

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

Pingyuan Gong^{a,b,1}, Jinting Liu^{a,1}, She Li^b, Xiaolin Zhou^{a,c,d}

^a Center for Brain and Cognitive Sciences and Department of Psychology, Peking University, Beijing 100871, China

^b Laboratory of Medical Molecular Biology, Henan University of Science and Technology, Luoyang 471003, China

^c Key Laboratory of Machine Perception (Ministry of Education), Peking University, Beijing 100871, China

^d PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing 100871, China

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.

© 2014 Elsevier Ltd. All rights reserved.

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 Rimschaet et al., 2013). It occurs in up to 50% of

Corresponding author at: Department of Psychology, Peking University, Beijing 100871, China. Tel.: +86 10 62756599; fax: +86 10 62761081.

E-mail address: xz104@pku.edu.cn (X. Zhou).

¹ Pingyuan Gong and Jinting Liu contributed equally to this work.

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 post-synaptic 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

2.3. Attachment test

Attachment components were measured with the Chinese version (

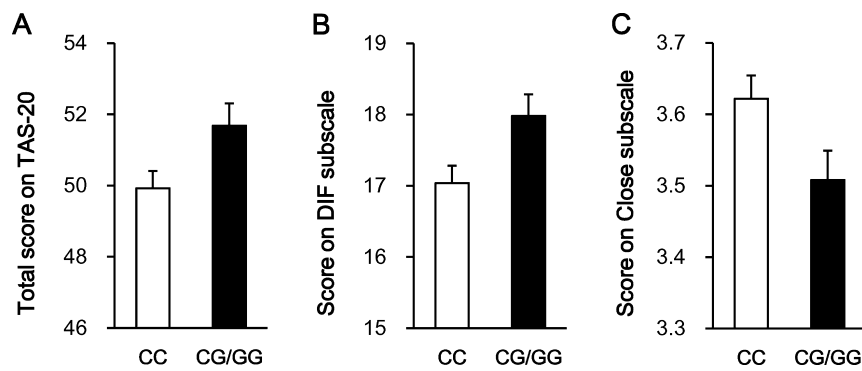


Figure 1 Effects of 5-HT1A C-1019G polymorphism on alexithymia and close attachment orientation. (A) Individuals with the CC genotype (N=316) had a lower mean total score on the 20-item Toronto Alexithymia Scale (TAS-20) than individuals with the CG/GG genotypes (N=188). (B) Individuals with the CC genotype reported a lower mean total score on the Difficulty Identifying Feelings (DIF) subscale of TAS-20.

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 Pan"lis 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 "rst 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>.

References

- Albert, P.R., Lemonde, S., 2004. 5-HT1A receptors, gene repression, and depression: guilt by association. *Neuroscientist* 10, 575,593.
- Anttila, S., Huuhka, K., Huuhka, M., Rontu, R., Hurme, M., Leinonen, E., Lehtimäki, T., 2007. Interaction between 5-HT1A and BDNF genotypes increases the risk of treatment-resistant depression. *J. Neural Transm.* 114, 1065,1068.
- Bagby, R.M., Taylor, G.J., Parker, J.D., 1994. The Twenty-item Toronto Alexithymia Scale...II. Convergent, discriminant, and concurrent validity. *J. Psychosom. Res.* 38, 33,40.
- Benetti, S., McCrory, E., Arulanantham, S., De Sanctis, T., McGuire, P., Mechelli, A., 2010. Attachment style, affective loss and gray matter volume: a voxel-based morphometry study. *Hum. Brain Mapp.* 31, 1482,1489.
- Burba, B., Oswald, R., Grigaliunien, V., Neverauskiene, S., Jankuviene, O., Chue, P., 2006. A controlled study of alexithymia in adolescent patients with persistent somatoform pain disorder. *Can. J. Psychiatry* 51, 468,471.
- Caspers, K.M., Paradiso, S., Yucuis, R., Troutman, B., Arndt, S., Philibert, R., 2009. Association between the serotonin transporter promoter polymorphism (5-HTTLPR) and adult unresolved attachment. *Dev. Psychol.* 45, 64,76.
- Collins, N.L., 1996. Working models of attachment: implications for explanation, emotion and behavior. *J. Pers. Soc. Psychol.* 71, 810,832.
- Czesak, M., Le Francois, B., Millar, A.M., Deria, M., Daigle, M., Visvader, J.E., Anisman, H., Albert, P.R., 2012. Increased serotonin-1A (5-HT1A) autoreceptor expression and reduced raphe serotonin levels in deformed epidermal autoregulatory factor-1 (Deaf-1) gene knock-out mice. *J. Biol. Chem.* 287, 6615,6627.
- Davila, J., Burge, D., Hammen, C., 1997. Why does attachment style change? *J. Pers. Soc. Psychol.* 73, 826,838.
- Davis, D., Shaver, P.R., Vernon, M.L., 2003. Physical, emotional, and behavioral reactions to breaking up: the roles of gender, age, emotional involvement, and attachment style. *Pers. Soc. Psychol. Bull.* 29, 871,884.
- de Haas, M.A., Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H., 1994. The Adult Attachment Interview and Questionnaires for attachment style, temperament, and memories of parental behavior. *J. Genet. Psychol.* 155, 471,486.
- de Lamballerie, X., Chapel, F., Vignoli, C., Zandotti, C., 1994. Improved current methods for amplification of DNA from routinely processed liver tissue by PCR. *J. Clin. Pathol.* 57, 466,467.
- De Pan"lis, C., Salvatore, P., Marchesi, C., Cazzolla, R., Tonna, M., Maggini, C., 2008. Parental bonding and personality disorder: the mediating role of alexithymia. *J. Pers. Disord.* 22, 496,508.
- Deng, Y., Ma, X., Tang, Q., 2013. Brain response during visual emotional processing: an fMRI study of alexithymia. *Psychiatry Res.* 213, 225,229.
- Drago, A., Ronchi, D.D., Serretti, A., 2008. 5-HT1A gene variants and psychiatric disorders: a review of current literature and selection of SNPs for future studies. *Int. J. Neuropsychopharmacol.* 11, 701,721.
- Frewen, P.A., Pain, C., Dozois, D.J., Lanius, R.A., 2006. Alexithymia in PTSD: psychometric and fMRI studies. *Ann. N. Y. Acad. Sci.* 1071, 397,400.
- Fink, K.B., Gothert, M., 2007. 5-HT receptor regulation of neurotransmitter release. *Pharmacol. Rev.* 59, 360,417.
- Frodl, T., Reinhold, E., Koutsouleris, N., Donohoe, G., Bondy, B., Reiser, M., Moller, H.J., Meisenzahl, E.M., 2010. Childhood stress, serotonin transporter gene and brain structures in major depression. *Neuropsychopharmacology* 35, 1383,1390.
- Fukunishi, I., Ichikawa, M., Ichikawa, T., Matsuzawa, K., Fujimura, K., Tabe, T., Iida, Y., Saito, S., 1992. Alexithymia and depression in families with alcoholics. *Psychopathology* 25, 326,330.
- Gillath, O., Shaver, P.R., Baek, J.M., Chun, D.S., 2008. Genetic correlates of adult attachment style. *Pers. Soc. Psychol. Bull.* 34, 1396,1405.
- Gong, P., Liu, J., Li, S., Zhou, X., 2014. Dopamine beta-hydroxylase gene modulates individuals' empathic ability. *Soc. Cogn. Affect. Neurosci.* 9, 1341,1345.

- Hannon, J., Hoyer, D., 2008. [Molecular biology of 5-HT receptors. Behav. Brain Res. 195, 198,213.](#)
- Hazan, C., Shaver, P., 1987. [Romantic love conceptualized as an attachment process. J. Pers. Soc. Psychol. 52, 511,524.](#)
- Heils, A., Teufel, A., Petri, S., Stober, G., Riederer, P., Bengel, D., Lesch, K.P., 1996. [Allelic variation of human serotonin transporter gene expression. J. Neurochem. 66, 2621,2624.](#)
- Honkalampi, K., Tolmunen, T., Hintikka, J., Rissanen, M.L., Kylmä, J., Laukkanen, E., 2009. [The prevalence of alexithymia and its relationship with youth self-report problem scales among Finnish adolescents. Compr. Psychiatry 50, 263,268.](#)
- Kano, M., Mizuno, T., Kawano, Y., Aoki, M., Kanazawa, M., Fukudo, S., 2012. [Serotonin transporter gene promoter polymorphism and alexithymia. Neuropsychobiology 65, 76,82.](#)
- Karukivi, M., Hautala, L., Kaleva, O., Haapasalo-Pesu, K.M., Liukkala, P.R., Joukamaa, M., Saarijärvi, S., 2010. [Alexithymia is associated with anxiety among adolescents. J. Affect. Disord. 125, 383,387.](#)
- Kishi, T., Yoshimura, R., Fukuo, Y., Okochi, T., Matsunaga, S., Umene-Nakano, W., Nakamura, J., Serretti, A., Correll, C.U., Kane, J.M., Iwata, N., 2013. [The serotonin 1A receptor gene confer susceptibility to mood disorders: results from an extended meta-analysis of patients with major depression and bipolar disorder. Eur. Arch. Psychiatry Clin. Neurosci. 263, 105,118.](#)
- Larisch, R., Klimke, A., Hamacher, K., Henning, U., Estalji, S., Hohlfeld, T., Vosberg, H., Tosch, M., Gaebel, W., Coenen, H.H., Müller-Gärtner, H.W., 2003. [Influence of synaptic serotonin level on \[18F\]altanserin binding to 5HT2 receptors in man. Behav. Brain Res. 139, 21,29.](#)
- Le Francois, B., Czesak, M., Steubl, D., Albert, P.R., 2008. [Transcriptional regulation at a HTR1A polymorphism associated with mental illness. Neuropharmacology 55, 977,985.](#)
- Lemondé, S., Turecki, G., Bakish, D., Du, L., Hrdina, P.D., Bown, C.D., Sequeira, A., Kushwaha, N., Morris, S.J., Basak, A., Ou, X.M., Albert, P.R., 2003. [Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. J. Neurosci. 23, 8788,8799.](#)
- Linnet, K., Koed, K., Wiborg, O., Gregersen, N., 1995. [Serotonin depletion decreases serotonin transporter mRNA levels in rat brain. Brain Res. 697, 251,253.](#)
- Meyer, J.H., Wilson, A.A., Sagrati, S., Hussey, D., Carella, A., Potter, W.Z., Ginovart, N., Spencer, E.P., Cheok, A., Houle, S., 2004. [Serotonin transporter occupancy of "ve selective serotonin reuptake inhibitors at different doses: an \[11C\]DASB positron emission tomography study. Am. J. Psychiatry 161, 826,835.](#)
- Montebarocci, O., Codispoti, M., Baldaro, B., Rossi, N., 2004. [Adult attachment style and alexithymia. Pers. Individ. Dif. 36, 499,507.](#)
- Mueller, A., Brocke, B., Fries, E., Lesch, K.P., Kirschbaum, C., 2010. [The role of the serotonin transporter polymorphism for the endocrine stress response in newborns. Psychoneuroendocrinology 35, 289,296.](#)
- Murthy, N.V., Selvaraj, S., Cowen, P.J., Bhagwagar, Z., Riedel, W.J., Peers, P., Kennedy, J.L., Sahakian, B.J., Laruelle, M.A., Rabiner, E.A., Grasby, P.M., 2010. [Serotonin transporter polymorphisms \(SLC6A4 insertion/deletion and rs25531\) do not affect the availability of 5-HTT to \[11C\] DASB binding in the living human brain. Neuroimage 52, 50,54.](#)
- Oskis, A., Clow, A., Hucklebridge, F., Bifulco, A., Jacobs, C., Love-day, C., 2013. [Understanding alexithymia in female adolescents: the role of attachment style. Pers. Individ. Dif. 54, 97,102.](#)
- Pedrosa Gil, F., Scheidt, C.E., Hoeger, D., Nickel, M., 2008a. [Relationship between attachment style, parental bonding and alexithymia in adults with somatoform disorders. Int. J. Psychiatry Med. 38, 437,451.](#)
- Pedrosa Gil, F., Weigl, M., Wessels, T., Irnich, D., Baumüller, E., Winkelmann, A., 2008b. [Parental bonding and alexithymia in adults with "bromyalgia. Psychosomatics 49, 115,122.](#)
- Pezawas, L., Meyer-Lindenberg, A., Drabant, E.M., Verchinski, B.A., Munoz, K.E., Kolachana, B.S., Egan, M.F., Mattay, V.S., Hariri, A.R., Weinberger, D.R., 2005. [5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat. Neurosci. 8, 828,834.](#)
- Radaelli, D., Sferazza Papa, G., Vai, B., Poletti, S., Smeraldi, E., Colombo, C., Benedetti, F., 2014. [Fronto-limbic disconnection in bipolar disorder. Eur. Psychiatry \[Epub ahead of print\].](#)
- Salo, J., Jokela, M., Lehtimäki, T., Keltikangas-Järvinen, L., 2011. [Serotonin receptor 2A gene moderates the effect of childhood maternal nurturance on adulthood social attachment. Genes Brain Behav. 10, 702,709.](#)
- Savitz, J., Lucki, I., Drevets, W.C., 2009. [5-HT\(1A\) receptor function in major depressive disorder. Prog. Neurobiol. 88, 17,31.](#)
- Sprouse, J.S., Aghajanian, G.K., 1987. [Electrophysiological responses of serotonergic dorsal raphe neurons to 5-HT1A and 5-HT1B agonists. Synapse 1, 3,9.](#)
- Stasiewicz, P.R., Bradizza, C.M., Gudleski, G.D., Coffey, S.F., Schlauch, R.C., Bailey, S.T., Bole, C.W., Gulliver, S.B., 2012. [The relationship of alexithymia to emotional dysregulation within an alcohol dependent treatment sample. Addict. Behav. 37, 469,476.](#)
- Taylor, G.J., 1984. [Alexithymia: concept, measurement, and implications for treatment. Am. J. Psychiatry 141, 725,732.](#)
- Towler, A.J., Stuhlmacher, A.F., 2013. [Attachment styles, relationship satisfaction, and well-being in working women. J. Soc. Psychol. 153, 279,298.](#)
- Troisi, A., D'Argenio, A., Peracchio, F., Petti, P., 2001. [Insecure attachment and alexithymia in young men with mood symptoms. J. Nerv. Ment. Dis. 189, 311,316.](#)
- Trueta, C., Cercos, M.G., 2012. [Regulation of serotonin release from different neuronal compartments. Salud Ment. 35, 435,443.](#)
- von Rimscha, S., Moergeli, H., Weidt, S., Straumann, D., Hegemann, S., Rufer, M., 2013. [Alexithymia and health-related quality of life in patients with dizziness. Psychopathology 46, 377,383.](#)
- Wearden, A., Cook, L., Vaughan-Jones, J., 2003. [Adult attachment, alexithymia, symptom reporting, and health-related coping. J. Psychosom. Res. 55, 341,347.](#)
- Wekerle, C., Wolfe, D.A., 1998. [The role of child maltreatment and attachment style in adolescent relationship violence. Dev. Psychopathol. 10, 571,586.](#)
- Wu, W., Zhang, W., Liu, X., 2004. [The reliability and validity of adult attachment scale \(AAS-1996 revised edition\) \[in Chinese\]. J. Sichuan Univ. \(Med. Sci. Ed.\) 35, 536,538.](#)
- Yi, J., Yao, S., Zhu, X., 2003. [The Chinese version of the TAS-20: reliability and validity \[in Chinese\]. Chin. Ment. Health J. 11, 763,767.](#)
- Zhou, F.C., Tao-Cheng, J.H., Segu, L., Patel, T., Wang, Y., 1998. [Serotonin transporters are located on the axons beyond the synaptic junctions: anatomical and functional evidence. Brain Res. 805, 241,254.](#)
- Zetsche, T., Preuss, U.W., Bondy, B., Frodl, T., Zill, P., Schmitt, G., Koutsouleris, N., Rujescu, D., Born, C., Reiser, M., Möller, H.J., Meisenzahl, E.M., 2008. [5-HT1A receptor gene C-1019 G polymorphism and amygdala volume in borderline personality disorder. Genes Brain Behav. 7, 306,313.](#)
- Zhang, K., Xu, Q., Xu, Y., Yang, H., Luo, J., Sun, Y., Sun, N., Wang, S., Shen, Y., 2009. [The combined effects of the](#)