

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

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## Background

Selective serotonin reuptake inhibitors (SSRIs), such as citalopram, which selectively block serotonin transporter (5-HTT) activity, are widely used in the treatment of depression and anxiety disorders. Numerous neuroimaging studies have examined the effects of SSRIs on emotional processes. However, there are considerable inter-individual differences in SSRI effect, and a recent meta-analysis further revealed discrepant effects of acute SSRI administration on neural responses to negative emotions in healthy adults.

## Aims

We examined how a variant of the serotonin-transporter polymorphism (5-HTTLPR), which affects the expression and function of 5-HTT, influenced the acute effects of an SSRI (citalopram) on emotion-related brain activity in healthy adults.

## Method

Combining genetic neuroimaging, pharmacological technique and a psychological paradigm of emotion recognition, we scanned the short/short (s/s) and long/long (l/l) variants of 5-HTTLPR during perception of fearful, happy and neutral

facial expressions after the acute administration of an SSRI (i.e. 30 mg citalopram administered orally) or placebo administration.

## Results

We found that 5-HTTLPR modulated the acute effects of citalopram on neural responses to negative emotions. Specifically, relative to placebo, citalopram increased amygdala and insula activity in l/l but not s/s homozygotes during perception of fearful faces. Similar analyses of brain activity in response to happy faces did not show any significant effects.

## Conclusions

Our combined pharmacogenetic and functional imaging results provide a neurogenetic mechanism for discrepant acute effects of SSRIs.

## Declaration of interest

None.

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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,<sup>1</sup> inhibit the reuptake of serotonin (5-HT) into the presynaptic cell and lead to increasing extracellular levels of 5HT.<sup>2</sup> 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.<sup>3</sup> The early changes in emotional processing that occur after the acute administration of an SSRI contribute to later mood improvements.<sup>4,5</sup> 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.<sup>6,7</sup>

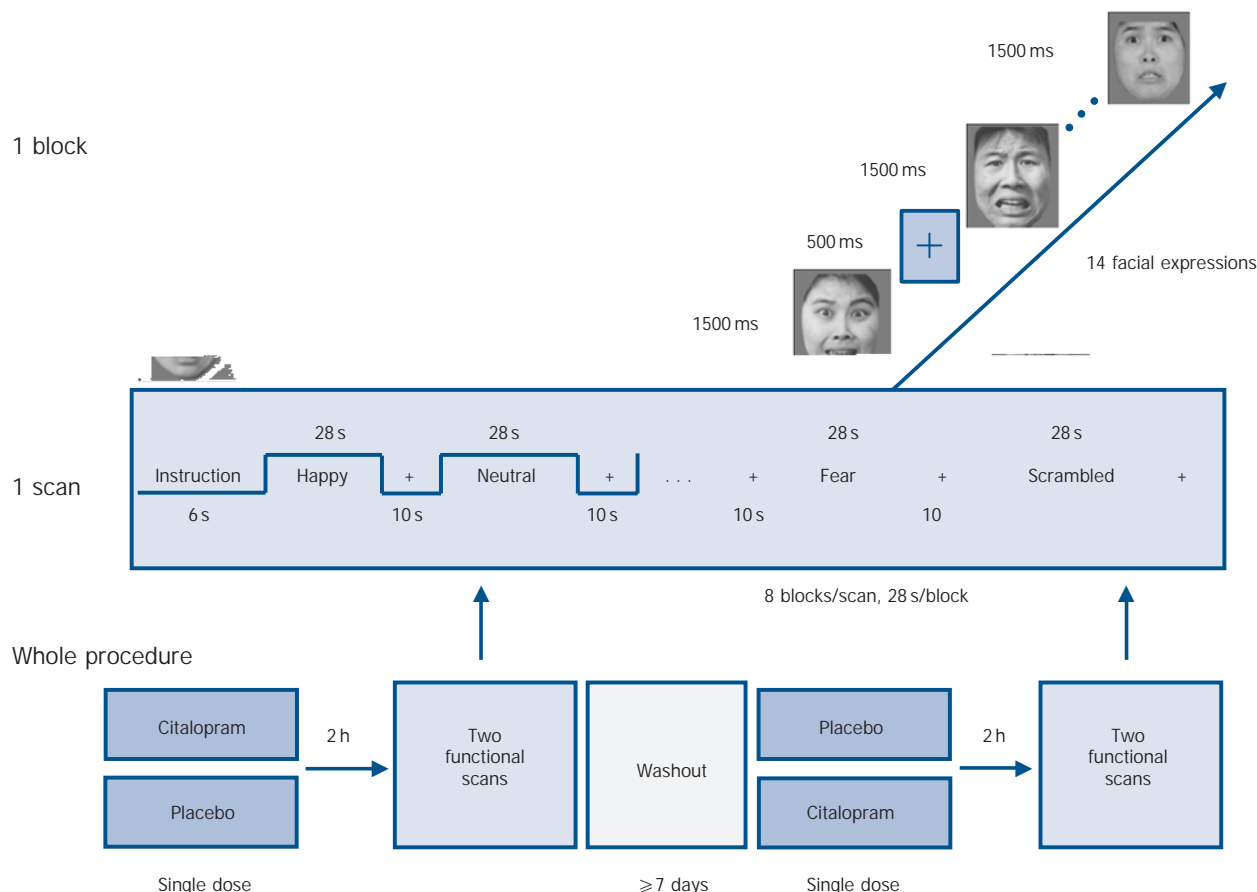
Twelve functional magnetic resonance imaging (fMRI) studies have examined the acute effects of SSRIs (single SSRI administration) on neural responses to negative emotions, while eight fMRI studies have examined acute effects of SSRI administration on neural response to positive emotions. Among these studies, four reported increased amygdala response<sup>8–11</sup> whereas eight reported decreased amygdala response to negative emotions<sup>11–18</sup> after SSRI *v.* placebo administration. Two studies reported increased amygdala response to positive emotions,<sup>10,19</sup> whereas six studies did not show SSRI effects on amygdala response to positive emotions.<sup>9,10,14–16,19</sup> Moreover, our recent meta-analysis<sup>20</sup> 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.<sup>21</sup> A sodium-dependent serotonin-transporter-linked polymorphic region (5-HTTLPR), which influences the expression and function of 5-HTT,<sup>22,23</sup> 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.<sup>24,25</sup> However, it remains unknown whether and how 5-HTTLPR polymorphism affects the acute effects of SSRIs on brain activity.

## Method

### Experimental design

We combined genetic neuroimaging, pharmacological technique and a psychological paradigm of emotion recognition to provide a better understanding of the neurogenetic mechanism of the acute effects of SSRIs on emotions. Specifically, we examined whether 5-HTTLPR modulates the acute effects of SSRIs on neural response to emotional facial expressions. Using a double-blind, within-subject, counterbalanced design (Fig. 1), we scanned s/s and l/l homozygotes during perception of fearful, happy and neutral facial expressions using fMRI after administration of a single oral dose of a SSRI (30 mg citalopram) and a matched



**Fig. 1** E-im na ʔc s . Eac in i i a a i a i n ʔfMRI s s i i n s s a a b a 7- a a s ʔ . In a c s s i i n , f n c i ʔna scannin a s c ʔn c s 2 a f c i a ʔ a m ʔ a c b ʔ a m i n i s a i ʔn . A b ʔc s i n a s s s i n scannin . ʔ ʔ f n c i ʔna scans a s i n 334 s i n a c ( c i a ʔ a m ʔ a c b ʔ ) s s i i n . Eac f n c i ʔna scan c ʔn s i s ʔ ʔ f i b ʔc s ( ʔ b ʔc s ʔ f a c s i m s c a ʔ ) ʔ f 14 s i m i ( 12 f a c s a n ʔ a s ) a s f ʔ m s a m s i m s c a ʔ . Eac f a c s i m s a s s n ʔ b a 1500 ms ; a i c i a n s n a s ʔ i a ʔ n a f i a i ʔ n c ʔ s s f ʔ 500 ms . ʔ ʔ s c c s s i w b ʔc s s a a ʔ b a 10 s f i a i ʔ n c ʔ s s . fMRI : f n c i ʔna m a n i c s ʔn a n c i m a i n .

placebo tablet with at least a 7-day washout period (at least 7 days apart, ranging from 7 to 29 days, mean = 14.3 days, s.d. = 6.7). Given that l/l compared with s/s homozygotes have been shown to exhibit increased 5-HTT expression and 5-HT uptake,<sup>26</sup> and a greater increase in 5HT neurotransmission after acute blockade of 5-HT reuptake,<sup>27</sup> blocking 5-HTT activity with citalopram may produce stronger effects on brain activity in l/l than s/s homozygotes. Thus, we predicted greater SSRI effects on the neural responses to emotional facial expressions in l/l than s/s homozygotes.

## Participants

Fifty Chinese men participated in this study as paid volunteers. We recruited only men to avoid any potential gender difference in citalopram effects. We used polymerase chain reaction to determine the genotypes of 5-HTTLPR. (See online supplementary material for DNA isolation and analysis.) Two l/l and two s/s homozygotes were excluded from the data analysis due to excessive head movement during scanning (exclusion criterion: 6 mm head motion or 3° for head rotation). Thus 23 s/s (18–23 years, mean = 19.4, s.d. = 1.8) and 23 l/l homozygotes (18–23 years, mean = 18.6, s.d. = 1.4), who did not differ significantly in age ( $t(44) = 1.296, P = 0.202$ ), were included in the data analysis. All participants were right-handed and had normal or corrected-to-normal vision. All participants had no history of cardiac,

hepatic, renal, pulmonary, neurological, psychiatric or gastrointestinal disorders, medication/drug use, and no family history of major depression or bipolar affective disorder. The study protocol was approved by the local ethics committee of the Department of Psychology at Peking University. Written informed consent was obtained prior to the study from all participants.

## General procedure

We used a  $2 \times 2$  factorial design with emotion (fearful *v.* neutral faces, or happy *v.* neutral faces) and treatment (citalopram *v.* placebo) as the between-subjects variables and genotype (*s/s v. l/l* genotype) as the between-subjects variable. The order of citalopram and placebo treatment was counterbalanced within each genotype group and across the *s/s* and *l/l* genotype groups. We used a single oral administration of 30 mg citalopram, which is within the dose range (20–60 mg) and has been used in previous studies.<sup>28,29</sup> We administered a single dose to examine the acute effects of SSRIs. Pharmacokinetic and plasma hormone concentration studies have shown that, in men, citalopram plasma concentration reaches a peak around 2 h.<sup>30,31</sup> Thus, functional scanning was conducted about 2 h after citalopram or placebo administration when citalopram reached its peak effect. During the waiting period, participants sat on a comfortable couch, resting or reading. A researcher explained the task and procedure to participants and participants practised a few trials to become

familiar with the task 30 min before scanning. Before taking citalopram or the placebo, we evaluated each participant's harm-avoidance tendency using the harm avoidance subscale from the Tridimensional Personality Questionnaire.<sup>32</sup> At the beginning and end of the citalopram or placebo session, we asked participants to complete the Positive and Negative Affect Scale<sup>33</sup> to monitor their mood changes.

### Functional imaging task

Four categories of facial expressions (fearful, happy, neutral and scrambled; 24 images in each category, half male models and half female models, from the Chinese Facial Affective Picture System)<sup>34</sup> were used during scanning. Scrambled faces were made by segmenting each face image (300 × 336 pixels) into 50 × 56 square grids (6 × 6 pixels) that were then randomly arranged. This rearranged picture was then masked by a stencil of the original face shape, resulting in a pixellated face on a grey background. Stimuli used during the scanning were delivered through a LCD projector onto a rear projection screen (SINORAD SA-9900). Each stimulus subtended a visual angle of 3.85° × 4.31° (width × height) at a viewing distance of 83 cm. Participants completed a typical repetition-detection task by responding to repeated facial expressions via a button press (Fig. 1). After scanning, participants were asked to rate the emotion intensity of 12 fearful and 12 happy faces randomly selected from the two categories on an 11-point Likert scale (0 = not at all fearful/happy; 10 = extremely fearful/happy).

### Imaging parameters

We acquired images of the brain using a Siemens 3-Tesla Trio MRI scanner at the Beijing MRI Center for Brain Research. We obtained blood oxygenation level-dependent gradient-echo echo-planar images using a 12-channel head coil (64 × 64 × 32 matrix with 3.44 × 3.44 × 5.0 mm spatial resolution, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, field of view = 24 × 24 cm) while the participants performed the repetition-detection task. We subsequently acquired a high-resolution, T<sub>1</sub>-weighted structural image (256 × 256 × 144 matrix with a spatial resolution of 1 × 1 × 1.33 mm, TR = 2530 ms, TE = 3.37 ms, inversion time (TI) = 1100 ms, flip angle = 7°).

### Imaging analysis

#### Preprocessing

We used the Statistical Parametric Mapping software, version 8 (Wellcome Trust Centre for Neuroimaging; <http://www.fil.ion.ucl.ac.uk/spm>) to analyse the functional image data; we analysed data using the general linear model for a block design. We realigned the functional images within and across runs to correct for head movement. We included six movement parameters (translation: x, y, z; rotation: pitch, roll, yaw) in the statistical model. We normalised the functional images to a standard Montreal Neurological Institute EPI template and we then spatially smoothed them using a 4-mm, full-width, half-maximum isotropic Gaussian kernel.

#### Regions of interest analysis

We obtained parameter estimates of signal intensity from structurally defined amygdala to assess genotype treatment interaction on emotional processes. We identified the amygdala using the Automated Anatomical Labeling (AAL) atlas (AAL templates) and we selected it using the Wake Forest University School of Medicine PickAtlas software toolbox. We subjected the

parameter estimates of signal intensity in the left and right amygdala to repeated-measures analyses of variance (ANOVA) with genotype (s/s v. l/l) as a between-subjects variable, and treatment (citalopram v. placebo) and emotion (fearful v. neutral facial expressions or happy v. neutral facial expressions) as between-subjects independent variables. To further clarify whether differential SSRI effects on amygdala activity were driven by neural response to emotional or neutral facial expressions, we calculated the contrast value related to fearful, happy and neutral facial expressions v. fixation cross, as used in previous studies.<sup>35</sup> We then subjected these contrast values to genotype treatment ANOVAs for fearful, happy and neutral facial expressions, respectively. We included the treatment (citalopram v. placebo) sequence as a covariate in region of interest (ROI) and whole-brain analyses to control for any potential effect of treatment order. We also conducted analyses that included treatment order as a between-subject variable in the ANOVA and this did not show significant treatment order effects.

#### Whole-brain analysis

We used a two-level, hierarchical, random-effects model for whole-brain analysis. At the individual level, we modelled the onset and duration of each block using a general linear model for five conditions: fearful, happy, neutral, scrambled facial expression and fixation cross. We used a box-car function to convolve with a canonical haemodynamic response in each condition. The contrasts of 'fearful v. neutral' and 'happy v. neutral' identified brain regions responsive to positive and negative emotional facial expressions, respectively. We then performed a whole-brain factorial design to reveal the genotype treatment interaction on the neural response to fearful or happy facial expressions. Significant activations were identified using a threshold of  $P < 0.05$  (topological false discovery rate (FDR) corrected for multiple comparisons correction).

## Results

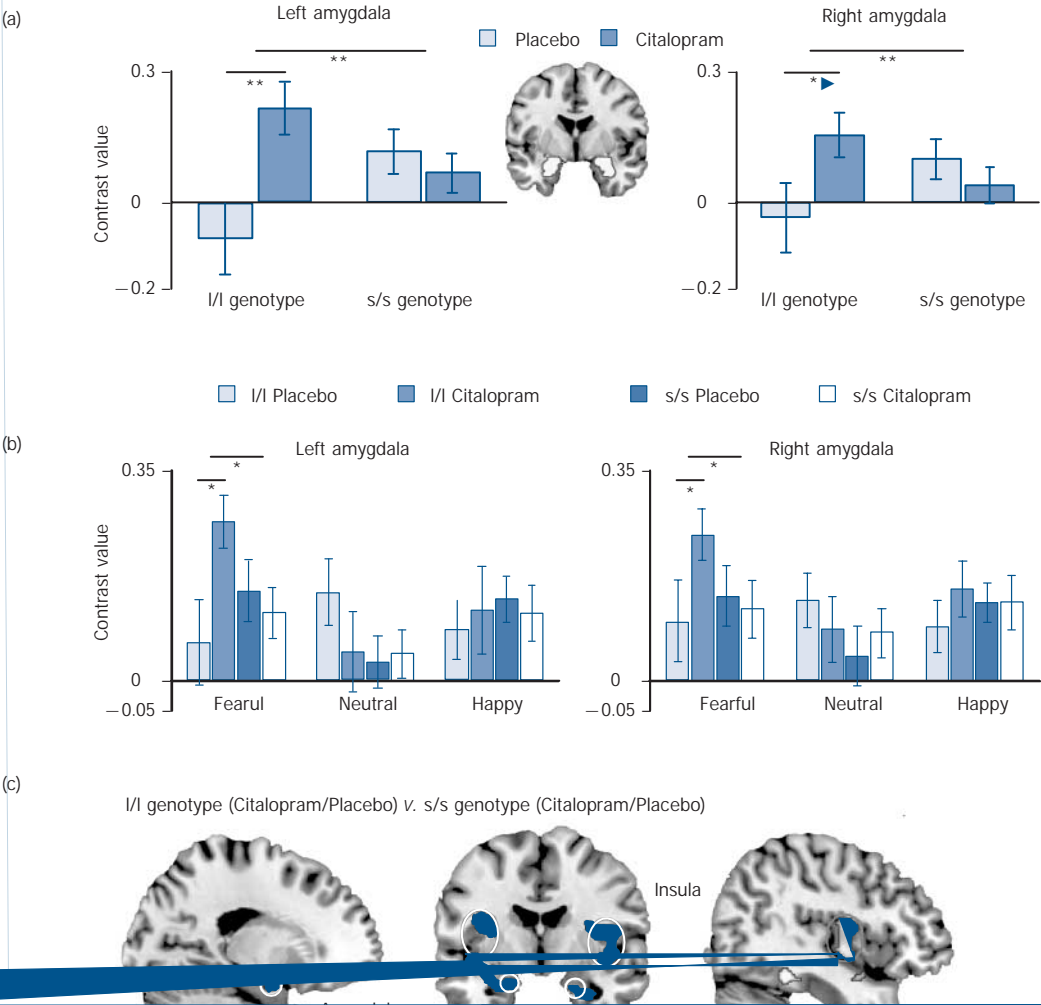
### Behavioural results

Response accuracy was high in the repetition-detection tasks during scanning (mean accuracy > 95%). We subjected response accuracy and reaction times to 2 (emotion: fearful v. neutral facial expressions, or happy v. neutral facial expressions) × 2 (treatment: citalopram v. placebo) × 2 (genotype: s/s v. l/l) ANOVAs, but did not show any significant effect ( $P > 0.05$ ).

We subjected self-reported mood changes from pre- to post-scan to a 2 (treatment: citalopram v. placebo) × 2 (genotype: s/s v. l/l) ANOVA. This did not show any significant effect ( $F < 1$ , Table DS1), suggesting that citalopram treatment did not have an effect on the participants' mood. Harm avoidance scores did not differ between s/s and l/l homozygotes (18.2 v. 16.0,  $t(44) = 1.07$ ,  $P = 0.291$ ). Participants rated fearful faces as less fearful after citalopram than placebo administration ( $F(1,43) = 5.44$ ,  $P = 0.024$ ), but this effect did not differ significantly between s/s and l/l homozygotes ( $F(1,43) = 2.44$ ,  $P = 0.126$ , Fig. DS1). Relative to l/l homozygotes, s/s homozygotes reported greater emotional intensity of happy facial expressions ( $F(1,43) = 7.30$ ,  $P = 0.010$ ), but neither the main effect of treatment nor its interaction with genotype was significant ( $P > 0.35$ ).

### Functional magnetic resonance imaging

Region of interest analyses of amygdala response to fearful v. neutral facial expressions in the placebo session revealed significantly stronger left amygdala response in s/s than l/l



–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.

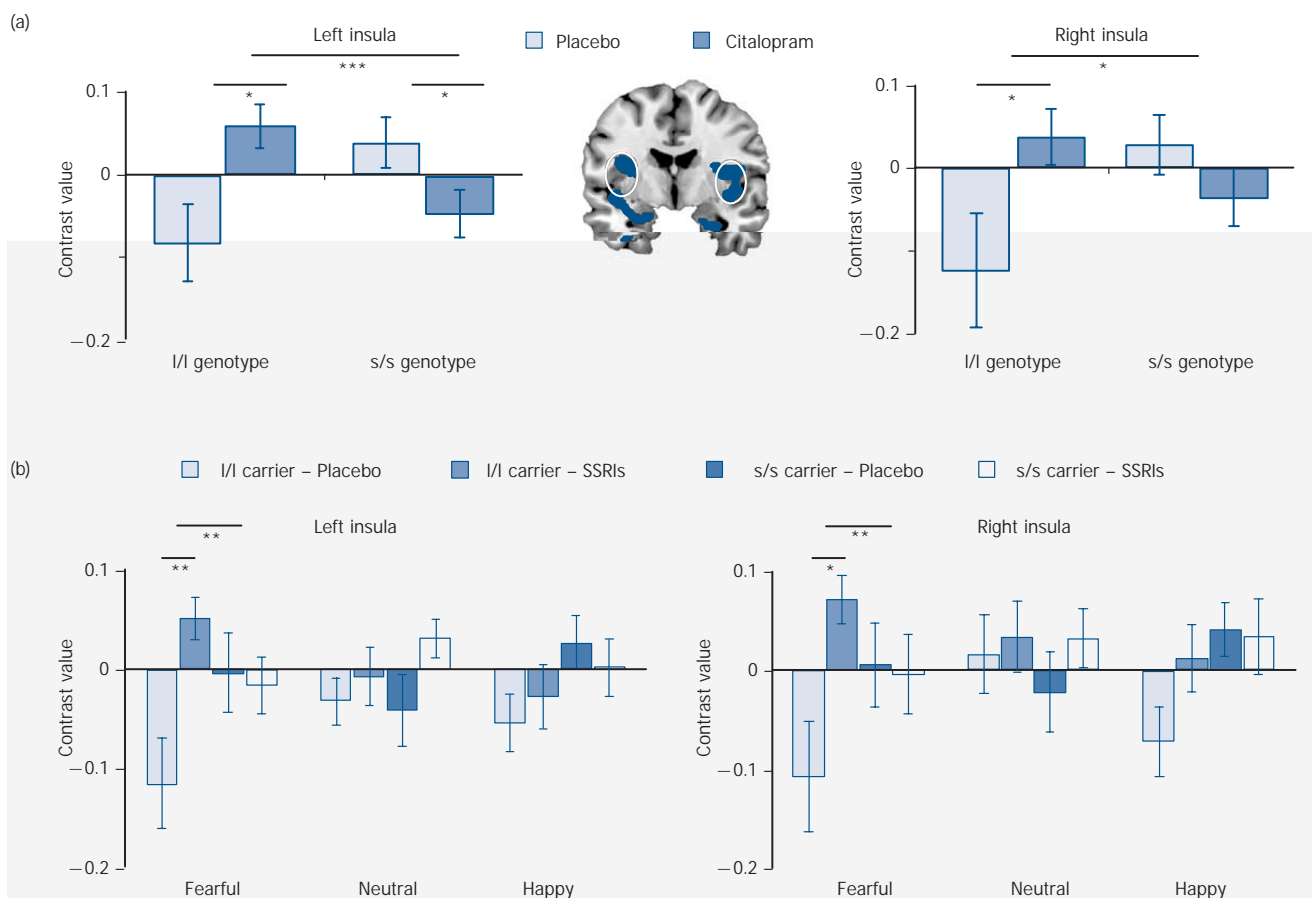
## Discussion

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.<sup>4,5</sup> The post-scan rating scores suggested decreased emotion-intensity rating of fearful facial expressions after citalopram *v.* placebo treatment. However, this effect was the same in the *s/s* and *l/l* genotypes. Similarly, 7 days of SSRI treatment decreased amygdala response to fearful facial expressions but failed to induce significant changes in clinical depression ratings.<sup>38</sup> Thus amygdala response may be more sensitive to how 5-HTTLPR modulates the acute administration of citalopram and thus provides a neurobiological index of genetic influences on the effect of SSRIs.

The 5-HTTLPR also modulated the acute effects of citalopram on insula response to fearful facial expressions. The insula plays a key role in how emotions are processed, such as detection of emotional salience<sup>39</sup> and anticipation of emotional stimuli.<sup>40</sup> Chronic SSRI treatment attenuates insula activation during perception of emotional facial expressions<sup>41</sup> and during anticipation of emotional stimuli<sup>42</sup> in healthy volunteers. The acute administration of an SSRI, however, increased insula response.<sup>13</sup> Our findings suggest that 5-HTT plays a pivotal role in producing the differential insula response in the *s/s* and *l/l*



**Fig. 3** Contrast values for insula response to fearful, neutral, and happy facial expressions. (a) Contrast values for Left and Right insula by genotype (*l/l* and *s/s*) for Placebo and Citalopram. (b) Contrast values for Left and Right insula by genotype (*l/l* and *s/s*) for Placebo and SSRI (Citalopram) across Fearful, Neutral, and Happy facial expressions (\* $P<0.05$ , \*\* $P<0.01$ , \*\*\* $P<0.001$ ). SSRI: selective serotonin reuptake inhibitor.



genotypes. Taken together, our results suggest that the 5-HTTLPR genotype may influence the effect of citalopram on neural response to negative emotions in different nodes (e.g. amygdala and insula) of the emotional neural network in a similar vein.

## Implications

Our pharmacogenetic and neuroimaging findings have important implications. First, whereas amygdala response is modulated by the intensity of both fearful and happy facial expressions,<sup>43</sup> the acute administration of an antidepressant in healthy volunteers did not show convergent response to positive emotions.<sup>20</sup> Some studies have reported that the acute administration of an SSRI facilitates recognition of happy facial expressions and increased amygdala response to happy facial expressions.<sup>10,18</sup> Other studies have failed to show significant SSRI effects on neural or behavioural responses to happy facial expressions.<sup>9,15,16,19</sup> Similarly, the acute administration of citalopram did not change subjective feelings or amygdala response related to happy facial expressions in both genotypes in the current study. Thus, 5-HTT may play a less important role in affective and neural responses to positive (relative to negative) emotion. Anhedonia (i.e. the inability to obtain pleasure from natural rewards and decreased interest in most activities) and negative emotional bias are two core features of depression. Depressed patients tend to interpret happy facial expressions as neutral, fail to experience pleasure from activities they previously experienced as rewarding and lack reward-motivated behaviours. By contrast, they pay more attention to negative emotions, remember negative affective materials better and are more likely to classify ambiguous/neutral facial expressions as negative.<sup>20</sup> Thus our findings suggest that citalopram may have distinct therapeutic implications for the treatment of different symptoms in depressed patients. Alternatively, the lack of 5-HTTLPR modulation of the acute effects of an SSRI on amygdala response to happy facial expressions may be due to the absence of amygdala activation to happy facial expressions in our experiment. This should be clarified in future research.

Second, the early changes in emotional processing after a single SSRI dose contribute to later mood improvements.<sup>3–5</sup> Thus, understanding the neural mechanisms underlying the acute effects of SSRIs has important implications for long-term treatment. Our findings of distinct acute effects of an SSRI on emotion-related neural activity in s/s and l/l homozygotes suggest that one's genetic structure should be considered when treating mood disorders with SSRIs. However, it remains unknown whether and how 5-HTTLPR modulates the chronic SSRI effects that lead to decreased response to negative emotions in both healthy controls and depressed patients.<sup>20</sup> Pharmacogenetic studies of antidepressant response reported better responses of the 'l' variant (compared with the 's' variant) of 5-HTTLPR to SSRIs in mood disorder patients.<sup>25,44,45</sup> Our fMRI results of differential acute effects of citalopram on amygdala and insula response in l/l and s/s homozygotes are consistent with the distinct SSRI effects on clinical assessment of improvement in patients with major depression.<sup>24</sup> These results together suggest more pronounced SSRI effects in l/l than in s/s homozygotes and are consistent with the findings of increased 5-HTT expression<sup>26</sup> and increased 5-HT neurotransmission after acute blockade of 5-HT reuptake<sup>27</sup> in l/l homozygotes than 's' carriers. Future research on genetic differences in chronic SSRI treatment may open an avenue for prescribing personalised antidepressants.

Third, our finding that citalopram increased amygdala response to fearful facial expressions in l/l homozygotes suggests a more anxiogenic action of acute SSRI treatment in this group.

This seems counterintuitive given that mood disorder patients with the 'l' variant (compared with the 's' variant) of 5-HTTLPR showed a better SSRI response.<sup>25,44,45</sup> However, opposite early effects of SSRIs in depression have been reported in clinical treatment. The acute administration of SSRIs may increase anxiety in some mood disorder patients.<sup>46</sup> Our findings thus provide a potential neurogenetic explanation for the opposite early effect of SSRIs in clinical trials. Future research should address whether and how early SSRI-induced changes in emotional processes can predict long-term treatment efficacy and whether one's genetic structure modulates the early and chronic effects of SSRIs in a similar way. Future research should also address whether such increased amygdala response to fearful facial expressions is dose-dependent; i.e. whether a lower or higher dose of citalopram could modulate this effect.

Finally, although the 's' allele frequency is different between Asian and White populations,<sup>47</sup> to date, we know little about whether the 's' allele frequency in a population is associated with a specific pattern of 5-HTTLPR modulation of brain activity. Previous research showed an association between the 's' allele and hyperactivity in the amygdala mainly in White populations.<sup>36,37,48</sup> Our study involving Chinese healthy volunteers in the placebo group also showed stronger amygdala response to fearful (v. neutral) facial expressions in the s/s than l/l genotype group. This is similar to the observation of 5-HTTLPR effects on amygdala response in White populations.<sup>36,37,48</sup> In addition, we found that l/l compared to s/s homozygotes tended to show greater amygdala response in the contrast of neutral facial expressions v. fixation in the placebo condition, replicating the previous findings in White populations.<sup>35</sup> These results suggest similar 5-HTTLPR effects on amygdala activity regardless of the difference in the 's' allele frequency in populations. Pharmacogenetic studies have reported inconsistent 5-HTTLPR effects on antidepressant drug response in White and Asian groups experiencing major depression.<sup>45</sup> However, the improved response to SSRIs in the 'l' variant of 5-HTTLPR seemed to be independent of ethnic differences,<sup>25</sup> which may be confirmed by future research.

## Limitations

A potential limitation of the present study was the sample size. To examine the power of our sample size, we calculated the effect size and conducted a power analysis. These analyses suggested that our study yielded a large effect size and appropriate sample size (see online supplementary material for details). We also reviewed published studies that examined 5-HTTLPR genotype differences on brain activity and studies that examined antidepressant effects on emotional neural responses. According to a recent meta-analysis, 26 fMRI studies examined 5-HTTLPR genotype differences in emotional reactivity.<sup>48</sup> The mean sample size of these 26 studies was 38. Mode of sample size was 28. Our recent meta-analysis summarised antidepressant effects on emotional responses.<sup>20</sup> Twenty-one fMRI studies used between-subjects treatment (the same design as the current study) to examine antidepressant effects on brain responses to emotions in healthy participants. The average sample size of these 21 studies was 15. Considering the effect size of the current work and comparing the sample size of published studies, the sample size of our study allowed us to reach a conclusion (albeit with caution) on 5-HTTLPR genotype differences in SSRI effects on emotional neural activity.

Another possible limitation was that only men were recruited for the current study. This did not allow us to test whether 5-HTTLPR modulates the SSRI effect on amygdala responses in men and women in a similar fashion. Previous research has revealed similar 5-HTTLPR effects on the reactivity of the



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

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