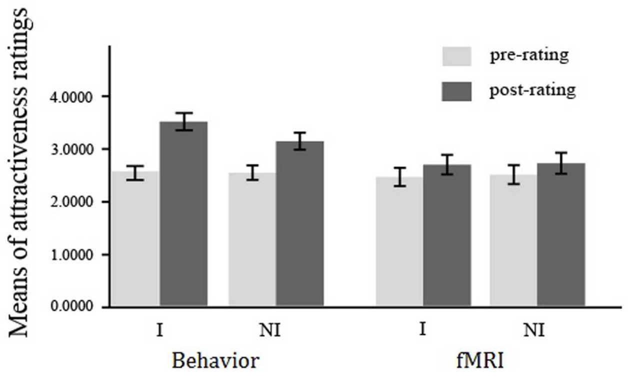

FIGURE 2 | Mean of attractiveness ratings in the behavioral and fMRI experiments. Mean of attractiveness ratings shown for each stimulus type with error bars indicating the standard error of the mean (SEM). I, interested condition; NI, not-interested condition.

activated (**Figure 3**), but not in the reverse comparison (not-interested > interested) (see **Table 1**). These results confirmed our hypothesis that the DLPFC should be involved in the learning process of mate copying.

DISCUSSION

The present study examined the effect of mate copying while manipulating models' attitude. The mate copying effect was confirmed in our behavioral experiment – greater increased attractiveness ratings for opposite-sex photographs were observed when they were paired with models with interested attitude than with models with not-interested attitude. However, the behavioral results of the fMRI experiment revealed no significant mate copying effect. The only difference between the two experiments was that the re-rating process was performed immediately after the observation of each compound image in the behavioral experiment, while during the fMRI study, participants observed all compound images in the scanner and then completed re-rating processes outside of the scanner. It may be indicated that mate copying did exist when observing models' attitude to potential mates. When asked to re-rate outside of the scanner in the fMRI study, mate copying effect may be weakened due to the time delay and/or the environmental change.

The fMRI data confirmed our hypothesis that the DLPFC is involved in the social learning process in human mate copying. In detail, the bilateral DLPFC were more active when participants observed models with an interested attitude than with a not-interested attitude. The DLPFC has been shown involved in cognitive execution within working memory (Owen, 2000; du Boisgueheneuc et al., 2006) and attention (Fox et al., 2006). It has been found to be particularly involved in integrating information from social context to enable an appropriate social decision. For example, Spitzer et al. (2007) scanned participants (Player A) while they made decisions about how much of a monetary endowment to split with another, anonymous participant (Player B) and found that the DLPFC is essential for integrating information about sanction threats into decision making to

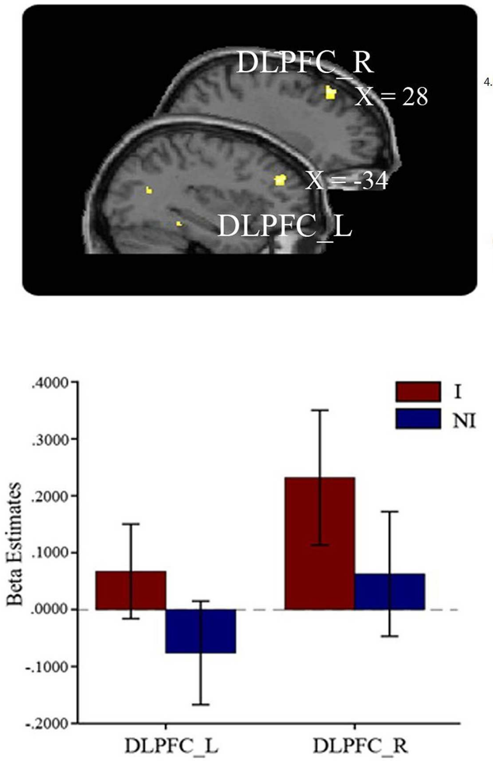

FIGURE 3 | Greater activations in bilateral DLPFC were found in the interested condition compared to the not-interested condition when participants viewing the compound images. Error bars indicate one SEM. I, interested condition; NI, not-interested condition.

TABLE 1 | Regions associated with the effect of mate copying.

Regions of activation	Side	MNI coordinates			*T*-score	Voxels
		X	*Y*	*Z*		
Interested > not-interested						
Vermis	R	2	42	−32	5.05	128
Middle occipital gyrus	L	−42	−72	20	4.69	123
DLPFC	L	−34	40	26	4.85	75
	R	28	32	50	4.65	61
Middle temporal gyrus	L	−64	−54	10	4.42	68
Fusiform	L	−32	−40	−12	4.46	57
Not-interested > interested						
Inferior occipital gyrus	L	−28	−94	−6	4.71	304
Fusiform	R	26	−80	−2	4.09	248
Lingual	R	22	−82	−4	4.05	
Middle temporal gyrus	R	52	−74	8	4.49	168
Inferior occipital gyrus	R	48	−78	−6	4.23	
Inferior temporal gyrus	R	42	−66	−8	4.10	

Coordinates (mm) are in MNI space. L, left, R, right. $p < 0.001$, uncorrected, $k > 50$. Sample size = 26.

incentivize norm-compliant behavior. The activation of DLPFC in the current study may reflect an involvement of cognitive execution function in the social learning process of mate copying in two aspects. First, it integrates and selects information from the observation, such as the social popularity and prestige of models, the mate values of the model and the target, or even how the model's and target's mate values compared to that of the observer (Vukomanovic and Rodd, 2007). Secondly, it guides to make an appropriate response in mate copying with the ability of DLPFC to maintain stable goal representations over time (Miller and Cohen, 2001).

CONCLUSION

The present study provided a novel experimental investigation of neural basis involved in the social learning process of human mate copying. The DLPFC was significantly activated in the comparison of interested > non-interested condition, suggesting that a cognitive integration and selection function may be involved when participants process information from conditions related to mate copying.

AUTHOR CONTRIBUTIONS

J-YZ developed the study concept and design. Testing and data collection were performed by JX, DH, and MF. JX and DH performed the data analysis and interpretation under the supervision of LZ and J-YZ. J-YZ drafted the manuscript, and LZ provided critical suggestions. All authors approved the final version of the manuscript for submission.

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How Does Adult Attachment Affect Human Recognition of Love-related and Sex-related Stimuli: An ERP Study

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In the present study, we investigated the relationship among three emotion-motivation systems (adult attachment, romantic love, and sex). We recorded event-related potentials in 37 healthy volunteers who had experienced romantic love while they viewed SEX, LOVE, FRIEND, SPORT, and NEUTRAL images. We also measured adult attachment styles, level of passionate love and sexual attitudes. As expected, results showed that, firstly, response to love-related image-stimuli and sex-related image-stimuli on the electrophysiological data significantly different on N1, N2, and positive slow wave (PSW) components. Secondly, the different adult attachment styles affected individuals' recognition processing in response to love-related and sex-related images, especially, to sex-related images. Further analysis showed that voltages elicited by fearful attachment style individuals were significantly lower than voltages elicited by secure and dismissing attachment style individuals on sex-related images at frontal sites, on N1 and N2 components. Thirdly, from behavior data, we found that adult attachment styles were not significantly related to any dimension of sexual attitudes but were significantly related to passionate love scale (PLS) total points. Thus, the behavior results were not in line with the electrophysiological results. The present study proved that adult attachment styles might mediate individuals' lust and attraction systems.

Keywords: adult attachment, love, sex, event-related potentials (ERPs), emotion-motivation system

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INTRODUCTION

Sexual relationship, in the context of human mating, plays an important role in the development as well as the evolution of human beings. There are three primary emotion-motivation systems in human brain during the development of human sexual relationship for mating, reproduction and parenting: lust, attraction, and attachment (Fisher, 1998). Sex drive (also called the libido or lust) is regarded as a craving for sexual gratification while romantic love (attraction, obsessive love, or passionate love) is considered as a powerful energy, feeling of exhilaration and focused attention on someone who catches our attention (Fisher et al., 2002). Attachment, previously regarded only as intensive bond between mother and infant (Bowlby, 1969/1982), now includes adult male-female attachment and is divided into three types, namely, secure, avoidant, and anxious (Hazan and Shaver, 1987). One of the most difficult dilemmas in relationship science is the interaction between sexual desire and love (Hatfield and Rapson, 1993; Regan and Berscheid, 1999; Diamond, 2004). Our study seeks to assess whether adult attachment could mediate recognition processing of love and sexual desire.

Love involves complex neural mechanisms and is a result of chemical, cognitive and directed behavioral components (Aron and Aron, 1986, 1996; Bartels and Zeki, 2000, 2004; Mashek et al., 2000; Buss, 2003; Aron et al., 2005; Esch and Stefano, 2005; Fisher et al., 2005). A study of relevance found that when individuals viewed pictures of their loved ones, the activity restricted foci in the medial insula and the anterior cingulate cortex, the caudate nucleus, and the putamen (Bartels and Zeki, 2000). A functional Magnetic Resonance Imaging (fMRI) study verified the hypothesis that love is a goal-directed state that leads to a range of emotions, rather than a specific emotion (Aron et al., 2005). Another study found that subliminal presentation of either a beloved's name (love prime) or a passion descriptor (passion prime) enhance reaction times in a similar fashion (Ortigue et al., 2007). These studies showed that, compared to friendship, romantic love is associated with mediating reward, emotion, and motivation systems (Bartels and Zeki, 2000, 2004; Aron et al., 2005; Fisher et al., 2005; Ortigue et al., 2007). Another study found that regional brain activity during early stage intense romantic love predicted relationship outcomes after 40 months (Xu et al., 2012). By using event-related potentials (ERPs), another study found that when participants viewed faces of their beloved, friend and unknown but beautiful people, the late positive potential (LPP) was larger in reaction to the face of the beloved than the other two types of faces (Langeslag et al., 2007). This entails that romantic love enhances one's lasting attention to faces of his/her beloved.

Different from romantic love, which is described as a delighted feeling or craving for established emotional union with preferred partner, sexual desire is defined as a motivation to have sex with any appropriate partners (Fisher, 2004). Sexual arousal in humans is a complex experience, which includes both physiological and psychological processes. Brain activity plays a crucial role in sexual desire. Researchers use fMRI and positron emission tomography (PET), to investigate regions of brain associated with erotic stimuli. These techniques provide high spatial resolution, allowing researchers to study brain regions at a very macroscopic level (Stoléru et al., 1999; Redouté et al., 2000; Bocher et al., 2001; Karama et al., 2002; Mouras et al., 2003; Ferretti et al., 2005). Three PET studies used ^{15}O-H$_2$O to measure responses of regional cerebral blood flow (rCBF) in healthy males elicited by visual erotic film clips. After comparing them with other neutral control clips, the studies found that sexual stimuli were related to activation of some paralimbic areas (like anterior cingulate gyrus, orbitofrontal cortex, right insula and right inferior frontal cortex (Stoléru et al., 1999; Redouté et al., 2000; Bocher et al., 2001). Mouras et al. (2003) found that sexual stimuli were associated with increased activation of the parietal lobes, the right parietooccipital sulcus, the left superior occipital gyrus and the precentral gyri. Another study investigated the effect of emotional valence and arousal value of non-erotic visual stimuli on ERPs and found that positive valence and high arousal resulted in larger P300 and PSW (Lankveld and Smulders, 2008). Based on these results, we can rightly consider sexual arousal as a composite psychophysiological state correlated with activation/deactivation of several brain regions including cognitive, emotional, motivational, and autonomic components (Redouté et al., 2000).

The attachment theory generated by Bowlby (1969/1982) was conceived after observing separation between infants and their primary caregivers. The study found that infants' reaction could be predictable in three ways- protest, despair and detachment. After including adult male-female attachment the three ways have been re-termed as- secure, avoidant, and anxious, indicating that attachment is not only limited to childhood but also could be translated to romantic love process (Hazan and Shaver, 1987). Bartholomew and Horowitz (1991) proposed a creative 4-group model of adult attachment style- secure, preoccupied, dismissing and fearful. Compared to insecure attachment, secure individuals are much more easily engaged in stable relationships (Hazan and Shaver, 1987; Kirkpatrick and Hazan, 1994). Feeney and Noller (1990) reported that adult attachment was intensively associated with various forms of love and beliefs of relationship. Another study reported that avoidant people could mistrust others and engage in less intensive romantic love (Sepah-Mansour et al., 2009). Ahmadi et al. (2013) reported that ambivalent attachment style could significantly predict obsessive love. Attachment style was reliable in predicting some sexual attitudes and behavior, especially anxiety attachment, which predicted sexual attitude in late adolescence (Feeney et al., 2000). Gentzler and Kerns (2004) also found that insecure attachment people had links with some sexual experience. For instance, avoidant attachment was associated with engagement in casual sex and anxious attachment was related to more unwanted but consensual sexual experiences. Birnbaum (2007) found that all attachment orientations were related to aversive sexual affect and cognitions within romantic relationships. Different adult attachment is also related to perception of emotional-laden stimuli, especially when the stimuli contain social information (Vrtička et al., 2012). From the above, we can conclude that adult attachment may affect various forms of love and sexual attitudes.

As mentioned above, the processing of romantic love stimuli and sexual stimuli were generally depicted by using fMRI and PET in the human sexual relationship, which involved the high spatial resolution but were limited in the temporal resolution. It is obvious that the limited of temporal resolution cannot measure the early stage of processing at the precise millisecond level. The present study aimed to use the method of ERPs, which have the high temporal resolution and could be time-locked to the onset of different categories stimuli. Therefore, ERP-measurement is suitable for measuring the early stage processing features of love-related stimuli and sex-related stimuli.

The first purpose of this study was to investigate ERPs in response to love-related images and sex-related images using electrophysiological data. Secondly, we also tested whether adult attachment styles affect one's recognition processing in response to love-related images and sex-related images. Thirdly, based on behavioral data, we tested whether individuals with different attachment styles show significant difference in levels of passionate love and sexual attitudes. Taking into consideration previous studies, high temporal resolution of ERPs would provide a valuable tool to investigate early stages of processing love-related stimuli and sex-related stimuli. Our study is the first to simultaneously investigate three primary emotion-motivation systems in human's brain- lust, romantic love and attachment, by using high temporal resolution ERP technology. We tested the following hypotheses: H1- response to love-related images will significantly differ from response to sex-related images on electrophysiological data. H2- different adult attachment styles will affect one's recognition processing in response to love-related images and sex-related images. H3- adult attachment style will affect individual's passionate love level and sexual attitudes based on behavior data as well as electrophysiological data.

MATERIALS AND METHODS

Participants

Participants were recruited using a poster at the university campus and on the Internet. Forty-five undergraduate and graduate students at Anhui University in China volunteered to participate in this study. Finally, 8 invalid data were discarded because of artifact rejection from EEG while 37 valid data remained for further analysis. The remaining 37 participants (17 males, 20 females; mean age 22.8, range 20–32) were all heterosexual and reported to either being in love or to have previously been in love using the questionnaire like. All participants were healthy, with normal or corrected-to-normal vision, no history of neurological or psychiatric disorder. Furthermore, all 37 participants were right-handed. Each participant signed a written informed consent before taking part in the experiment and received 50 RMB (approximately US $8) as compensation.

Ethics Statement

Each participant to the study provided written informed consent after receiving an explanation of the study's purpose and procedure. The study was approved by the Human Research Ethics Committee of Anhui University of China according to the principles expressed in the Declaration of Helsinki. Participants were undergraduate and postgraduate students. We did not obtain informed consent from guardians of participants whose age was under 18. These young college students were considered to have comparable intelligence and ability to adult students, and able to take charge of their behaviors. According to the General principles of the Civil Law of the People's Republic of China; "A minor aged 10 or over shall be a person with limited capacity for civil conduct and may engage in civil activities appropriate to his age and intellect; in other civil activities, he shall be represented by his agent ad litem or participate with the consent of his agent ad litem" (Article 12, Chapter II).

Measures

Attachment to romantic partners: participants completed the Chinese version of Experiences in Close Relationships (ECR) Questionnaire (Li and Kato, 2006). This 36-item questionnaire includes 18 items measuring avoidance attachment, the other 18 items measuring anxiety attachment about romantic relationships. Each item was rated on a 7-point Likert scale (ranging from 1 = strongly disagree to 7 = strongly agree). The Cronbach's alphas for the avoidance and anxiety scales were high (0.832 for both scales). According to the method of Griffin and Bartholomew (1994a,b), we divided the participants into four attachment styles groups (secure, preoccupied, dismissing and fearful).

Passionate love level: in order to test this, we used the short version of PLS, developed by Hatfield and Sprecher (1986). This scale consists of 30 items and each item is rated on a 9-point Likert scale (ranging from 1 = strongly disagree to 9 = strongly agree), higher scores indicating higher levels of love. The Cronbach's alpha of this scale was 0.857.

Sexual attitude: participants completed the Brief Sexual Attitudes Scale (BSAS), which has four subscales of Permissiveness, Birth Control (formerly called Sexual Practices), Communion, and Instrumentality. This scale includes 23 items and each item is rated on a 5-point Likert scale (ranging from 1 = strongly disagree to 5 = strongly agree). Higher scores indicated higher open sexual attitude. The Cronbach's alpha of this total scale was 0.851.

We engaged two colleagues to translate the above two scales from English to Chinese and engaged another pair of colleagues to translate it back to English. We compared the translations and came up with the best translation.

Materials

Materials for the experiment included video clips and visual images. We obtained three different copyright-free video clips (erotic, non-erotic love, and friendship) from publicly shared online videos. Erotic video clip showed heterosexual couples engaged in intercourse, non-erotic love video clip showed heterosexual couples in romantic love without any sexual behavior and friendship video clip showed male-female friendship. Each video clip lasted for not more than 6 min and all participants used earphones to listen to the sound of the videos during the experiment. We used the video clips as cues for image-stimuli that followed and were not analyzed in detail. The three types of video clips were used for creating three different states and making subjects a better understanding of the followed three image-stimuli (erotic, non-erotic love and friendship).

As mentioned in the introduction, previous related ERPs studies used faces of beloved or friends, erotic sex pictures, sports pictures, and neutral pictures as experimental materials (Langeslag et al., 2007; Lankveld and Smulders, 2008). The previous love-related ERP studies chose the love-related and friend-related facial stimuli as the experimental materials for control some other confounded variables such as familiarity and perceived beauty (Langeslag et al., 2007). As to the sex-related study, researchers chose the sport stimuli as the contrast stimuli for separating the ERP-contributions of erotic content from that of arousal value and hedonic valence, that is the erotic picture was equivalent to the category of high-energy sports pictures on the dimensions of valence and arousal (Lankveld and Smulders, 2008). In order to compare love-related stimuli and sex-related stimuli simultaneously, we divided the original visual images of our study into five categories. (1) 20 SEX images (nude heterosexual couples engaging in intercourse while showing female breasts, but without showing female or male genital areas in close-up). (2) 20 LOVE images (heterosexual couples dating, kissing and hugging without any erotic behavior). (3) 20 FRIEND images (friends of opposite sex talking and playing with no physical contact). (4) 20 SPORT images (fencing, kickboxing, skiing, and running) and (5) 20 NEUTRAL images (beautiful scenery like forests, mountains, and rivers). Images from the first three categories (LOVE, FRIEND, and SEX) were taken from erotic, non-erotic love and friendship video clips (as mentioned in the above paragraph) respectively, while images from the other two categories (SPORT and NEUTRAL) were downloaded from free sites on the Internet. We chose the SPORT images to match possible motion factors in the SEX images during the ERP experiment whilst FRIEND images were chosen to match possible friendship factors in the LOVE images during the ERP experiment. Each image depicted people's behavior only and contained two opposite sex persons of Asian origin. All images were standardized for brightness, saturation and size (600 pixels × 450 pixels) with Photoshop CS4. Before the experiment began, eight males and eight females, not involved in the study, independently rated these images on levels of quality (1-extremely bad to 7-extremely good), sexual arousal (1- no arousal to 7- highest arousal level) and love arousal (1- no arousal to 7-highest arousal level). According to their mean scores, 40 images were selected for the formal experiment, each category included eight images. In addition, the center of each image had a cross-shaped image (65 pixels × 65 pixels; white background and black foreground) which contained two shapes in which horizontal line was longer than vertical line or vertical line was longer than horizontal line. Two cross-shaped images occurred in the five categories randomly. When the shape changed, participants were instructed to press "1" on the keyboard, using the right hand. The task was used to keep participants focused on the images.

Procedure

After arriving at the laboratory, participants read and signed an informed consent form, which included a brief description of the procedure. Participants then filled in questionnaires and provided information about the duration of their recent romantic relationships as well as other demographic variables. Next, we placed electrodes on participants' heads and instructed them to limit movements and eye blinks during experiment. The participants sat in a comfortable chair in a soundproof, dimly lit room and put on their earphones. Images were displayed on a 49-cm monitor, with a maximum size of 27 cm × 37 cm, presented approximately 1.25 m from the participant's eyes with a visual angle of 16° horizontally and 12° vertically. Stimuli were presented in two blocks of 24 images each and each block contained 8 images from three different categories. One block called LOVE was about love, and the other block called SEX was about sex. The order of two blocks was counter-balanced across participants to control for any sequence or carryover effects. Stimuli of the same categories appeared in random order within each block. Stimuli presentation was controlled by E-Prime software.

Before each block, we showed participants a video clip (erotic; before the SEX block) or two video clips (friendship and non-erotic love; before the LOVE block) to make participants understand the relationship between the two persons of the following stimuli, which could render the love-related or sexual-related emotions. We did not analyze the recorded EEG during the video time. There was a 1-min break after video clip(s). Each block started with a black fixation cross (5 cm × 5 cm) in the center of the white computer screen and lasted for 500 ms. Then stimuli were presented for 350 ms. Specifically, the stimuli were presented in the order of FRIEND-NEUTRAL-LOVE (in LOVE block) or SPORT-NEUTRAL-SEX (in SEX block). Images in the same categories appeared in random order within each block. Each category (SEX, LOVE, FRIEND, SPORT, and NEUTRAL) contained eight images and each image was presented 50 times in one block, thus, the study consisted 2400 trials. Furthermore, once participants found the cross-shaped image in the center of each stimuli and pressed "1" on the keyboard using the right hand, the shape changed. There were several times for resting during the experiment.

Electroencephalogram (EEG) Recording and Signal Processing

The electroencephalogram (EEG) was recorded using a 64-channel amplifier (SynAmps 2, Neuroscan) and data acquisition software (SCAN4.3, Neuroscan). The 64 Ag–AgCl active electrodes were placed on the scalp by means of a head cap, according to the 10–20 International System. Scalp impedance for each electrode was kept below 5 kΩ. Vertical electro-oculogram (VEOG) was recorded by attaching additional electrodes above and below the left eye. The REF electrode served as reference and the forehead GND electrode was used as ground. All signals were digitized with a sample rate of 500 Hz, a 24-bit A/D conversion and a 0.05–100 Hz band pass filter.

The offline analysis of ERP data was performed with Neuroscan 4.3 software. Data were filtered using a band pass filter of 0.5–25 Hz with zero phase shifts (24 dB/octave slope). Ocular artifact correction was applied according to the Gratton and Coles algorithm. Data epochs were extracted from a time window between 200 ms before and 750 ms after the stimuli onset. The mean 200 ms pre-stimuli period was used for baseline correction. Artifact rejection criteria were minimum and maximum baseline-to-peak -50 to $+50$ μV. According to previous studies and the purpose of current study, average ERPs were then computed for each participant and the five images categories (SEX, LOVE, NEUTRAL, SPORT, and FRIEND). The following nine electrode positions were analyzed: F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4 (cf. Langeslag et al., 2007; Lankveld and Smulders, 2008). The voltages and waves that were elicited by SEX, LOVE, SPORT and FRIEND stimuli images during the experiment were recorded.

Analysis

The questionnaire and ERP data were analyzed using SPSS 11.0 for Windows, the mean ERP voltages in the time windows 100–200 ms (referred to as N1 component), 200–300 ms (referred to as N2 component), and 500–750 ms (referred to as PSW component) were tested at several electrodes (frontal: F3, Fz, F4; central: C3, Cz, C4; parietal: P3, Pz, P4). The considered two difference waves were created through the SEX minus SPORT (referred to as SEX-MINUS-SPORT wave) and LOVE minus FRIEND (referred to as LOVE-MINUS-FRIEND wave). The minus waves were created for further analysis. Using repeated measures ANOVAs with the within-subject factors categories (SEX-MINUS-SPORT, LOVE-MINUS-FRIEND) and nine electrodes (frontal: F3, Fz, F4; central: C3, Cz, C4; parietal: P3, Pz, P4), and with N1, N2, and PSW as dependent variables. The interaction effects between difference waves (SEX-MINUS-SPORT wave, LOVE-MINUS-FRIEND wave) and the between-subject factors four attachment styles (secure, preoccupied, dismissing, and fearful) were tested using the method of repeated measures ANOVAs. Only effects involving the factor condition of interest were reported. Greenhouse-Geisser correction for violations of the sphericity assumption in repeated measures analyses was used when appropriate. Effects were considered significant when $p < 0.05$. Significant interaction effects were followed-up by paired-samples *t*-tests.

RESULTS

Electrophysiological Data

Dependent variables were area measures under the two ERP difference waveforms (SEX-MINUS-SPORT wave, LOVE-MINUS-FRIEND wave) in the latency windows of interest. **Figure 1** shows the grand average waveforms per difference image stimuli at frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4) electrode sites. Apparently, the amplitude of SEX-MINUS-SPORT wave was larger than the LOVE-MINUS-FRIEND wave especially at parietal. **Figure 2** shows the voltage scalp distributions for the two minus-difference waveforms between 100 and 200 ms, 200 and 300 ms, and 500 and 750 ms after image-stimuli onset.

N1 (100–200 ms)

A 2 (SEX MINUS SPORT wave, LOVE MINUS FRIEND wave) × 9 (electrodes) repeated within-subjects ANOVA was tested on this time window (100–200 ms). Both the main effect of two difference waves [$F(1,36) = 31.30$, $p < 0.00$] and nine electrodes [$F(8,288) = 7.236$, $p < 0.00$] were significant. The interaction between stimuli categories and electrode was also significant [$F(8,288) = 11.972$, $p < 0.00$].

N2 (200–300 ms)

A 2 (SEX MINUS SPORT wave, LOVE MINUS FRIEND wave) × 9 (electrodes) repeated within-subjects ANOVA was tested on this time window (200–300 ms). Both the main effect of two difference waves [$F(1,36) = 50.25$, $p < 0.00$] and nine electrodes [$F(8,288) = 9.96$, $p < 0.00$] were significant. The interaction between stimuli categories and electrode was also significant [$F(8,288) = 40.58$, $p < 0.00$].

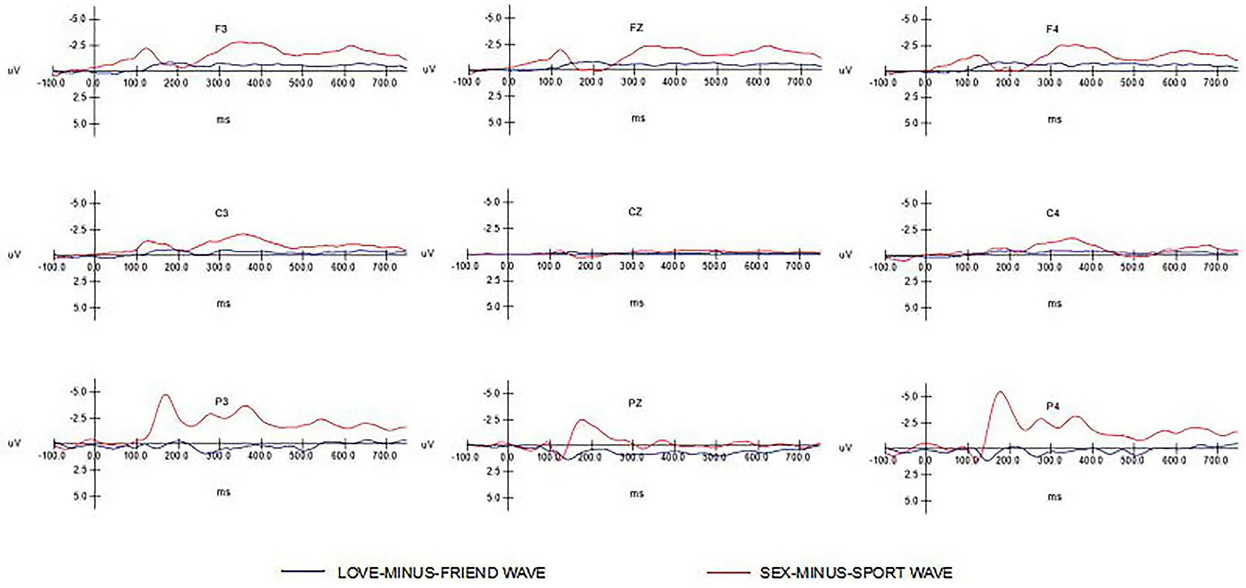

FIGURE 1 | Grand-average (*N* = 37) event-related potentials (ERPs) at various electrode sides as a function of difference waveforms types (SEX MINUS SPORT wave, LOVE MINUS FRIEND wave).

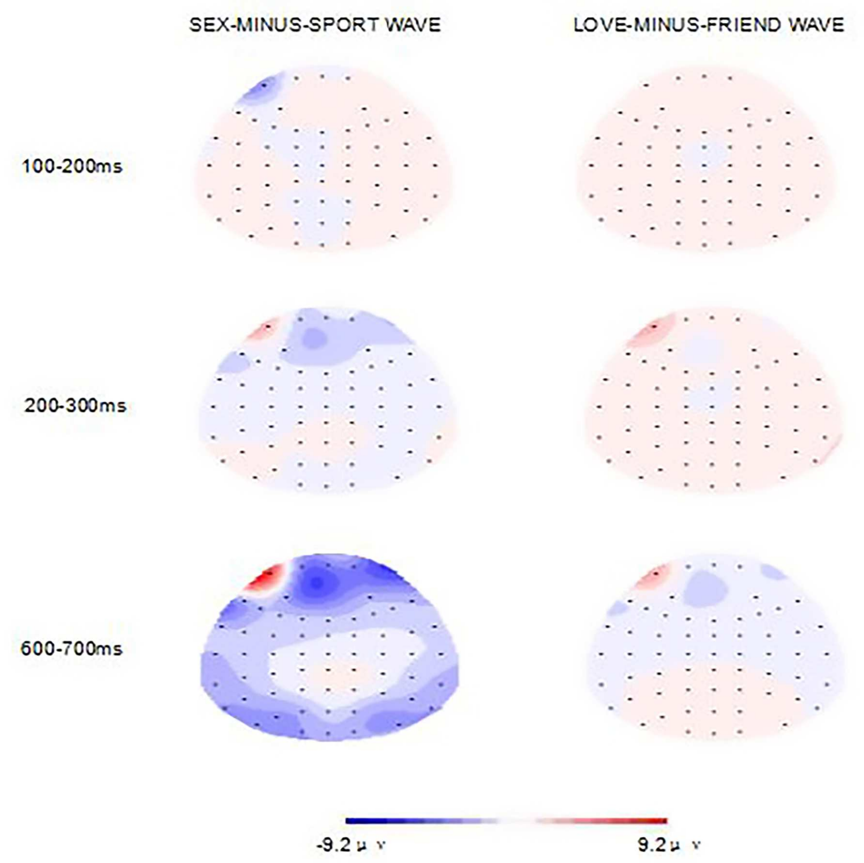

FIGURE 2 | Voltage scalp distributions for the two difference waveforms between 100 and 200 ms, 200 and 300 ms, and 600 and 700 ms after image-stimuli onset.

PSW (500–750 ms)

A 2 (SEX MINUS SPORT wave, LOVE MINUS FRIEND wave) × 9 (electrodes) repeated within- subjects ANOVA was tested on this time window (500–750 ms). Both the main effect of two difference waves $[F(1,36) = 39.42, p < 0.00]$ and nine electrodes $[F(8,288) = 18.67, p < 0.00]$ were significant. The interaction between stimuli categories and electrode was also significant $[F(8,288) = 10.11, p < 0.00]$.

Effects of Image Stimuli Categories and Attachment Style

According to the ECR Questionnaire, we divided participants into four attachment style groups- secure ($n = 7$), fearful ($n = 17$), preoccupied ($n = 9$), and dismissing ($n = 4$).

We performed a two-way repeated measure ANOVA to test whether four adult attachment styles (secure, preoccupied, dismissing, and fearful) could have interaction effects with the grand average voltages of SEX-MINUS-SPORT wave and LOVE-MINUS-FRIEND wave on N1, N2, and PSW components at each electrode. The interaction effects results are shown in **Table 1**. Results showed that adult attachment styles had significant interaction effects with difference waves at electrodes (F3, FZ, and F4) on N1 and N2 components, at electrodes (CZ, C4, and PZ) on N2 component, at electrode C4 on PSW component.

We further tested multiple comparisons in order to understand specific differences among the four adult attachment styles at the above significant electrodes on N1.

TABLE 1 | Interaction effects between difference wave (SEX-MINUS-SPORT wave, LOVE-MINUS-FRIEND wave) and adult attachment on N1, N2, and positive slow wave (PSW) per electrode.

Electrodes	N1 (100–200 ms)	N2 (200–300ms)	PSW (500–750ms)
F3	3.057*	3.658*	1.123
FZ	3.775*	4.461**	1.405
F4	4.106*	4.731**	2.417
C3	0.765	0.212	0.687
CZ	1.855	3.630*	0.289
C4	2.200	5.939**	4.282*
P3	2.311	0.487	0.459
PZ	1.403	3.200*	0.306
P4	1.634	0.902	0.663

$^{*}p < 0.05$, $^{**}p < 0.01$.

TABLE 2 | Result of one-way ANOVA of adult attachment styles, PLS total points and sexual attitudes.

	Secure ($n = 7$)	Fearful ($n = 17$)	Preoccupied ($n = 9$)	Dismissing ($n = 4$)	
	M ± SD	**M ± SD**	**M ± SD**	**M ± SD**	***F***
PLS total	85.71 ± 7.97	94.71 ± 16.56	107.11 ± 11.69	90.75 ± 15.00	3.34*
Permissiveness	4.03 ± 0.58	3.61 ± 0.86	4.00 ± 0.84	3.55 ± 0.44	0.88
Birth control	1.62 ± 0.95	1.80 ± 1.00	1.63 ± 0.63	1.50 ± 0.58	0.19
Communion	1.77 ± 0.26	2.39 ± 0.17	1.89 ± 0.23	2.40 ± 0.35	1.98
Instrumentality	3.26 ± 0.40	3.01 ± 0.76	3.11 ± 0.45	2.45 ± 0.66	1.48

*$p < 0.05$.

We found that voltages that were elicited by secure attachment style individuals were larger than those elicited by fearful attachment style individuals on SEX-MINUS-SPORT wave at electrodes F3 ($p < 0.05$) and F4 ($p < 0.01$). Voltages elicited by secure attachment style individuals were larger than those elicited by preoccupied attachment style individuals on SEX-MINUS-SPORT wave at electrode F4 ($p < 0.05$). Voltages elicited by dismissing attachment style individuals were larger than those elicited by preoccupied attachment style individuals on SEX-MINUS-SPORT wave at electrode F4 ($p < 0.05$).

We also tested multiple comparisons to assess differences among the four adult attachment styles at the above significant electrodes on N2. We found that voltages elicited by secure attachment style individuals were larger than those elicited by fearful attachment style individuals on SEX-MINUS-SPORT wave at electrodes F3 ($p < 0.01$), FZ ($p < 0.01$), and C4 ($p < 0.01$). Voltages elicited by secure attachment style individuals were larger than voltages elicited by preoccupied attachment style individuals on SEX-MINUS-SPORT wave at electrode FZ ($p < 0.05$), F4 ($p < 0.01$) and CZ ($p < 0.05$). Voltages elicited by dismissing attachment style individuals were larger than voltages elicited by fearful attachment style individuals on SEX-MINUS-SPORT wave at electrode FZ ($p < 0.05$), F4 ($p < 0.05$), and C4 ($p < 0.05$). Voltages elicited by dismissing attachment style individuals were larger than both preoccupied and fearful attachment style individuals on LOVE-MINUS-FRIEND wave at electrode FZ ($p < 0.05$).

In summary, our results showed that adult attachment styles are related to recognition of different stimuli (SEX or LOVE) especially at frontal sites on N1 and N2 ERP components. Further comparisons showed that voltages elicited by secure attachment style individuals are significantly larger than voltages elicited by fearful and preoccupied attachment style individuals on SEX-MINUS-SPORT wave, at frontal sites, on N1 and N2 components. Finally, voltages elicited by dismissing attachment style individuals are larger than voltages elicited by fearful attachment style individuals on SEX-MINUS-SPORT wave at frontal sites, on N2 components.

Behavior Data and Electrophysiological Data

We used One-Way ANOVA analyses to test whether the four adult attachment styles (secure, preoccupied, dismissing, and fearful) are significantly different among between love-related and sexual-related behavior variables (i.e., PLS total points, sexual attitude dimensions: permissiveness, birth control, communion, and instrumentality). Results showed that the four adult attachment styles were significantly different in PLS and total points [$F(3,33) = 3.34$, $p < 0.05$]. LSD *post hoc* tests showed that PLS scores of preoccupied attachment style individuals were significantly higher than scores of secure attachment style individuals ($M_{\mathrm{D}} = 22.93$, $p < 0.01$) and fearful attachment style individuals ($M_{\mathrm{D}} = 13.29$, $p < 0.05$). See **Table 2** for detailed results.

Results from electrophysiological data showed that adult attachment styles were related to recognition of different stimuli (SEX or LOVE) especially at frontal sites on the N1 and N2 ERP components. Further, electrophysiological voltage differences of adult attachment styles were more significant on the recognition of sex-related stimuli images, while behavior data found that adult attachment styles were not significantly related to all dimensions of sexual attitudes. Thus, results from behavior data were different from electrophysiological data.

DISCUSSION

In the present study, we found some interesting results. Firstly, based on our electrophysiological data, response to love-related image-stimuli and sex-related image-stimuli significantly differed on N1, N2, and PSW components. Secondly, different adult attachment styles significantly affected individuals' recognition processing in response to love-related images and sex-related images, especially response to sex-related image-stimuli. Thirdly, adult attachment styles were significantly different in passionate love.

As discussed in the introduction, we tested attachment style, level of passionate love and sexual attitudes to understand mediation effect of adult attachment style on individuals' processing of love-related variable (passionate love level) and sex-related variable (sexual attitudes). Our results showed that the four adult attachment styles (secure, preoccupied, dismissing, and fearful) were significantly different in PLS total points. Further analysis showed that preoccupied attachment style was significantly higher than secure and fearful attachment styles in PLS total points. This implies that preoccupied attachment individuals are extremely passionate in romantic relationships (Hatfield and Sprecher, 1986). Bartholomew and Horowitz

(1991) reported that preoccupied attachment individuals are associated with more expressiveness and less coldness. Further, ambivalent attachment style can significantly predict obsessive love (Ahmadi et al., 2013). Thus, attachment style can influence individuals' performance in sexual relationship, particularly, unsecure attachment individuals are considered more likely to fall in obsessive love.

As shown in **Figure 1**, we found that N1 (from 100 ms after stimuli onset) was more pronounced in sex-related stimuli than love-related stimuli at frontal and parietal sites. This suggests that cortical neural response was activated more by sex-related stimuli than by love-related stimuli. In the present study, sexual-related stimuli induced lager N1 components than the other categories, which, just like other emotional expressions, gets prior and more attention at early stages of cognition processing. Sex-related pictures are not only considered as one category of emotional pictures but also as a biological stimulus (Anokhin et al., 2006), which are crucial for human survival and reproduction. This helps us better understand why brain activities pay more attention to sex-related stimuli than love-related stimuli. Evolutionary and biological information from visual scenes may hence affect human brain mechanism of processing these relevant visual stimuli. Such brain mechanism could preferentially discriminate sex-related stimuli from stimuli from other categories in early stage processing. Early ERP components contain top-down regulation of sensory processing (Foxe and Simpson, 2002). These brain activities may modulate the processing in order to facilitate discerning information of biological stimuli.

Between 200 and 300 ms after stimuli onset, N2 was less pronounced in sex-related stimuli than love-related stimuli and neutral stimuli at three prefrontal electrodes. The ERP components included N1, P2, N2, and P3. N1 and P2 are regarded as early components of brain processes in response to stimuli, relying on physical properties of stimuli (strength, type, frequency, etc.), which are called exogenous components. N2 and P3 are related to human perception, recognition, attention and memory, named endogenous components. Thus, current finding of a decreased N2 for sex-related stimuli may be due to physical properties of stimuli. Besides, N2 has been found to be smaller for emotional facial stimuli than neutral facial stimuli at prefrontal electrodes (Eimer and Holmes, 2002, 2007). As such, sexual-related stimuli may be a special emotional category, which could influence this early component. Discriminative response to different picture categories starts in anterior regions of the scalp, suggesting that an involvement of the prefrontal cortex in the discrimination of specific contents.

As expected, we found that PSW (between 500 and 750 ms after stimuli onset) was lager for sex-related stimuli than love-related stimuli and neutral stimuli at frontal and parietal sites. This finding is in line with earlier studies, both in females and males (Anokhin et al., 2006). Van-Lankveld and Smulders (2008) compared difference among males in response to erotic pictures and sport pictures and found that erotic pictures induced lager P300 and PSW components. PSW is treated as the index of attention maintenance (Bradley, 2000; Schupp et al., 2003), which meanings need much more attention materials. Anokhin et al. (2006) investigated difference in neuroelectric response between erotic pictures and other picture categories and found that emotionally arousing pictures, regardless of their content, produce a larger late positive wave than neutral pictures. As we know, sex-related stimuli contain more biology information than love-related pictures and neural pictures, which are crucial for human's survival and reproduction. Whether in early or late processing stages, sex-related stimuli always catch more attention and need more processing materials in our brain.

In our study, we tested the mediation effect of adult attachment on individuals' processing of stimuli from different categories on ERP components (N1, N2, and PSW). Results showed that adult attachment styles were related to recognition of difference stimuli (SEX or LOVE) especially a frontal site on N1 and N2 ERP components. Further analyses showed that voltages elicited by secure attachment style individuals were significant larger than voltage elicited by fearful and preoccupied attachment style individuals on SEX-MINUS-SPORT at frontal sites, on N1 and N2 components. Voltages elicited by dismissing attachment style individuals were larger than voltages elicited by fearful attachment style individuals on SEX-MINUS-SPORT wave at frontal sites, on N2 components. Compared to individuals of the other three adult attachment styles, fearful attachment style individuals are usually frightened and anxious during sexual relationship, which explains the decreased response to sex-related image-stimuli. These results are consistent with results of previous behavior studies that showed that individuals with fearful attachment style engage less in sexual behaviors (Russell and McNulty, 2011), express disgust toward sexual experiences and find it hard to enjoy sexual life (Lambert et al., 2003).

In addition, adult attachment styles may influence level of obsessive love, sexual attitude and sexual experiences in common romantic relationships (Hazan and Shaver, 1987; Kirkpatrick and Hazan, 1994; Feeney et al., 2000; Gentzler and Kerns, 2004). Importantly, individuals with dismissing attachment style have been found to be cold and less expressive (Bartholomew and Horowitz, 1991). In present study, the electrophysiological voltage differences in adult attachment styles were significantly related to recognition of sex-related images while behavior data found that adult attachment styles were not significantly related to any dimension of sexual attitudes. The difference in results between behavior data and electrophysiological data helps to prove that implicit ERP technology results may not be the same with explicit questionnaire behavior data. However, Chinese people's view of sex is relatively conservative, so self-reported behavior questionnaire method may have many weaknesses for such variables, as individuals tend to report the more reasonable and socially desirable responses. Thus, compared to behavior method, ERP technology can be used widely in future studies to investigate the most spontaneous and real potential reactions of the human brain.

One limitation of the present study merits consideration. In order of presentation of stimuli, in the LOVE block; stimuli were presented in FRIEND-NEUTRAL-LOVE, order while in the SEX block; stimuli were presented in SPORT-NEUTRAL-SEX, order. The fixed order may have affected participants' attention to different image-stimuli. Future studies should balance the order to capture full attention of participants during the experiment.

CONCLUSION

From electrophysiological data, the current study found that response to love-related image-stimuli and sex-related image-stimuli were significantly different on N1, N2, and PSW components. Our results suggest that different adult attachment styles may affect one's recognition processing in response to love-related images and sex-related images, especially, to sex-related images. Further, from behavior data, we found that adult attachment styles were not significantly related to any dimension of sexual attitudes but showed significant difference in PLS total points. These behavior results were not in line with electrophysiological results. The present study provides evidence that during development of sexual relationship for mating, reproduction, and parenting, there are three primary emotion-motivation systems in human brains, called lust, attraction, and attachment. Using electrophysiological technology, our study also found that adult attachment styles may influence human lust and attraction systems.

AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: JH, XC, JL, FY, JNH, and XF. Performed the experiments: JH, XC, JL, FY, and JNH. Analyzed the data: JH, XC, JL, FY, JNH, RM, YZ, JL, and LL. Contributed reagents/materials/analysis tools: JH, XC, JL, FY, JNH, RM, YZ, JL, and LL. Wrote the paper: JH, XC, YN, RM, YZ, and XF. Discussed the result: JH, ZH, YN, RM, YZ, JL, LL, and XF. Final approval of the version to be published: JH, YN, JL, LL, and XF.

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Decreased Empathic Responses to the 'Lucky Guy' in Love: The Effect of Intrasexual Competition

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People have a greater desire to date highly attractive partners, which induces intrasexual competition between same-sex individuals. The present study used functional magnetic resonance imaging to explore whether and how intrasexual competition modulates pain empathy for a same-sex rival and the underlying neural mechanism. Participants were scanned while processing the pain of a same-sex 'lucky guy' who had an attractive partner and one with a plain partner. The results revealed that participants reported lower pain intensity for the lucky guy. Neurally, reduced pain-related activations in anterior insula and anterior mid-cingulate cortex and increased activations in right superior frontal gyrus (SFG) and medial prefrontal gyrus (MPFC) were found for the lucky guy compared to the one with a plain partner. Right SFG and MPFC activations could predict participants' subsequent pain intensity ratings for the lucky guy. These findings suggest intrasexual competition can modulate normal empathic responses.

Keywords: pain empathy, intrasexual competition, fMRI, AI, aMCC, MPFC

INTRODUCTION

Evolutionarily speaking, physical attractiveness is linked to youth, health, and female fertility (Sugiyama, 2005). Physical attractiveness also provides information about mate-relevant economic or social factors, such as income or hunting ability (Harper, 2000) and plays an important role in mate selection (Grammer et al., 2003; Gangestad and Scheyd, 2005). Both males and females have a greater desire to date highly attractive partners (Greitemeyer, 2010). The common motive to obtain and maintain access to partners, especially highly desirable partners, can often induce intrasexual competition (Buunk and Massar, 2012). Emerging evidence has demonstrated that intrasexual competition can affect people's attitudes. That is, people tend to dislike same-sex rivals, exhibiting negative evaluations and hostile behaviors toward them (Fisher, 2004; Griskevicius et al., 2009). Previous studies have revealed that the attitudes held toward others impact empathy for their suffering and pain (Singer et al., 2006; Cheng et al., 2010). This leads to the question: are empathic responses to the same-sex rival, especially when the rival is a 'lucky guy' who obtains the love of a highly attractive partner, modulated by intrasexual competition? The goal of the present study was to investigate the impact of intrasexual competition on empathy and the underlying neural mechanisms.

Empathy refers to the ability to understand and experience the emotional and affective states of another person (Decety and Jackson, 2004; Singer and Lamm, 2009; Decety, 2011). Recently, a number of neuroimaging studies on pain empathy have demonstrated that the perception or imagining of others' pain activates a pain matrix similar to what is engaged in the first-hand experience of pain (Derbyshire, 2000; Price, 2000; Jackson et al., 2006), including the bilateral anterior insula (AI), anterior cingulate cortex (ACC), and anterior mid-cingulate cortex (aMCC; e.g., Singer et al., 2004; Jackson et al., 2006; Lamm et al., 2007, 2011; Saarela et al., 2007; Fan et al., 2011; Guo et al., 2012, 2013; Zheng et al., 2016). In addition, activation in medial prefrontal cortex (MPFC) was associated with decreased empathic responses to others' pain (Cheng et al., 2007). Converging with evidence showing the role of MPFC in cognitive inhibitory control and emotion regulation (Floden and Stuss, 2006; Banks et al., 2007; Phillips et al., 2008), activation in MPFC during empathy for others' pain may reflect a down-regulation of empathic pain (Cheng et al., 2007).

Although, a key feature of empathy is the observer's experience of an affective state that is isomorphic to another person's affective state, empathy is not simply an automatic resonance of the target's state (De Vignemont and Singer, 2006). Previous neuroimaging studies have revealed that individuals' attitudes toward empathy targets influence empathy for their pain. Decety et al. (2010) found that, compared with healthy controls, the more participants blamed targets for contracting AIDS from illegal intravenous drug use, the less empathy participants had for the target's pain, indicating that empathic responses were modulated by an *a priori* negative attitude toward the empathy target. In a study conducted by Singer et al. (2006), participants, especially males, showed decreased responses in brain regions associated with empathy when observing an unfair person who they disliked receiving pain. Given that intrasexual competition leads to negative attitudes toward same-sex rivals (Fisher, 2004; Griskevicius et al., 2009), we predicted that observers would show reduced behavioral and neural empathic responses to their pain.

To test this prediction, an functional magnetic resonance imaging (fMRI) study was designed. Before the experiment, four plain models (two females and two males) and two attractive models (one female and one male) were selected. Participants were informed that one of two plain same-sex models had an attractive partner (PlainAtt), i.e., the 'lucky guy' in love in the experiment; another had a plain partner (PlainPlain). Then participants were scanned while viewing a series of pictures showing PlainPlain or PlainAtt (targets were always the same-sex as the participants) in painful or non-painful situations (**Figure 1**). We predicted that participants would report more negative attitudes and decreased pain intensity ratings for PlainAtt than for PlainPlain. At the neural level, decreased pain-related brain activations in AI and ACC/aMCC and increased activation in MPFC, which has been associated with the regulation of empathic pain, would be observed for PlainAtt relative to PlainPlain.

METERIALS AND METHODS

Participants

Twenty right-handed participants (12 females, mean age = 21.70, *SD* = 1.89) were recruited from the university community to participate in this experiment. None of the participants had a history of neurological or psychiatric disorders. All participants received monetary compensation for their participation. All of them had normal or corrected-to-normal vision. All participants gave informed consent before scanning. The study was approved by the local ethics committee.

Materials

A total of 192 pictures collected from two females and two males volunteers were used as stimuli. For each volunteer, 24 painful pictures, depicting their bilateral ears (not including faces), palms, and index fingers in four kinds of nociceptive situations (cutting with a knife or a pair of scissors and pricking with a needle or an awl), were paired with a corresponding non-painful situation, in which the nociceptive tool did not touch the ear, palm, or finger, but was placed next to the body part (in total, 48 pictures for each volunteer). All of the pictures were 500 × 350 pixels in size. Ninety-six pictures from the two males volunteers were used as stimuli for male participants, while ninety-six other pictures from the two females volunteers were used as stimuli for female participants.

Procedure

Before the experiment, we collected 38 free face pictures (19 females and 19 males) from the Internet. From 19 females candidates, one attractive female model and two plain females models were selected according to the attractiveness and liking ratings of 10 males (not participants). The attractive model got the highest attractiveness and liking ratings, while the two plain models were ranked in the last quarter of the ratings. There were significant differences between the attractiveness and liking ratings of the attractive model and the plain models ($ts > 3.46$, $ps < 0.01$), but no significant attractiveness or liking rating differences between the two plain models. From 19 male candidates, one attractive male model and two plain male models were selected in the same way, with significant differences between the attractive model and plain models ($ts > 6.20$, $ps < 0.01$) and no significant differences between the two plain models. For each participant, face pictures of two couples were presented during the fMRI scan. The first couple was composed of one of the two plain same-sex models paired with the attractive opposite-sex model. The second couple was composed of the other plain same-sex model paired with one of the two plain opposite-sex models. Which plain model was paired with the attractive opposite-sex model was counterbalanced between participants.

Before scanning, participants were informed that they would view pictures of two couples and that the same-sex models from these couples would be their empathy targets. They were told they would view a series of pictures depicting the empathy target in painful or non-painful situations.

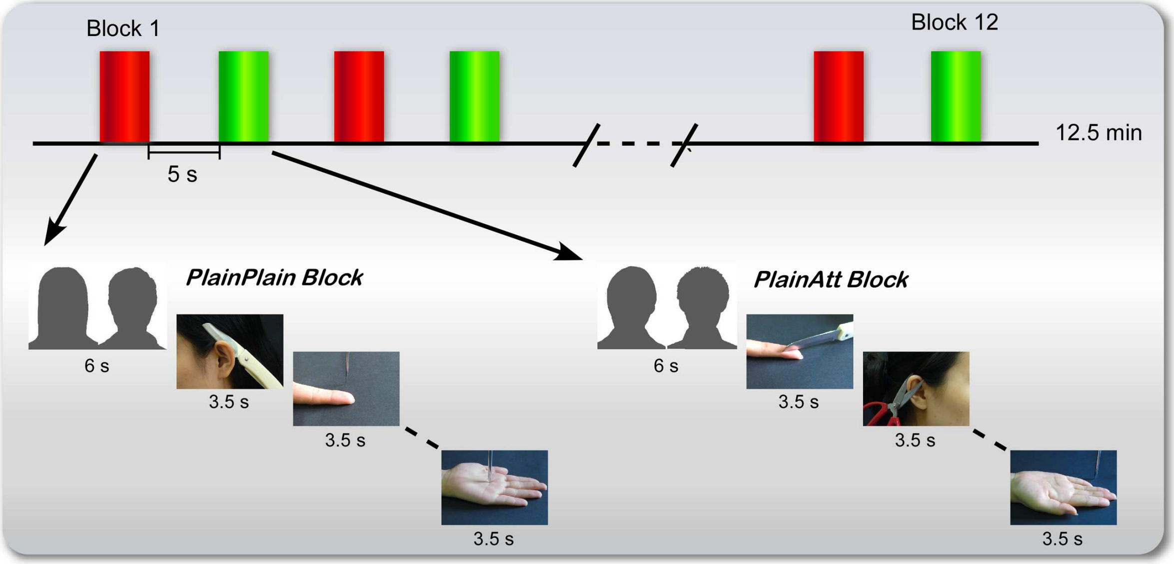

FIGURE 1 | Procedure for female participants. There were six blocks for each plain model (red for PlainPlain and green for PlainAtt), with a 6-s cue presented before each block to indicate which plain model would be the target in the following block. The cues (here indicated by silhouettes) were pictures of two couples in the experiment. Four painful pictures and four non-painful pictures of that specific model were randomly presented with null trials, each lasting 3.5 s. The presentation order of attractive and plain model blocks was counterbalanced across participants. For male participants, the same procedure was used, with changed cues and pictures.

During the experiment, six blocks were set for each plain same-sex model (PlainAtt or PlainPlain; **Figure 1**). Before each block, a 6-s cue trial (i.e., a picture of one of the couples) was presented to inform the participants which plain same-sex model was the target in the following block. Each block consisted of four painful pictures and four non-painful pictures of the model indicated by the cue with null events (only fixation cross) randomly interspersed. Each trial was presented for 3.5 s followed by a jittered fixation cross from 0.5 to 1.5 s. PlainAtt and PlainPlain blocks were alternated. The presentation orders of the different blocks were counterbalanced across the participants. Each block lasted for 48.5 s, followed by a 5-s rest. The participants were asked to view the pictures attentively. The manipulation of grouping events into different blocks aimed to reduce the possible influence of participants' cognitive loads to switch between two empathy targets on the modulation of neural empathic responses by intrasexual competition.

After scanning, participants were presented with the same stimuli that they viewed in the scanner again and asked to rate how much pain they felt in each situation (0–9 point Likert-type scale where 0 indicated no pain and 9 indicated extreme pain). Then, they were presented with the same cue pictures as in the scanner and asked to rate the attractiveness of the empathy targets who had an attractive or plain partner and how much they envied and liked the empathy targets with 1 point (not at all)-7 point (extreme) Likert-type scales.

fMRI Image Acquisition and Analysis

Imaging was performed on a 3T Siemens Trio system (East China Normal University, Shanghai) with a standard head coil. Functional images were obtained using a gradient echo echo-planar imaging (GRE-EPI) sequence. Thirty-five transversal slices with 3 mm slice thickness and a 0.3-mm spatial gap were acquired (TR = 2200 ms, TE = 30 ms, FOV = 220 mm, flip angle = 90°, matrix size = 64 × 64). There was only one run of functional scanning which was about 13 min (346° EPI volumes). Before the functional imaging, a high-resolution structural image was acquired using a T1-weighted, multiplanar reconstruction sequence (MPR; 1 mm× 1 mm× 1 mm).

Participants' data were analyzed separately using SPM8 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK). During data preprocessing, the first five volumes were discarded to allow for T1 equilibration effects. The functional images were corrected for the delay in slice acquisition and were realigned to the first image to correct for interscan head movements. The individual T1-weighted, 3D structural image was co-registered to the mean EPI image generated after realignment. The co-registered structural image was then segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using a unified segmentation algorithm (Ashburner and Friston, 2005). The functional images after slice timing and realignment procedures were spatially normalized to the Montreal Neurological Institute (MNI) space (resampled to 2 mm × 2 mm × 2 mm) using the normalization parameters estimated during unified segmentation and then spatially smoothed with a Gaussian kernel of 8 mm full-width half-maximum (FWHM).

Statistical analyses were then carried out with the general linear model (GLM) implemented in SPM8. At the first-level analysis, four types of conditions were defined based on the attractiveness of the empathy target's partner and painful or non-painful stimuli the target received: (1) PlainAtt in the painful situations (PlainAttP); (2) PlainAtt in the non-painful situations (PlainAttN); (3) PlainPlain in the painful situations (PlainPlainP); (4) PlainPlain in the non-painful situations (PlainPlainN). All the conditions were modeled as 3.5 s long from the onset time of the pictures and convolved with a canonical hemodynamic response function (HRF). The models additionally included cues (also convolved with a canonical HRF) and six movement parameters derived from realignment as covariates of no interest. High pass temporal filtering with a cutoff of 180 s was also applied in the models. For each participant, simple main effects for each of the four conditions were computed with the '10' contrast, respectively, at the first-level analysis. The resulting four first-level individual contrast images for each participant were then fed into a second-level full factorial ANOVA.

The main effect of pain was defined using the (PlainAttP + PlainPlainP) – (PlainAttN + PlainPlainN) and the reverse contrasts. The interaction between pain and partner's attractiveness defined by the (PlainPlainP – PlainPlainN) – (PlainAttP – PlainAttN) and the reverse contrasts were also computed to explore how the empathic brain responses changed. A cluster-level threshold of $p < 0.05$ (FWE) and a voxel-level threshold of $p < 0.001$ (uncorrected) were used to define activations.

RESULTS

Behavioral Results

The means and standard deviations of participants' pain intensity, liking, attractiveness, and envy ratings were shown in **Table 1**. A 2 (pain: painful vs. non-painful) × 2 (partner's attractiveness: PlainPlain vs. PlainAtt) repeated-measures ANOVA on pain intensity ratings revealed significant main effects of pain and partner's attractiveness [$Fs(1,19) > 23.89$, $ps < 0.01$]. The interaction was also significant [$F(1,19) = 17.31$, $p < 0.01$]. *Post hoc* analyses revealed significantly higher pain intensity ratings for painful situations than non-painful situations in both PlainPlain and PlainAtt conditions [$ts(19) > 13.17$, $ps < 0.001$]. Further analyses showed higher pain intensity rating difference (painful–non-painful) for PlainPlain than PlainAtt [$t(19) = 4.16$, $p = 0.001$].

Participants reported significantly less liking and higher envy [$t(19) = 12.22$, $p < 0.01$] for PlainAtt than for PlainPlain [$t(19) = 5.41$, $p < 0.01$]. No significant difference on the attractiveness ratings was found between PlainAtt and PlainPlain.

fMRI Results

Main Effects

Brain regions related to painful stimuli vs. non-painful stimuli [(PlainAttP + PlainPlainP) – (PlainAttN + PlainPlainN)] were bilateral AI, aMCC, supplementary motor area, bilateral supramarginal gyrus, right inferior occipital gyrus, and cerebellum. The reverse contrast revealed significant activations in right superior occipital gyrus, right angular gyrus, left precuneus, aMCC, right middle frontal gyrus, right middle orbital gyrus, bilateral middle temporal gyrus, and left angular gyrus (**Table 2**). We did not report the main effect of partner's attractiveness for it was of no interest in the current study.

Interactions

The interaction between pain and partner's attractiveness identified by the (PlainPlainP – PlainPlainN) – (PlainAttP – PlainAttN) contrast revealed significant activations in right AI, aMCC, left thalamus, left precuneus, and left precentral gyrus, while the reverse contrast revealed significant activations in MPFC, right superior frontal gyrus (SFG) and right angular gyrus (**Table 3**). Percent signal changes were extracted from all the significant voxels in the 6 mm-radius spherical regions centered on the peak or local maximum coordinates identified in the interactions (coordinates can be found in **Table 3**). Further *post hoc* analyses revealed that, when watching painful pictures, greater percent signal changes in aMCC, right AI, left thalamus, left precuneus, and left precentral gyrus were detected for PlainPlain than for PlainAtt [$ts(19) > 3.48$, $ps < 0.01$], whereas in MPFC, right SFG and right angular gyrus, greater percent signal changes was observed for PlainAtt than for PlainPlain [$ts(19) > 5.98$, $ps < 0.01$; **Figure 2**]. When watching non-painful pictures, no significant difference was found between PlainAtt and PlainPlain in any brain regions (**Figure 2**). Interestingly, for both MPFC and right SFG, we found that the difference in percent signal change between PlainAttP condition and PlainAttN condition was negatively correlated with the corresponding pain intensity rating difference (MPFC: $r = -0.56$, right SFG: $r = -0.52$, both $p < 0.05$), whereas similar analyses found no significant correlation for PlainPlain trials.

DISCUSSION

The present study investigated how the empathic responses were modulated by intrasexual competition. Results showed that, at the behavioral level, participants reported less liking, lower empathic pain intensity, and higher envy for PlainAtt, the lucky guy with an attractive partner, than PlainPlain, the one with a plain partner.

TABLE 1 | Mean (± SD) for envy, attractiveness, liking, and pain intensity ratings.

				Pain intensity	
	Envy	Attractiveness	Liking	Painful	Non-painful
PlainPlain	2.10 ± 1.07	3.35 ± 1.18	4.30 ± 1.26	7.09 ± 1.28	0.50 ± 1.16
PlainAtt	5.45 ± 1.05	3.00 ± 1.59	2.05 ± 0.94	5.38 ± 1.71	0.17 ± 0.51

TABLE 2 | Brain regions showing a significant main effect of pain.

		Coordinates				
Regions of activation	**Side**	***x***	***y***	***z***	***T*-value**	**Volumes (mm^3)**
Painful – Non-painful						
Supplementary motor area	R	8	12	58	10.52	223952
Anterior insula	L	–30	22	4	9.54	
Anterior insula	R	42	10	0	9.24	
Anterior middle cingulate cortex	L	–6	14	42	9.07	
Supramarginal gyrus	L	–62	–22	34	9.36	30040
Supramarginal gyrus	R	68	–24	38	7.11	13400
Cerebelum	R	18	–70	–22	6.52	9136
Inferior occipital gyrus	R	32	–94	–8	5.88	1648
Non-painful–Painful						
Superior occipital gyrus	R	18	–88	20	6.98	19896
Angular gyrus	R	46	–60	28	6.86	13272
Precuneus	L	–10	–56	20	5.31	10624
Middle frontal gyrus	R	26	28	44	7.30	8848
Middle orbital gyrus	R	8	42	–12	4.87	4752
Middle temporal gyrus	R	62	–4	–18	4.87	3320
Angular gyrus	L	–46	–78	30	4.69	2760
Middle temporal gyrus	L	62	–4	–18	4.71	2360

Coordinates (mm) are in Montreal Neurological Institute (MNI) space. L = left hemisphere; R = right hemisphere. Cluster-level, $p < 0.05$, FWE corrected; voxel-level, $p < 0.001$, uncorrected.

TABLE 3 | Brain regions showing significant interactions.

		Coordinates				Volumes (mm^3)
Regions of activation	**Side**	***x***	***y***	***z***	***T*-value**	
(PlainPlainP – PlainPlainN) – (PlainAttP – PlainAttN)						
Precentral gyrus	L	–36	–12	44	4.16	7760
Anterior middle cingulate cortex	L	–6	10	34	4.13	
Thalamus	L	–10	–26	16	4.72	5288
Precuneus	L	–12	–54	54	5.08	4960
Anterior insula	R	36	12	14	4.09	2504
(PlainAttP –PlainAttN) – (PlainPlainP – PlainPlainN)						
Angular gyrus	R	54	–58	34	6.09	8056
Superior frontal gyrus	R	16	36	46	5.53	5760
Medial prefrontal cortex	R	12	54	20	3.77	

Coordinates (mm) are in MNI space. L = left hemisphere; R = right hemisphere. Cluster-level, $p < 0.05$, FWE corrected; voxel-level, $p < 0.001$, uncorrected.

At the neural level, increased activations in AI and aMCC were observed in the painful situations relative to the non-painful situations. More importantly, decreased pain-related AI and aMCC activations and stronger MPFC and right SFG activations were found for PlainAtt than for PlainPlain, indicating behavioral and neural empathic responses to others' pain were modulated by intrasexual competition.

Anterior insula and ACC/aMCC have been considered to be involved in encoding the affective dimension of first-hand pain and to play a key role in empathy for others' pain (Singer et al., 2004). In the present study, AI and aMCC responded more strongly to the painful relative to the non-painful stimuli, which was consistent with the findings of previous studies that these areas were critically involved in empathic pain processing (Fan et al., 2011; Lamm et al., 2011). Furthermore, it has been shown that empathic neural responses in AI and aMCC are modulated by many situational factors (e.g., Xu et al., 2009; Guo et al., 2012, 2013; Feng et al., 2016). For example, a recent study found that social hierarchies established based on incidental skill in a perceptual task affected AI and aMCC activations during empathy for pain. Specifically, empathic brain activations in AI and aMCC were reduced when responding to the pain of superior-status targets relative to that of inferior-status targets (Feng et al., 2016). Interestingly, our data revealed that AI and aMCC were also involved in the modulation of pain empathy by intrasexual competition. Compared with the

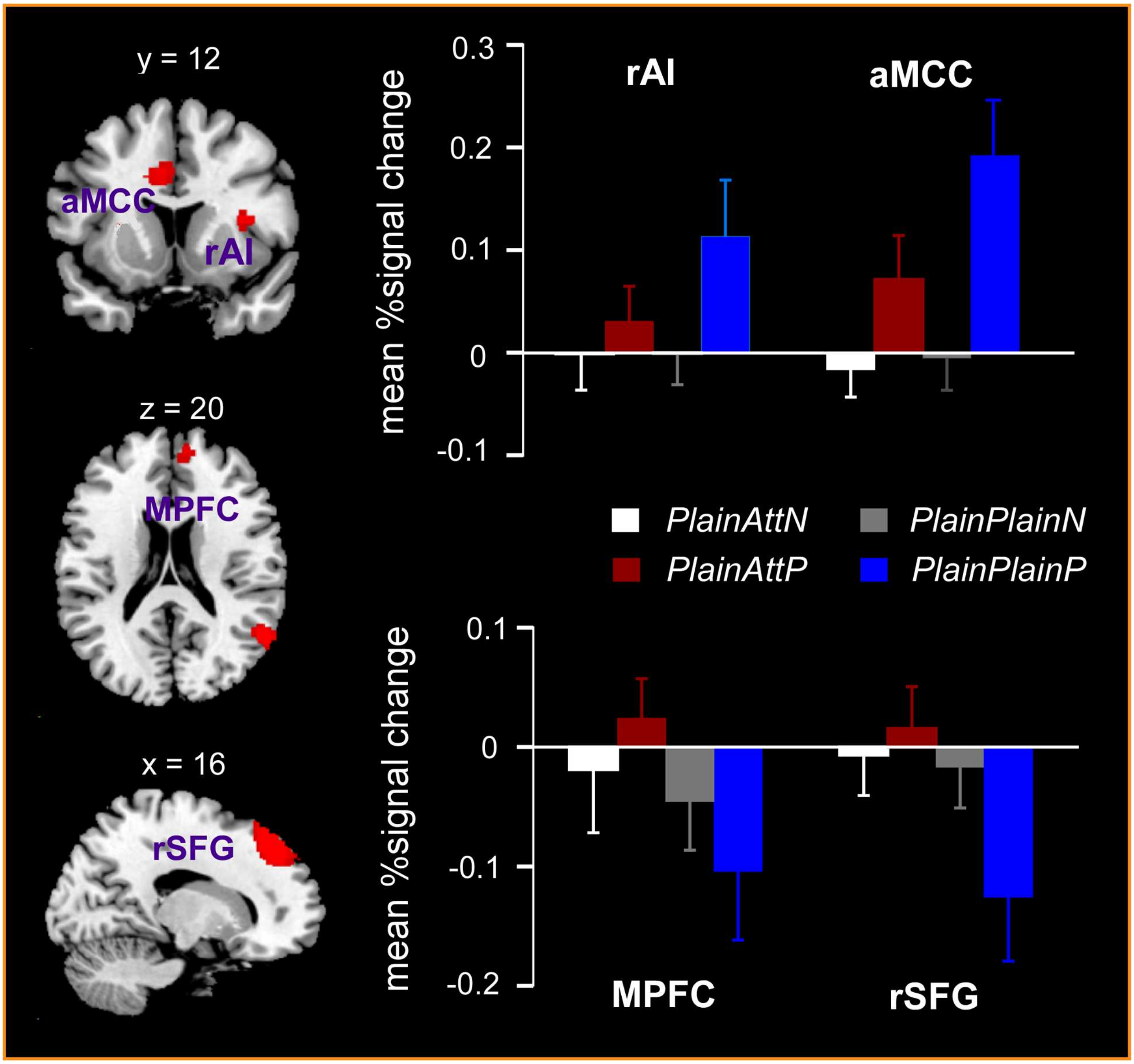

FIGURE 2 | Significant activations in the interaction between pain and the partner's attractiveness. Right anterior insula (AI) and anterior mid-cingulate cortex (aMCC) responded more strongly to painful simulations applied to PlainPlain than PlainAtt, whereas stronger activations in medial prefrontal cortex (MPFC) and right superior frontal gyrus (SFG) were observed for PlainAtt's pain than for PlainPlain's pain. No activation difference was found between PlainAtt and PlainPlain in any brain region when responding to non-painful simulations. L = left hemisphere; R = right hemisphere. Error bars indicate standard error of the mean. Cluster-level, $p < 0.05$, FWE corrected; voxel-level, $p < 0.001$, uncorrected.

guy with a plain partner, when participants saw the lucky guy suffering pain, reduced AI and aMCC activations and lower pain intensity ratings were observed, indicating that the normal empathic response for the lucky guy was suppressed. It should be noted that, accompanying the decrease of empathic responses, participants reported more negative attitudes (i.e., less liking and higher envy) toward the lucky guy, suggesting that intrasexual competition altered their attitudes, which might have affected the empathy for others' pain. This converging evidence may indicate that AI and aMCC activities are not just responsible for automatic bottom–up processing of others' pain, but are also sensitive to the top–down regulation of pain empathy by various situational factors, such as intrasexual competition and social hierarchies.

Interestingly, the present study also found greater activation in MPFC for PlainAtt than for PlainPlain. Previous studies have demonstrated that MPFC plays an important role in cognitive inhibitory control and emotion regulation (Floden and Stuss, 2006; Banks et al., 2007; Phillips et al., 2008). Recent brain imaging studies also revealed the engagement of MPFC in the empathy for others' pain (Cheng et al., 2007; Rameson et al., 2012).

Cheng et al. (2007) observed increased MPFC activation and also negative functional connectivity between MPFC and AI when physicians who practice acupuncture (versus matched controls) viewed painful stimuli, which was interpreted as reflecting cognitive inhibition of the affective processing in the pain matrix, revealing that MPFC was related to the down-regulation of empathy for pain. The data of the present study revealed greater MPFC activation for PlainAtt than for PlainPlain during the painful (relative to non-painful) situations. Further evidence from correlation analyses showed that when participants saw the lucky guy in pain, stronger activation in MPFC was observed and lower pain intensity ratings were reported, providing support for the argument that MPFC was associated with the evaluation of others' physical pain. Additionally, we also found that MPFC activation in the present study was accompanied by activity in right SFG. In addition to MPFC activity, Cheng et al. (2007) also observed increased right SFG activation and negative functional connectivity between right SFG and AI when physicians (versus controls) viewed painful stimuli. In the present study, right SFG was more active while processing the painful stimuli for the lucky guy and its activation predicted participants' pain intensity ratings for the lucky guy. This evidence suggests that right SFG may have a similar function to MPFC in evaluating others' physical pain.

The present study used fMRI to explore pain empathy for the lucky guy in love. The results revealed that individuals had more negative attitudes and reported lower pain intensity for the lucky guy with an attractive partner compared to the one with a plain partner. Neurally, reduced responses in AI and aMCC and increased activations in MPFC and right SFG were observed for the pain of the lucky guy compared to the one with a plain partner. These findings indicate intrasexual competition can affect attitudes toward same-sex rivals and modulate normal empathic responses to their suffering.

AUTHOR CONTRIBUTIONS

XG conceived of the project; XG, Li Zheng, and Lei Zhu designed the experiments; Li Zheng programmed the experimental scenario; Li Zheng and QW performed the experiments; JX analyzed the data with the help of Li Zheng; FZ and CW wrote the paper; all authors read and approved the manuscript. Li Zheng and FZ contributed equally to this work.

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