Neurosci Bull February 1, 2013, 29(1): 1–2. http://www.neurosci.cn
DOI: 10.1007/s12264-013-1302-6


·Research Highlight·

# Influence of 5-HTTLPR genotypes on structural and functional connectivity within amygdala–prefrontal cortex circuitry

Ke Xu[1], Fei Wang[2]

[1]*Department of Radiology, The First Affiliated Hospital, China Medical University, Shenyang 110001, China*

[2]*Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06511, USA*

Corresponding authors: Ke Xu and Fei Wang. E-mail: kexu@vip.sina.com, fei.wang@yale.edu



Anxiety and depression are highly heritable disorders that lead to significant impairment in affected individuals across gender, ethnicity and race; these disorders are frequently the leading causes of disability and suicide in many countries. One could assume that the same pathophysiological mechanisms underlie anxiety and depression in all affected individuals; however, the observed clinical heterogeneity within these disorders raises doubts and questions as to the validity of this assumption. Moreover, no single gene is thought to underlie anxiety and depression. Instead, it is thought that a convergence of multiple genetic factors contributes to the clinical manifestations of these disorders, adding yet another layer of complexity to understanding the pathophysiology of anxiety and depression.

Imaging genetics was developed to examine the effects of genetic variation on neuroimaging measurements that reflect neurobiological functioning and structure in the hope that it can help bridge the mechanistic gap between genes and phenotypes in psychiatric disorders. The study by Long *et al*. in this issue highlights the importance of imaging genetic studies in anxiety and depression.

Deficits within the neural circuitry subserving emotional processing are strongly implicated in anxiety and depression, including key regions such as the prefrontal cortex (PFC) and amygdala[1-4]. Multi-modal neuroimaging studies provide considerable support for abnormalities in the structure, function, and functional connectivity of the PFC and amygdala in these disorders[5-9]. In addition, recent studies have also implicated abnormalities in the white matter connections between the PFC and amygdala in anxiety and depression, particularly in the ventral prefrontal white matter[10,11].

An important candidate gene for the development and pathophysiology of anxiety and depression is the gene encoding the serotonin transporter promoter protein (locus, *SLC6A4*; variant, 5-HTTLPR). The serotonin transporter (5-HTT) is central to the regulation of serotonergic activity. As the PFC–amygdala neural circuitry is rich in serotonin, 5-HTT likely plays important modulatory roles within this circuitry. A functional polymorphism in humans in 5-HTTLPR is associated with effects on transcription and the level of serotonin transporter function[12]. The presence of the short allele (S) has been associated with anxiety-related traits[13] and a vulnerability to depression in individuals exposed to stressful life events[14] in Caucasian populations. In addition, 5-HTTLPR affects the development of cortico–limbic circuitry and alters the functional connectivity during emotional processing between the amygdala and medial PFC in Caucasian populations[15]. However, these associations are less clear in Asian populations.

In contrast to the findings in Caucasian populations, Long *et al*.[16] found reduced functional coupling between the PFC and amygdala during the resting state in Chinese Han subjects carrying the long allele (L) for 5-HTTLPR. They also found decreased structural integrity of the uncinate fasciculus, an important component of the ventral prefrontal white matter, in L carriers. Interestingly, they also demonstrated that decreased functional and structural connectivity within the PFC–amygdala circuitry correlated with the severity of anxiety and depression. Other studies in Asian populations by other groups have also demonstrated contrasts to Caucasian populations. Such studies have shown that the S allele of 5-HTTLPR is associated with a

positive response to selective serotonin reuptake inhibitors in Asian populations; studies in Caucasian populations have found that L carriers show a better response to selective serotonin reuptake inhibitors than homozygotes for the S allele[17,18]. Another study found that, in an Asian population, individuals carrying the L/L genotype for 5-HTTLPR are susceptible to depression when exposed to negative life events[19], whereas Caspi *et al*. found that Caucasian individuals carrying the S allele are vulnerable to depression with exposure to negative life events[14]. In summary, Long *et al*[16]. used an integrated approach to studying genetic influences on structural and functional connectivity within the PFC–amygdala circuitry in a Chinese Han population. This study contributes to the understanding of the structural and functional organization of the neural circuitry subserving emotional regulation, as well as the understanding of the pathophysiology of anxiety and depression. Importantly, the findings of Long *et al*. underscore the importance of genetic influences on neural process and the need to consider racial and ethnic backgrounds in studies of psychiatric disorders. Such considerations could lead to advances in the identification of at-risk individuals, effective early intervention, and more targeted treatment strategies at both individual and neural system levels, and thus improve the prognosis for disorders such as anxiety and depression.

## REFERENCES


[1] Garcia R, Vouimba RM, Baudry M, Thompson RF. The amygdala modulates prefrontal cortex activity relative to conditioned fear. Nature 1999, 402: 294–296.

[2] LeDoux JE. Emotion circuits in the brain. Annu Rev Neurosci 2000, 23: 155–184.

[3] Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. Proc Natl Acad Sci U S A 1998, 95: 13290–13295.

[4] Quirk GJ, Likhtik E, Pelletier JG, Pare D. Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. J Neurosci 2003, 23: 8800–8807.

[5] Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, *et al.* Subgenual prefrontal cortex abnormalities in mood disorders. Nature 1997, 386: 824–827.

[6] Tang Y, Wang F, Xie G, Liu J, Li L, Su L, *et al.* Reduced ventral anterior cingulate and amygdala volumes in medication-naive females with major depressive disorder: A voxel-based morphometric magnetic resonance imaging study. Psychiatry Res 2007, 156: 83–86.

[7] Drevets WC. Neuroimaging abnormalities in the amygdala in mood disorders. Ann N Y Acad Sci 2003, 985: 420–444.

[8] Ball TM, Ramsawh HJ, Campbell-Sills L, Paulus MP, Stein MB. Prefrontal dysfunction during emotion regulation in generalized anxiety and panic disorders. Psychol Med 2012: 1–12.

[9] Kim MJ, Loucks RA, Palmer AL, Brown AC, Solomon KM, Marchante AN, *et al.* The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. Behav Brain Res 2012, 223: 403–410.

[10] Tromp do PM, Grupe DW, Oathes DJ, McFarlin DR, Hernandez PJ, Kral TR, *et al.* Reduced structural connectivity of a major frontolimbic pathway in generalized anxiety disorder. Arch Gen Psychiatry 2012, 69: 925–934.

[11] Korgaonkar MS, Grieve SM, Koslow SH, Gabrieli JD, Gordon E, Williams LM. Loss of white matter integrity in major depressive disorder: evidence using tract-based spatial statistical analysis of diffusion tensor imaging. Hum Brain Mapp 2012, 32: 2161–2171.

[12] Murphy DL, Li Q, Engel S, Wichems C, Andrews A, Lesch KP, *et al.* Genetic perspectives on the serotonin transporter. Brain Res Bull 2001, 56: 487–494.

[13] Osher Y, Hamer D, Benjamin J. Association and linkage of anxiety-related traits with a functional polymorphism of the serotonin transporter gene regulatory region in Israeli sibling pairs. Mol Psychiatry 2000, 5: 216–219.

[14] Caspi A, Sugden K, Moffit TE, Taylor A, Craig IW, Harrington H, *et al.* Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003, 301: 386–389.

[15] Hariri AR, Drabant EM, Weinberger DR. Imaging genetics: perspectives from studies of genetically driven variation in serotonin function and corticolimbic affective processing. Biol Psychiatry 2006, 59: 888–897.

[16] Long H, Liu B, Hou B, Wang C, Li J, Qin W, *et al.* The long rather than the short allele of 5-HTTLPR predisposes Han Chinese to anxiety and reduced connectivity between prefrontal cortex and amygdala. Neurosci Bull 2013, 29: 4–15.

[17] Kim H, Lim SW, Kim S, Kim JW, Chang YH, Carroll BJ, *et al.* Monoamine transporter gene polymorphisms and antidepressant response in koreans with late-life depression. JAMA 2006, 296: 1609–1618.

[18] Smeraldi E, Zanardi R, Benedetti F, Di Bella D, Perez J, Catalano M. Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. Mol Psychiatry 1998, 3: 508–511.

[19] Zhang K, Xu Q, Xu Y, Yang H, Luo J, Sun Y, *et al.* The combined effects of the 5-HTTLPR and 5-HTR1A genes modulates the relationship between negative life events and major depressive disorder in a Chinese population. J Affect Disord 2009, 114: 224–231.