Psychoneuroendocrinology (2014) 50, 274—279

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Serotonin receptor gene (*5-HT1A*) modulates alexithymic characteristics and attachment orientation

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Received 3 June 2014; received in revised form 6 August 2014; accepted 2 September 2014

KEYWORDS
Alexithymia;
Attachment;
Serotonin;
Genetic polymorphism;
5-HT1A

Summary Previous studies have indicated that alexithymia is associated with the availability of serotonin in the brain and with the insecure attachment orientation. Inspired by the finding that the receptor *5-HT1A* modulates the level of serotonin in the brain, this study investigated to what extent a polymorphism (C-1019G, rs6295) of *5-HT1A* gene modulates individuals' alexithymic characteristics and attachment orientation in 504 Chinese Han people. Results showed significantly higher total scores on the 20-item Toronto Alexithymia Scale (TAS-20) for individuals carrying the CG/GG genotype than for individuals carrying the CC genotype. Specifically, individuals with the CG/GG genotype reported greater difficulty in identifying own feelings than individuals with the CC genotype. Results also showed that individuals carrying the CG/GG genotype seemed to be less comfortable with having close relationships to others than individuals with the CC genotype. These findings provide the first evidence for the link between *5-HT1A* and the development of alexithymic characteristics and attachment orientation.

1. Introduction

Alexithymia is a cluster of sub-clinical symptoms characterized by difficulties in identifying and describing one's own emotions, lacking of imagination, and an externally oriented thinking style (Taylor, 1984). It is related to emotion dysregulation (Stasiewicz et al., 2012) and health-related quality of life (von Rimscha et al., 2013). It occurs in up to 50% of

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http://dx.doi.org/10.1016/j.psyneuen.2014.09.001
0306-4530/

psychiatric patients, such as those suffering from depression or somatoform pain (Fukunishi et al., 1992; Burba et al., 2006), and in about 8% of the general population (Honkalampi et al., 2009; Karukivi et al., 2010; Deng et al., 2013). Twin studies established that a large portion of individual differences in alexithymia can be attributed to genetic factors, with heritability of 30—42% (Honkalampi et al., 2009; Karukivi et al., 2010; Deng et al., 2013). A study associating the serotonin transporter promoter region (5-HTTLPR) in serotonin transporter gene (*5-HTT*) with alexithymia (Kano et al., 2012) demonstrated that, compared with individuals carrying the SS/LS genotype, individuals with the LL genotype registered higher scores on Toronto Alexithymia Scale (TAS-20) which is a commonly used self-report instrument assessing alexithymic characteristics (Bagby et al., 1994). It is possible that the level of serotonin in the brain affects individuals' alexithymic characteristics given that the significant association between *5-HTT* gene and alexithymia and the link between the higher activity of 5-HTT and a higher serotonin uptake rate and lower serotonin level in synaptic cleft (Linnet et al., 1995; Meyer et al., 2004).

The serotonin level in the brain is regulated not only by the serotonin transporter (Heils et al., 1996) but also by the serotonin receptor (Larisch et al., 2003; Le Francois et al., 2008; Trueta and Cercos, 2012). However, it is not clear to what extent individuals' alexithymic characteristics can be modulated by the genotype of serotonin receptor genes. In this study, we investigated the possible association between the receptor gene, *5-HT1A* (*HTR1A*), and the level of alexithymia in a normal population.

5-HT1A is one of the most abundantly expressed serotonin receptors in the mammalian brain. It is a key component of the serotonin system, acting at both pre- and postsynaptic neurons in several brain areas (Drago et al., 2008). In cerebral cortex and hippocampus, the excitation of *5-HT1A* receptors on the dendrites of 5-HT neurons diminishes the firing rate of serotonergic neurons and produces a negative feedback to the release of serotonin (Sprouse and Aghajanian, 1987). On the other hand, the expression of *5-HT1A* receptors is controlled by the gene *5-HT1A*, which has a single nucleotide polymorphism C-1019G. The polymorphism of C-1019G regulates the expression of *5-HT1A* receptors (Lemonde et al., 2003; Albert and Lemonde, 2004; Le Francois et al., 2008). Compared with the C allele, the G allele is associated with higher expressions in raphe neurons, leading to decrease in firing frequency and serotonin level in synaptic cleft (Lemonde et al., 2003; Albert and Lemonde, 2004; Czesak et al., 2012).

Previous studies have shown that C-1019G in *5-HT1A* is involved in the development of mental disorders, in which the G allele is associated with higher risk of depression (Anttila et al., 2007; Savitz et al., 2009; Kishi et al., 2013). Given that alexithymia is prevalent in this affective disorder, it is possible that C-1019G polymorphism in *5-HT1A* is associated directly with individual differences in vulnerability to alexithymia and that individuals with the G allele have increased alexithymic characteristics when compared with individuals with the C allele.

Previous studies have also evidenced the association between alexithymia and the insecure attachment orientation (Montebarocci et al., 2004; Oskis et al., 2013). Attachment orientation refers to particular internal working models that determine individuals' behavioral responses to real or imagined separation from and reunion with their attachment figures (de Haas et al., 1994; Davila et al., 1997). Individuals can be categorized into different orientations such as secure, anxious, and avoidant according to their emotional and behavioral dynamics in relation to others (Hazan and Shaver, 1987). Alexithymia and the insecure attachment orientation have overlapping psychological symptoms and etiology, both having difficulties in describing feelings, regulating emotions, and dealing with social or interpersonal situations (Davis et al., 2003; Benetti et al., 2010; Towler and Stuhlmacher, 2013) and both with traumatic childhood experiences as one cause of these difficulties (Wearden et al., 2003). Given these associations and given the finding that individual differences in attachment orientation are modulated by genetic variations, such as rs6313 in serotonin receptor 2A (Gillath et al., 2008; Salo et al., 2011), 5-HTTLPR of serotonin transporter (Caspers et al., 2009), and TaqIA in dopamine receptor 2 (Gillath et al., 2008), a secondary purpose of this study was to investigate whether the C-1019G polymorphism in *5-HT1A* affects attachment orientation, with individuals having the G allele showing increased insecure orientation than individuals having the C allele.

2. Methods

2.1. Participants

Five hundred and four unrelated, unselected Chinese Han students (70% female, mean age = 24.1 ± 1.4 years) were recruited from Henan University of Science and Technology, China. This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Department of Psychology, Peking University. Written informed consents were obtained from each participant.

2.2. Alexithymia test

Alexithymia was measured with the Chinese version (Yi et al., 2003) of the TAS-20 (Bagby et al., 1994), which is the most commonly used self-report instrument assessing alexithymic characteristics. Respondents were asked to rate on a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree) to what extent each item could be used to describe themselves. These items, such as ''I am often confused about what emotion I am feeling'', are differentiated into three subscales, with one subscale referring to the difficulty in identifying feelings and distinguishing them from bodily sensations (DIF), one subscale referring to the difficulty in describing and communicating feelings (DDF), and the third subscale referring to a preference to describe external events rather than inner feelings or underlying causes (EOT) during communications. Cronbach's alphas for the Chinese version of TAS-20 were .83 in Yi et al. (2003) and .81 in the present sample. The scoring procedure followed suggestions in Bagby et al. (1994).

2.3. Attachment test

Attachment components were measured with the Chinese version (Wu et al., 2004) of the 18-item Revised Adult Attachment Scale (RAAS) (Collins, 1996). RAAS is a commonly used scale with established psychometric properties (Collins, 1996); it measures three components underlying adult attachment orientations: the close subscale measures the extent to which an individual is comfortable with closeness and intimacy; the depend subscale measures the extent to which an individual feels he/she can trust and depend on others when needed; and the anxiety subscale assesses the extent to which a individual is worried about being abandoned or unloved by others. Participants were asked to respond to each item on a 5-point Likert scale (1 = not at all characteristic of me, 5 = very characteristic). Each subscale has 6 items. In this sample, Cronbach's alphas for the close, depend, and anxiety subscales were .58, .56, and .79, respectively. The scoring procedure followed suggestions by Collins (1996).

The Alexithymia test and attachment test were conducted in groups, with 7—19 participants in each group. The paper-and-pencil test was conducted firstly for TAS-20 and then for RAAS. Each participant was paid 40 Yuan (about $6) for completing the battery of questionnaires.

2.4. Genotyping

For each participant, we collected 3—5 hairs with hair follicle cells by sterilized tweezers, cut the hairs into 2—3 cm fragments by a sterile blade, and saved the fragments in a 1.5 ml centrifuge tube. Genomic DNA was extracted from hair follicle cells by Chelex-100 method (de Lamballerie et al., 1994). Considering the relatively low concentration and relatively low purity of the DNA samples we extracted, we employed polymerase chain reaction with single strand conformational polymorphism (PCR-SSCP), which has been evidenced to be highly reliable in previous studies (Gong et al., 2014), to genotype the rs6295 polymorphism. -C1019G in *5-HT1A* was amplified by PCR. The upstream primer, 5′-TTGTTGTCGTCGTTGTTCGT-3′ and the downstream primer, 5′- ATCGTGTCAGCATCCCAGAG -3′, were recruited. The PCR reaction system contained 2.50 μL 2× reaction MIX (Golden Easy PCR System, TIANGEN), 0.50 μL DNA Template, 2.50 μL ddH_2O, 0.25 μL (25 pmol) upstream primer, and 0.25 μL (25 pmol) downstream primer. A product of 236 bp was amplified with an initial 3 min denaturation at 94 °C, followed by 35 cycles of 94 °C for 30 s, 61 °C for 30 s, 72 °C for 30 s, and a final extension at 72 °C for 10 min. Genotyping was performed by single strand conformation polymorphism (SSCP) method with 13% polyacrylamide gel electrophoresis in 250 V for 40 min and 150 V for 15 h at 4 °C, which was followed by silver staining. On genotyping, six randomly selected samples were sequenced to confirm the alleles of genotyping results. In the current sample of 504 individuals, the distribution of genotypes (CC = 316, CG = 165, GG = 23) showed no deviation from Hardy—Weinberg Equilibrium ($\chi^2 = .061$, $p = .805$). The genotype frequencies are similar to those found in other Chinese samples (Zhang et al., 2009; Zhou et al., 2013).

3. Results

3.1. Alexithymia test

A total score and three subscale scores of TAS-20 were used to examine the effect of genotype on alexithymic characteristics. Independent-samples *t*-test revealed a significant difference in the total score between individuals carrying the CC genotype (M ± SD: 49.9 ± 8.6) and individuals carrying the CG/GG genotype (51.7 ± 8.6), $t(502) = -2.211$ $p = .027$, Cohen's $d = .20$ (Fig. 1A). For the subscales of TAS-20, a 3 (subscales: DIF vs. DDF vs. EOT) × 2 (genotype: CC vs. CG/GG) repeated-measures ANOVA revealed a main effect of genotype, $F(1,502) = 4.401$, $p = .036$. Bonferroni-adjusted post hoc *t*-tests revealed that individuals with the CC genotype (17.0 ± 4.4) reported fewer difficulties in identifying feelings on the DIF subscale than those with the CG/GG genotype (18.0 ± 4.2), $t(502) = -2.388$; uncorrected $p = .017$, Bonferroni-adjusted $p = .052$, Cohen's $d = .22$ (Fig. 1B). However, the difference on the DDF subscale did not reach significance, CC group (12.8 ± 3.2) vs. CG/GG group (13.1 ± 3.2), $t(502) = -1.089$; uncorrected $p = .277$, Bonferroni-adjusted $p = .830$, Cohen's $d = .10$. Neither the difference on the EOT subscale, CC group (20.1 ± 3.2) vs. CG/GG group (20.6 ± 3.4), $t(502) = -1.636$; uncorrected $p = .102$, Bonferroni-adjusted $p = .307$, Cohen's $d = .15$.

3.2. Attachment test

Consistent with previous studies (Troisi et al., 2001; Pedrosa Gil et al., 2008), the total score on TAS-20 was negatively correlated with the scores on the RAAS close subscale, $r = -.280$, $p < .001$, and the depend subscale, $r = -.256$, $p < .001$, and positively correlated with the score on the anxiety subscale, $r = .398$, $p < .001$.

For the subscales of RAAS, although ANOVA with subscales as a within-participant factor and genotype as a between-participant factor did not find a significant main effect of genotype, $F(1,492) = 1.542$, $p = .215$, given the previous studies showing that individual differences in attachment orientation are modulated by HTR2A and 5-HTT variations (Caspers et al., 2009; Gillath et al., 2008; Salo et al., 2011), we tentatively conducted *t*-tests for the scores on the three subscales to examine the effect of genotype on attachment orientation. For the close subscale, individuals with the CC genotype (3.62 ± .58) reported higher scores than individuals with the CG/GG genotype (3.51 ± .57), $t(502) = 2.142$; uncorrected $p = .033$, Bonferroni-adjusted $p = .098$, Cohen's $d = -.19$ (Fig. 1C), indicating that the former seemed to be more comfortable with intimacy than the latter. No difference was found between the two groups on the depend subscale, CC group (3.36 ± .61) vs. CG/GG group (3.33 ± .61), $t(500) = -.609$; uncorrected $p = .543$, Bonferroni-adjusted $p = 1.000$, Cohen's $d = .06$, or on the anxiety subscale, CC group (2.50 ± .74) vs. CG/GG group (2.41 ± .77), $t(494) = 1.359$; uncorrected $p = .175$, Bonferroni-adjusted $p = .524$, Cohen's $d = .13$.

To make sure that the effects of genotype on alexithymia and attachment orientation survive even when we partial out the potential contributions of environmental factors, we collected data concerning childhood abuse and parental

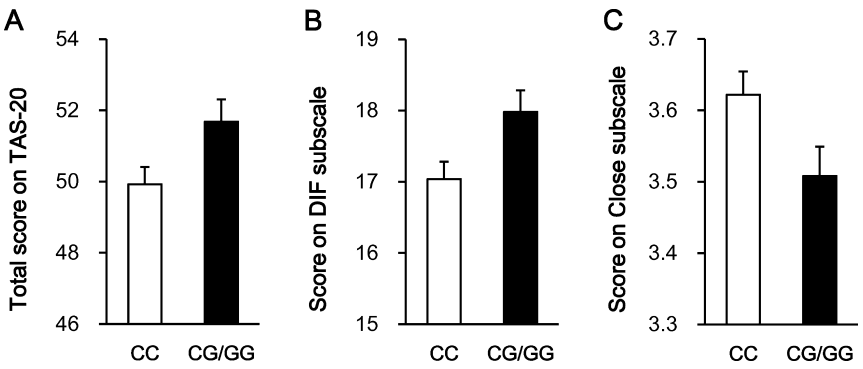

Figure 1 Effects of *5-HT1A* C-1019G polymorphism on alexithymia and close attachment orientation. (A) Individuals with the CC genotype ($N = 316$) had a lower mean total score on the 20-item Toronto Alexithymia Scale (TAS-20) than individuals with the CG/GG genotypes ($N = 188$). (B) Individuals with the CC genotype reported a lower mean total score on the Difficulty Identifying Feelings (DIF) subscale of TAS-20 than individuals with the CG/GG genotype. (C) Individuals with the CC genotype reported a higher mean score on the close subscale of Revised Adult Attachment Scale than individuals with the CG/GG genotype. Standard errors of the means are shown as error bars.

bonding and entered them as covariates into hierarchical regression (see *Supplementary Materials*). The effects of *5-HT1A* genotype remained to be significant.

4. Discussion

This study investigated to what extent of C-1019G in *5-HT1A* modulates individuals' alexithymic characteristics and attachment orientation. In line with previous studies showing the increased risk of G alleles in mental disorders (Anttila et al., 2007; Savitz et al., 2009; Kishi et al., 2013), we found that individuals with the G allele showed higher vulnerability to alexithymic symptoms and reported less comfort with intimate relations than individuals with the C allele.

Our findings provided new evidence demonstrating that a serotonin receptor gene is related to the development of alexithymia. A recent study have also shown that individuals with L/L genotype of 5-HTTLPR in serotonin transporter gene (*5-HTT*) scored higher on TAS-20 and on the DIF subscale than those with L/S or S/S genotype (Kano et al., 2012). *5-HTT* and *5-HT1A* may play differential roles in the pathology of alexithymia. Although the 5-HTTLPR does not affect the availability of 5-HTT in the living human brain of healthy adult (Murthy et al., 2010), the effects of 5-HTTLPR genotypes on brain function in adults are likely attributable to earlier developmental changes (Frodl et al., 2010; Mueller et al., 2010). During the childhood, the L allele of 5-HTTLPR in *5-HTT* increases the gray matter volumes in anterior cingulate and amygdale (Pezawas et al., 2005), which are related to the development of alexithymia (Frewen et al., 2006; Radaelli et al., 2014), and leads to a higher risk of alexithymic symptoms (Kano et al., 2012). Unlike the 5-HTTLPR, the C-1019G in *5-HT1A* regulates the serotonin levels in synaptic cleft with the G allele linked to the decreased serotonin level (Lemonde et al., 2003; Albert and Lemonde, 2004; Czesak et al., 2012) and exerts significant effects on the reactivity and volumes of amygdala (Le Francois et al., 2008; Zetzsche et al., 2008). Thus, individual differences in the development of alexithymic characteristics are partly due to the changes in serotonin levels which are modulated by *5-HT1A*; lower serotonin level in brain is associated with higher risk of alexithymia.

It should be noted, however, that 5-HTT and *5-HT1A* have differential modes in regulating the serotonin level in the brain. 5-HTT, as a hub to inactivate serotonin, distributes on pre-synaptic membranes (Zhou et al., 1998) whereas *5-HT1A* receptors, as modulators of serotonin release, distribute on both pre- and post-synaptic membranes. Stimulating the *5-HT1A* receptors on pre-synaptic membranes inhibits the serotonin release from nerve terminals (Fink and Gothert, 2007), thereby lowering the serotonin level in synaptic cleft. Activating 5-HTT on pre-synaptic membranes also lowers the serotonin level through enhancing reuptake of serotonin in synaptic cleft (Zhou et al., 1998). However, stimulating the *5-HT1A* receptors on post-synaptic membranes can not only inhibit serotonin release from pre-synaptic membranes (Hannon and Hoyer, 2008) but also inhibit the activity of post-synaptic neurons (Fink and Gothert, 2007). It is plausible that alexithymia is also related to *5-HT1A* acting on the post-synaptic membranes.

While alexithymia refers to sub-clinical inability in identifying and describing one's own feelings (Taylor, 1984), the insecure attachment orientation refers to the difficulty in responses to separation from and reunion with others (de Haas et al., 1994; Davila et al., 1997). Nevertheless, previous clinical research showed overlapped psychological symptoms for alexithymia and insecure attachment (Davis et al., 2003; Benetti et al., 2010; Towler and Stuhlmacher, 2013). A previous study showed that a functional polymorphism (T102C, rs6313) in serotonin receptor 2 gene (*5-HT2A*) is associated with the avoidance attachment, such that individuals with the TT genotype, relating to higher receptor expression level, scored higher on avoidance than individuals with CC/CT genotype (Gillath et al., 2008). Consistent with this study, the current study showed that individuals with the GG genotype of *5-HT1A*, relating to higher receptor expression level, reported less comfort with intimate relations than individuals with the CG/GG genotype, although this result did not survive Bonferroni correction. Overall, these two studies provide a basis, at the genetic level, for the link between alexithymia and attachment orientation.

Previous studies have shown that early family experiences, such as childhood abuse and parental bonding, are crucial for the development of alexithymia or insecure attachment (Wekerle and Wolfe, 1998; Wearden et al., 2003; De Panfilis et al., 2008; Pedrosa Gil et al., 2008). Nevertheless, our results showed that the effects of *5-HT1A* on alexithymia and attachment still hold after controlling for the effects of these factors. This suggests that *5-HT1A* may play an important role in regulating the development of alexithymia and attachment orientation independently of early family experiences.

In conclusion, by differentiating individuals according to the polymorphism C-1019G of *5-HT1A* and measuring them with the Toronto Alexithymia Scale and the Revised Adult Attachment Scale, we demonstrated for the first time the impact of *5-HT1A* upon the development of alexithymic characteristics and attachment orientation. Clinical implications of targeting the *5-HT1A* receptors as a way to treat alexithymia-related mood disorders may be investigated in further studies.

Role of the funding sources

This study was supported by grants from National Basic Research Program of China (973 Program: 2010CB833904), Natural Science Foundation of China (30970889, 30110972) to Xiaolin Zhou and from China Postdoctoral Science Foundation (2013M530002) to Pingyuan Gong. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

The authors declare that there is no conflict of interests.

Acknowledgments

This study was supported by grants from National Basic Research Program of China (973 Program: 2010CB833904), Natural Science Foundation of China (30970889, 30110972) to Prof. Xiaolin Zhou and from China Postdoctoral Science Foundation (2013M530002) to Dr. Pingyuan Gong. We thank Mr. Peizhe Zhang, Miss Yunxia He and Miss Lin Lei for their assistance in data collection, Dr. Hongyun Liu for advice on statistical analysis and Mr. Tonggui Li and Mr. Philip Blue for the preparation of the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2014.09.001.

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