Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressants and have been used to treat mood disorders, such as depression and anxiety disorder. Selective serotonin reuptake inhibitors such as citalopram selectively block serotonin transporter (5-HTT) activity,[1] inhibit the reuptake of serotonin (5-HT) into the presynaptic cell and lead to increasing extracellular levels of 5HT.[2] Although clinical trials have shown that SSRIs typically have a delay of several weeks in the onset of their clinical effects, SSRI effects can occur soon after their administration.[3] The early 4,5

Therefore, understanding the neural mechanisms underlying the acute effects of SSRIs is important for decisions about long-term treatment. However, recent neuroimaging studies have reported inconsistent acute effects of SSRIs on neural responses in emotion-related brain regions such as the amygdala, whose hyperactivity has been suggested as an endophenotype of anxiety disorder and major depression.[6,7]

Twelve functional magnetic resonance imaging (fMRI) studies have examined the acute effects of SSRIs (single SSRI administration) on neural responses to negative emotions, while eight fMRI studies have examined acute effects of SSRI administration on neural response to positive emotions. Among these studies, four reported increased amygdala response[8–11] whereas eight reported decreased amygdala response to negative emotions[11–18] after SSRI v. placebo administration. Two studies reported increased amygdala response to positive emotions,[10,19] whereas six studies did not show SSRI effects on amygdala response to positive emotions.[9,10,14–16,19] Moreover, our recent meta-analysis[20] revealed that the acute effects of antidepressants on positive emotions did not show any convergent activation in healthy adults. Acute antidepressant administration showed discrepant effects on neural responses to negative emotions. Specifically, single antidepressant administration led to convergent increases as well as decreases in a similar neural network underlying negative emotions. Although age, gender or disease conditions may contribute to individual differences in psychometric outcome and discrepant SSRI effects on amygdala response, the genetic structure of individuals also affects drug responses.[21] A sodium-dependent serotonin-transporter-linked polymorphic region (5-HTTLPR), which influences the expression and function of 5-HTT,[22,23] may be implicated in SSRI efficacy. For example, major depression patients with the long (l) allele of 5-HTTLPR showed better responses to SSRI treatment compared to homozygotes for the short variant (s/s) of 5-HTTLPR.[24,25] However, it remains unknown whether and how 5-HTTLPR

placebo tablet with at least a 7-day washout period (at least 7 days

genotype groups ($F(1, 43) = 4.15$, $P = 0.048$, Fig. 2a), replicating previous findings.[36,37] We assessed the differential citalopram effects on amygdala response to fearful v. neutral facial expressions in the two genotypes by conducting a 2 (emotion: fearful v. neutral) × 2 (treatment: citalopram v. placebo) × 2 (genotype: s/s v. l/l) ANOVA of parameter estimates of signal intensity. This revealed a significant main effect of emotion in both left and right amygdala ($F(1,43) = 5.40$ and 4.124[illegible]

−34/−12/16, T = 3.91; right: 40/−4/12, T = 3.35, P < 0.05, topological FDR corrected; Fig. 2c), suggesting variations of citalopram effects on insula response as a function of 5-HTTLPR polymorphism (Fig. 3). A similar whole-brain analysis of the contrast of happy v. neutral facial expressions did not show any significant brain activation.

Discussion

Current research has focused on elucidating the neural substrates underlying the heterogeneity of the acute effects of SSRIs in healthy volunteers. We have provided pharmacogenetic and neuroimaging evidence that 5-HTTLPR polymorphism modulates the acute effects of citalopram on neural activity related to emotion processing. Specifically, we found that the acute administration of citalopram (v. placebo) increased amygdala and insula activity in the l/l but not the s/s genotype of 5-HTTLPR. The genotype differences in the acute effects of an SSRI were evident in the neural responses to fearful but not happy facial expressions, indicating that such genotype differences do not reflect the non-specific effects of citalopram, such as changes in arousal or drowsiness. Our results indicate that an individual's genetic structure may influence the acute effects of citalopram on neural response to negative emotions and that 5-HTT is a key molecular transporter that contributes to the differential neural responses to negative emotions in healthy adults. Our findings provide a possible neurogenetic mechanism for understanding the previous inconsistent results regarding how the acute administration of SSRIs modulates neural responses to negative emotions.

Self-reported mood was not influenced by 5-HTTLPR genotype or citalopram administration. Therefore, 5-HTTLPR modulation of the effect of citalopram on amygdala response cannot be simply attributed to general mood changes. This is consistent with a cognitive neuropsychological model of SSRI action that emotional processes are sensitive to early SSRI-induced changes in the absence of mood variation.

24 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**: 508–11.

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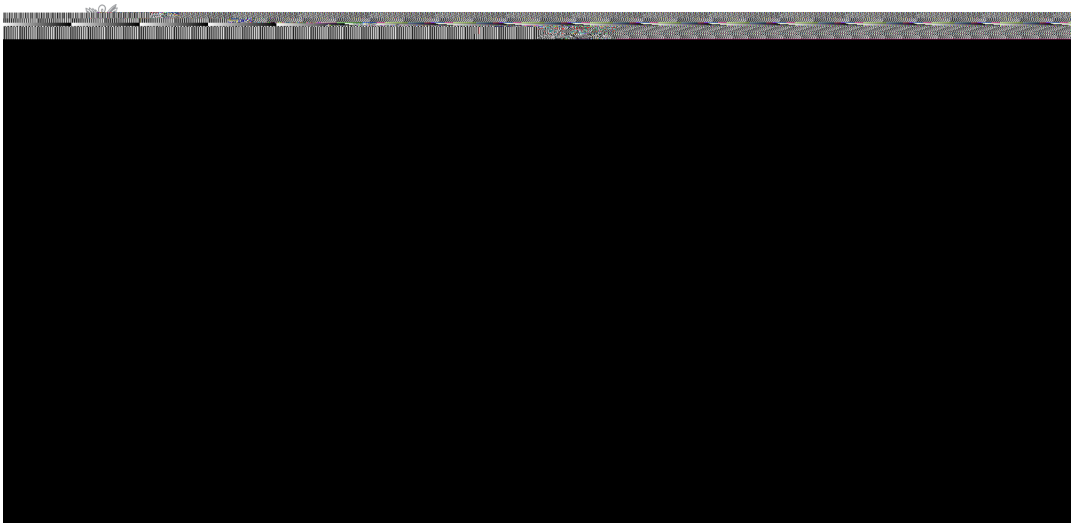

Allelic variation in 5-HTTLPR and the effects of citalopram on the emotional neural network

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