5-HTTLPR Polymorphism Modulates Neural Mechanisms of Negative Self-Reflection

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Cognitive distortion in depression is characterized by enhanced negative thoughts about both environment and oneself. Carriers of a risk allele for depression, that is, the short (s) allele of the serotonin transporter promoter polymorphism (5-HTTLPR), exhibit amygdala hyperresponsiveness to negative environmental stimuli relative to homozygous long variant (l/l). However, the neural correlates of negative self-schema in s allele carriers remain unknown. Using functional MRI, we scanned individuals with s/s or l/l genotype of the 5-HTTLPR during reflection on their own personality traits or a friend's personality traits. We found that relative to l/l carriers, s/s carriers showed stronger distressed feelings and greater activity in the dorsal anterior cingulate (dACC)/dorsal medial prefrontal cortex (dmPFC) and the right anterior insula (AI) during negative self-reflection. The 5-HTTLPR effect on the distressed feelings was mediated by the AI/inferior frontal (IF) activity during negative self-reflection. The dACC/dmPFC activity explained 20% of the variation in harm-avoidance tendency in s/s but not l/l carriers. The genotype effects on distress and brain activity were not observed during reflection on a friend's negative traits. Our findings reveal that 5-HTTLPR polymorphism modulates distressed feelings and brain activities associated with negative self-schema and suggest a potential neurogenetic susceptibility mechanism for depression.

Keywords: 5-HTTLPR, anterior cingulate, anterior insula, FMRI, negative self-schema

Introduction

A negative information-processing style plays a key role in the etiology of depression. Early psychodynamic accounts of depression noticed the association between depression and self-blame (Freud 1957). Later cognitive models of depression suggested a triad of negative views about oneself, environment, and future in depression (Beck 1976; Beck et al. 1979). These distorted negative schemas develop in early childhood and make individuals susceptible to depression (Beck 1976; Garber and Kaminski 2000).

Neuroimaging studies have suggested amygdala hyperactivity as a neural substrate of negativity bias toward environmental stimuli in depression (Sheline et al. 2001; Siegle et al. 2002, 2007; Abler et al. 2007; Dannlowski et al. 2007). Moreover, carriers of the short (s) allele of the serotonin transporter promoter polymorphism (5-HTTLPR), which has been recognized as a risk allele for depression (Bellivier et al. 1998; Lotrich and Pollock 2004; Lasky-Su et al. 2005; Uher and McGuffin 2008), exhibited stronger amygdala activity to negative environmental stimuli relative to homozygous long variant (l/l) (Hariri et al. 2002; Canli et al. 2005; Heinz et al. 2005). Together with an association between stressful life events and risk for depression in s allele carriers (Caspi et al. 2003; Taylor et al. 2006), the genetic neuroimaging findings suggest that enhanced amygdala activity to negative environmental stimuli in s allele carriers compared with l/l genotype individuals may serve as a genetic susceptibility mechanism for depression.

However, the neurogenetic mechanism of negative self-schema associated with depression remains unclear. Behavioral studies indicate that negative self-evaluation is associated

synaptic cleft (Canli and Lesch 2007). Given that s carriers are vulnerable to depression and depressed individuals are characterized by negative self-schema, we hypothesize that relative to the l/l variant, s allele carriers are more sensitive to negative thoughts about the self. Specifically, we predicted that individuals homozygous for the s allele (s/s genotype group) compared with l/l genotype individuals would show stronger activation during self-reflection on negative personality traits in brain regions such as the dmPFC/dACC and insula that are engaged in negative self-reflection in healthy subjects (Moran et al. 2006; Longe et al. 2010) and are sensitive to SSRI administration during self-reflection (Matthews et al. 2010; Di Simplicio et al. 2012).

We used functional MRI to test our hypotheses. Experiment 1 scanned s/s and l/l genotype groups while they rated self-relevance of positive and negative personality traits. Participants were also asked to complete the harm-avoidance (HA) subscale from the Tridimensional Personality Questionnaire (Cloninger et al. 1993). HA indicates a heritable tendency to respond intensely to signals of aversive stimuli (Cloninger 1987) and relates to serotonergic activity (Cloninger 1987; Hansenne et al. 1997). Moreover, the HA score is positively correlated with depression (Brown et al. 1992; Richter et al. 2000; Farmer et al. 2003; Abrams et al. 2004; Smith et al. 2005) and the genetic vulnerability to depression (Farmer et al. 2003; Pezawas et al. 2005). If negative self-schema is associated with the risk for depression, the neural activity underlying negative self-reflection may predict HA scores, especially in s/s genotype participants who may exhibit stronger neural activation during negative self-reflection. To further test whether the 5-HTTLPR effect on the neural activity linked to negative self-schema is specific to self-reflection, Experiment 2 scanned independent s/s and l/l genotype groups during refl

Imaging Parameters

Functional brain images were acquired using 3.0-Tesla Siemens Trio at the Beijing MRI Center for Brain Research. Blood oxygen-level–dependent (BOLD) gradient echo planar images were obtained 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 participants performed trait judgments. A high-resolution T_1-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°) was subsequently acquired.

Imaging Data Analysis

The functional image data were analyzed using the general linear model for event-related designs in the statistical parametric mapping (SPM) software (the Wellcome Trust Centre for Neuroimaging, London, UK). The functional images were corrected for differences in acquisition time between slices for each whole-brain volume and realigned within and across runs to correct for head movement. Six movement parameters (translation: *x*, *y*, *z* and rotation: pitch, roll, yaw) were included in the statistical model. The anatomical image was coregistered with the mean realigned image and then normalized to the standard T1 Montreal Neurological Institute (MNI) template. The normalizing parameters were applied to the functional images, which were resampled to 2 mm of isotropic voxel size and spatially smoothed using an isotropic Gaussian kernel of 8-mm full-width half-maximum.

Trials during self-reflection were sorted into 4 conditions based on the valence of each trait adjective and participants' responses regarding self-relevance. Similar to Moran et al. (2006) the positive and negative traits were subdivided into low (rated with 1 or 2) and high in self-relevance (rated with 3 or 4) categories. Functional image data were analyzed using a voxelwised 2 (self-relevance: high vs. low) × 2 (trait valence: positive vs. negative traits) ANOVA on the neural activity related to self-reflection. Events were modeled using a canonical hemodynamic response function and its time derivatives. Since participants showed the traditional bias of classifying positive traits high in self-relevance and negative traits low in self-relevance, the number of trials differed among the 4 conditions. Thus, for each participant, we chose the same number of trials (randomly selected) of each condition for data analysis based on the minimal number of trials across the 4 conditions. The mean numbers of trials per condition used for fMRI data analysis was 22 and did not differ between s/s and l/l genotype groups. Random-effect analyses at the second group level were conducted based on statistical parameter maps from each participant to allow population inference.

The contrast of $\text{Negative}_{(\text{high}-\text{low self-relevance})}$ minus $\text{Positive}_{(\text{high}-\text{low self-relevance})}$ identified brain activity related to negative self-reflection that was independent of influences of perceptual/semantic processing and motor responses. Two-sample *t*-test was then conducted to examine the genotype differences in neural activity at the whole-brain level. The HA scores were considered as a covariate in the 2-sample *t*-test. Similar analysis was conducted for Experiment 2 except that personality trait judgments were performed on a friend. Significant activations in the whole-brain analysis were identified using a threshold of $P < 0.05$ (false discovery rate (FDR) corrected for multiple comparisons).

Correlation and Mediation Analyses

Because the whole-brain analysis revealed significant dACC/dmPFC and bilateral anterior insular (AI)/IF activations during self-reflection on negative personality traits across all participants, we defined regions of interest (ROIs) in the dACC/dmPFC and bilateral AI/IF clusters at the threshold of $P < 0.05$ (FDR corrected for multiple comparisons) to further assess the association between subjective distress and the activities in these brain regions. The parameter estimates of signal intensity were calculated from each ROI using MarsBaR 0.38 (http://marsbar.sourceforge.net) and subjected to correlation analysis of distressed feelings and HA scores.

Because we observed significant 5-HTTLPR genotype effect on negative self-reflection-induced distressed feelings and the distressed feelings were associated with AI/IF activity during negative self-reflection, we further conducted a mediation analysis to examine whether AI/IF activity underlying negative self-reflection mediated the 5-HTTLPR genotype effect on distressed feelings. We chose a classic approach to establish mediation (Judd and Kenny 1981; Baron and Kenny 1986). Three different regression models were constructed, as shown below:

$$Y = \beta_{11}\, x + \beta_{10} \quad (1)$$

$$\text{Mediator} = \beta_{21} x + \beta_{20} \quad (2)$$

$$Y = \beta_{31} x + \beta_{32}\, \text{Mediator} + \beta_{30} \quad (3)$$

Four conditions for establishing mediation are 1) in Equation (1), the independent variable (genotype group) must predict the dependent variable (subjective distress induced negative self-reflection), β_{11} is significant; 2) in Equation (2), the independent variable (genotype group) must predict the mediator (AI/IF activity during negative self-reflection), β_{21} is significant; 3) in Equation (3), when regressing the dependent variable (subjective distress) onto the mediator (AI/IF activity) and the independent variable (genotype group), the mediator must predict the dependent variable (subjective distress), β_{32} is significant; and 4) in Equation (3), the effects of the independent variable (genotype group) on the dependent variable (subjective distress) must be reduced or even eliminated, $\beta_{31} < \beta_{11}$ (in absolute value, partial mediation) or β_{31} is insignificant (full mediation). The Sobel test (Sobel 1982) was conducted to further confirm the significance of the mediator.

Results

Experiment 1

A 2 (Referent: self vs. friend) × 2 (Genotype: s/s vs. l/l) repeated measures analysis of variance (ANOVA) of subjective distress showed that reflection on one's own negative traits induced greater distress compared with thinking about a friend's negative traits ($F_{1,58} = 164.6$, $P < 0.001$), and this effect was significantly stronger in s/s than l/l genotype group ($F_{1,58} = 9.2$, $P = 0.004$, Fig. 1*a*). Relative to l/l carriers, s/s carriers felt more distressed when thinking about negative traits of themselves ($F_{1,58} = 4.4$, $P = 0.041$) but not of their friends ($F < 1$). The 2 (Valence: positive vs. negative) × 2 (Self-relevance: high vs. low) × 2 (Genotype: s/s vs. l/l) ANOVAs of response ratio and reaction times (RTs) showed that participants judged more positive traits as high in self-relevance and more negative traits as low in self-relevance ($F_{1,58} = 133.8$, $P < 0.001$). Participants took longer to acknowledge negative and deny positive traits than to admit positive and deny negative traits ($F_{1,58} = 11.0$, $P = 0.002$). However, the patterns of response ratio and RTs did not differ significantly between s/s and l/l genotype groups (*P*s > 0.05, Supplementary Fig. 1).

fMRI data analysis first calculated the contrast of $\text{Negative}_{(\text{high}-\text{low self-relevance})}$ minus $\text{Positive}_{(\text{high}-\text{low self-relevance})}$ across all participants to identify the neural substrates involved in negative self-reflection. This revealed significant activations in the bilateral AI/IF (left: −33/21/−6; −45/21/27; right: 48/27/−6, 42/24/3) and in the midline cortical structure including the dACC, dmPFC, and SMA (−3/21/54, −3/33/42) (Supplementary Fig. 2). More importantly, a whole-brain 2-sample *t*-test confirmed that, relative to l/l carriers, s/s genotype participants showed greater activity in the dACC/dmPFC and right AI during negative self-reflection (Fig. 1*b–d*). Separate analyses showed that negative self-reflection significantly activated the bilateral AI/IF and a cluster of the mPFC (Supplementary Fig. 3 and Supplementary Table 1) in the s/s genotype group. The cluster of the mPFC area included dACC

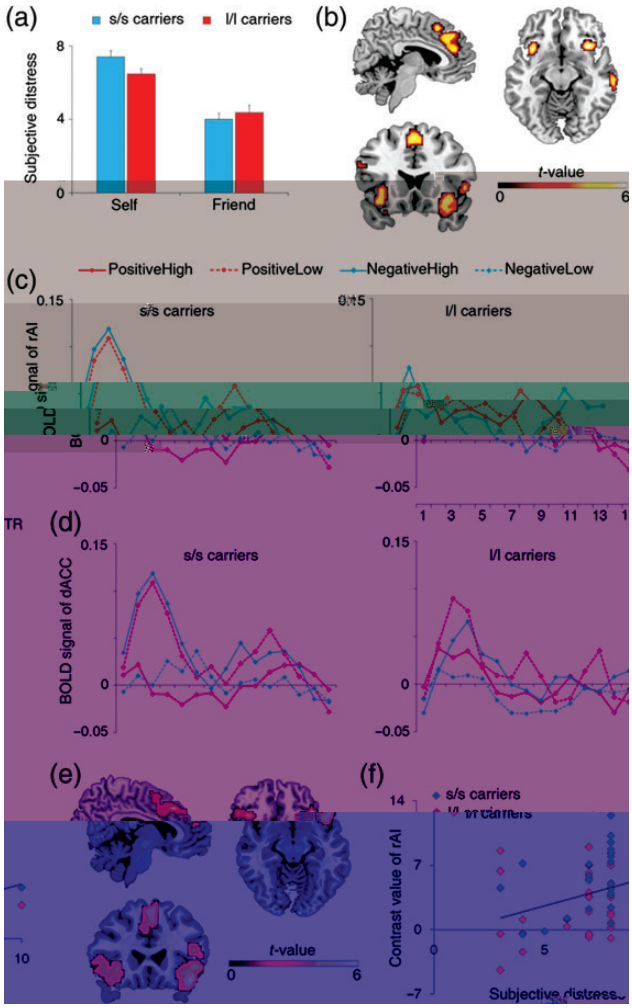

Figure 1. Behavioral and whole-brain fMRI results in Experiment 1. (*a*) Participants rated distressed feelings induced by thinking about weakness of oneself and a friend (0 = do not feel distressed at all, 10 = feel extremely distressed). The s/s genotype individuals ($n = 30$) reported greater distress associated with reflection on one's own negative traits compared with the l/l genotype individuals ($n = 30$). However, thinking about a friend's weakness did not induce differential distress in the 2 genotype groups. (*b*) The whole-brain 2-sample analysis revealed genotype differences in the neural activity involved in negative self-reflection. Relative to l/l carriers, s/s genotype individuals showed stronger activations in the dACC (MNI coordinates: 0/42/39, $k = 267$, $T = 5.03$) and the right AI (33/21/−12, $k = 103$, $T = 5.57$) in the contrast of $\text{Negative}_{(\text{high}-\text{low self-relevance})}$ minus $\text{Positive}_{(\text{high}-\text{low self-relevance})}$. (*c*)/(*d*) BOLD signals in the right AI and dACC showed larger amplitude to both negative trait adjectives judged high versus low in self-relevance and positive trait adjectives judged low versus high in self-relevance. (*e*) The conjunction analysis of the contrasts of $\text{Negative}_{(\text{high}-\text{low self-relevance})}$ and $\text{Positive}_{(\text{low}-\text{high self-relevance})}$ showed significant activations in the dACC (4/28/32; 3/42/39; $k = 389$, $T = 7.26$) and bilateral AI (left: −45/24/−15; −36/26/−12; $k = 268$, $T = 6.27$; right: 36/27/−15; 33/24/−6; $k = 149$, $T = 4.37$) in s/s genotype group. (*f*) The right AI/IF activity defined in the contrast of $\text{Negative}_{(\text{high}-\text{low self-relevance})}$ minus $\text{Positive}_{(\text{high}-\text{low self-relevance})}$ was positively correlated with self-reported distress related to reflection on one's own negative traits across all participants.

(6/30/26), SMA (3/18/57), and dmPFC (6/30/39; 0/36/42), and the AI/IF cluster included the bilateral IF (left: −45/21/30; right: 42/18/30) and bilateral AI (left: −33/21/−3; −36/15/−12; right: 33/21/−12; 42/21/−15). However, l/l genotype group did not show any significant activation during negative self-reflection.

To examine whether judging negative traits as high in self-relevance and judging positive traits as low in self-relevance similarly activated the dACC/dmPFC and the AI/IF in the s/s genotype group, we calculated the contrasts of $\text{Negative}_{(\text{high}-\text{low self-relevance})}$ and $\text{Positive}_{(\text{low}-\text{high self-relevance})}$, respectively. Both contrasts revealed significant activations in the dACC/dmPFC and AI/IF clusters in s/s genotype group ($\text{Negative}_{(\text{high}-\text{low self-relevance})}$: dACC/dmPFC (6/30/36; 0/42/39), left AI (−30/21/−18; −33/21/−6), left IF (−54/21/30; −45/18/39); right AI (42/27/−15; 33/24/−12); $\text{Positive}_{(\text{low}-\text{high self-relevance})}$: dACC/dmPFC (6/27/39; 0/36/42; 0/24/54), left AI/IF (−45/18/27; −36/21/3; −42/18/−15), right AI/IF (36/21/3; 48/18/−9, 42/12/36), Supplementary Fig. 4). A conjunction analysis of the 2 contrasts further confirmed that among s/s genotype participants, there were common dACC/dmPFC and bilateral AI/IF activations when judging negative traits as highly self-relevant and when judging positive traits as low in self-relevance (Fig. 1*e*). Direct comparison of these 2 contrasts did not show any significant difference, suggesting comparable dACC/dmPFC and AI/IF activity linked to the acknowledgement of one's possession of negative traits and one's lack of positive traits. Similar conjunction analysis did not show any significant activation in l/l genotype group.

We next examined the relationship between subjective ratings and brain activity during negative self-reflection. A linear regression analysis showed a positive correlation between AI/IF activity and self-reported distress across all participants (right: $\beta = 0.422$, $P = 0.001$, Fig. 1*f*; left: $\beta = 0.333$, $P = 0.009$). Individuals who felt more distressed when thinking about their negative traits activated the bilateral AI/IF more strongly during negative self-reflection. Separate regression analyses were also conducted for s/s and l/l genotype groups. We found that the relationship between AI/IF activity and self-reported distress was significant in the s/s genotype group (right: $\beta = 0.384$, $P = 0.036$, left: $\beta = 0.399$, $P = 0.029$) but not in the l/l genotype group (right: $\beta = 0.312$, $P = 0.093$, left: $\beta = 0.152$, $P = 0.423$).

We then conducted mediation analysis to test whether the AI/IF activity underlying negative self-reflection mediated the 5-HTTLPR genotype effect on distressed feelings. As expected, the 5-HTTLPR genotype was a significant predictor of AI/IF activity (right: $\beta = 0.536$, $P < 0.001$, left: $\beta = 0.357$, $P = 0.005$), as well as a significant predictor of subjective distress ($\beta = 0.265$, $P = 0.041$). Importantly, the inclusion of AI/IF activity into the regression model predicting subjective distress from the 5-HTTLPR genotype resulted in absence of a significant genotype effect (right AI/IF: $\beta = 0.055$, $P = 0.699$, left AI/IF: $\beta = 0.168$, $P = 0.209$, see Table 2 for statistic details). A Sobel test (Sobel 1982) further confirmed the significance of the mediation effect (right AI/IF: $z = 1.977$, $P = 0.048$, left AI/IF: $z = 2.856$, $P = 0.004$), thus showing that the AI/IF activity fully mediated the influence of 5-HTTLPR on subjective distress induced by negative self-reflection.

Finally, we examined whether neural responses to negative self-reflection may predict individuals' general harm-avoidance tendency. We found that dACC/dmPFC activity was significantly positively correlated with the HA scores in the s/s genotype group ($r = 0.461$; $r^2 = 0.213$, $P = 0.010$), suggesting that the dACC/dmPFC activity explained 21.3% of the variation of harm-avoidance tendency in s/s genotype participants. However, the dACC/dmPFC activity was not associated with the HA scores in the l/l genotype group ($\beta = 0.127$; $r^2 = 0.016$, $P = 0.502$). This suggested that s variant of the 5-HTTLPR may predispose individuals with stronger neural responses to negative self-reflection to higher risk for depression.

Table 2
Results of the mediation analysis to test AI/IF activity as a mediator of 5-HTTLPR genotype and subjective distress during negative self-reflection

Variable	B	SEB	β	R^2
Left AI/IF activity as a mediator of 5-HTTLPR genotype and subjective distress				
Regression Model 1				
Independent: Genotype (dummy code)	0.933	0.445	0.265*	0.070
Dependent: Subjective distress				
Regression Model 2				
Independent: Genotype (dummy code)	2.353	0.808	0.357**	
Independent: Genotype (dummy code)	05903	0.643	01608	

Experiment 2

Participants judged more positive traits as high in friend-relevance and more negative traits as low in friend-relevance ($F_{1,\ 38} = 30.646$, $P < 0.001$). A similar analysis on response speed did not show any significant effect (*P*s > 0.2). Response ratio and RTs did not significantly differ between s/s and l/l genotype groups (*F*s < 1, Supplementary Fig. 5).

fMRI data analysis focused on a 2-sample *t*-test of the contrast of Negative$_{(\text{high} - \text{low friend-relevance})}$ minus Positive$_{(\text{high} - \text{low friend-relevance})}$, which, however, did not show any differential neural activity between s/s and l/l genotype groups (see Fig. 2). Analyses were also conducted for s/s and l/l genotype groups, respectively, but failed to show any significant brain activation. Thus, the genotype difference in dACC/dmPFC and AI/IF activity during negative self-reflection observed in Experiment 1 cannot be generalized to negative reflection on personality traits of another individual. (To test whether the absence of dACC/dmPFC and AI/IF activations in Experiment 2 was due to a smaller sample size compared with that in Experiment 1, we randomly selected 20 participants from s/s and l/l genotype groups in Experiment 1 and conducted similar analyses. This again showed significantly greater dACC/dmPFC and AI/IF activations linked to negative self-reflection in s/s than in l/l genotype participants. Thus, the absence of dACC and AI/IF activation in Experiment 2 cannot be explained by the sample size of s/s and l/l genotype groups used in data analysis.)

Discussion

Our findings demonstrate a novel effect of 5-HTTLPR on distressed feelings and neural activities in responses to negative self-reflection of personality traits. Across all participants, we found that negative self-reflection significantly activated the bilateral AI/IF and the dACC/dmPFC and that self-reported distress induced by negative self-reflection was associated with the AI/IF activity. Most importantly, we found that, compared with l/l variant of 5-HTTLPR, s/s genotype individuals reported greater distress and showed stronger activity in the dACC/dmPFC and right AI during negative self-reflection. Moreover, the 5-HTTLPR genotype effect on the subjective distress was fully mediated by AI/IF activity during negative self-reflection. While previous research documented a negative view of the self in depression (Beck 1976; Brown et al. 1986; Bifulco et al. 1998; Northoff 2007) and high risk for depression in the short 5-HTTLPR variant (Bellivier et al. 1998; Lotrich and Pollock 2004; Lasky-Su et al. 2005; Uher and McGuffin 2008), onc findings uncovered a neurobiological mechanism of negative self-schema in individuals who carry the risk allele for depression.

Education, gender, and age were matched between the s/s and l/l genotype groups to control for possible influences of these factors on the neural activity underlying negative self-reflection. Similar patterns of behavioral performance in the scanner in the 2 groups ruled out task difficulty or response bias as explanations for onc findings. The result that the s/s and l/l variants did not differ in arousal ratings or in neural responses to arousal induced by negative traits (see Supplementary Results and Supplementary Fig. 6 for detailed results of neural activity related to arousal) confirmed that the 5-HTTLPR effects would not arise from differential encoding of arousal ratings between the s/s and l/l genotype groups. In addition, the stronger dACC/dmPFC and right AI activity to negative self-reflection in the s/s than l/l variants could not be explained by harm-avoidance tendency, because HA scores did not differ between the 2 genotype groups. The differential activations between the 2 genotype groups were found even after considering HA scores as covariates in the whole-brain analysis. Furthermore, the 5-HTTLPR allele-dependent effect on dACC/dmPFC and right AI responsiveness did not reflect a nonspecific tendency of overactivation in neural responses in s/s genotype participants because the 2 genotype groups did not differ in neural responses to negative thoughts about a friend in a similar trait judgment task.

Interestingly, although the 2 genotype groups did not differ significantly in the HA measure, they showed different patterns of the association between the HA scores and the neural activity involved in negative self-reflection. Specifically, the dACC/dmPFC activity in response to negative self-reflection predicted the harm-avoidance scores in s/s but not l/l genotype individuals. Similarly, a previous study found that the HA scores predicted the cingulate-amygdala functional coupling in s/s but not in l/l carriers while the HA scores did not differ between the 2 genotype groups (Pezawas et al. 2005). These findings suggest that the 5-HTTLPR mainly modulates the association between brain activity and self-report harm-avoidance tendency. The harm-avoidance tendency reflects a temperament related to the risk for depression (Brown et al. 1992; Richter et al. 2000; Farmer et al. 2003; Abrams et al. 2004; Smith et al. 2005). Thus, it may be speculated that the online neural activity engaged in negative self-reflection may contribute to the development of anxiety trait and affect the risk for depression in the s/s variant of 5-HTTLPR. In contrast, negative self-reflection may not constitute a direct factor to affect the risk for depression in l/l genotype individuals. These should be clarified in future research.

Neuroimaging studies in healthy subjects have demonstrated recruitment of the dorsal/ventral mPFC, dACC, and

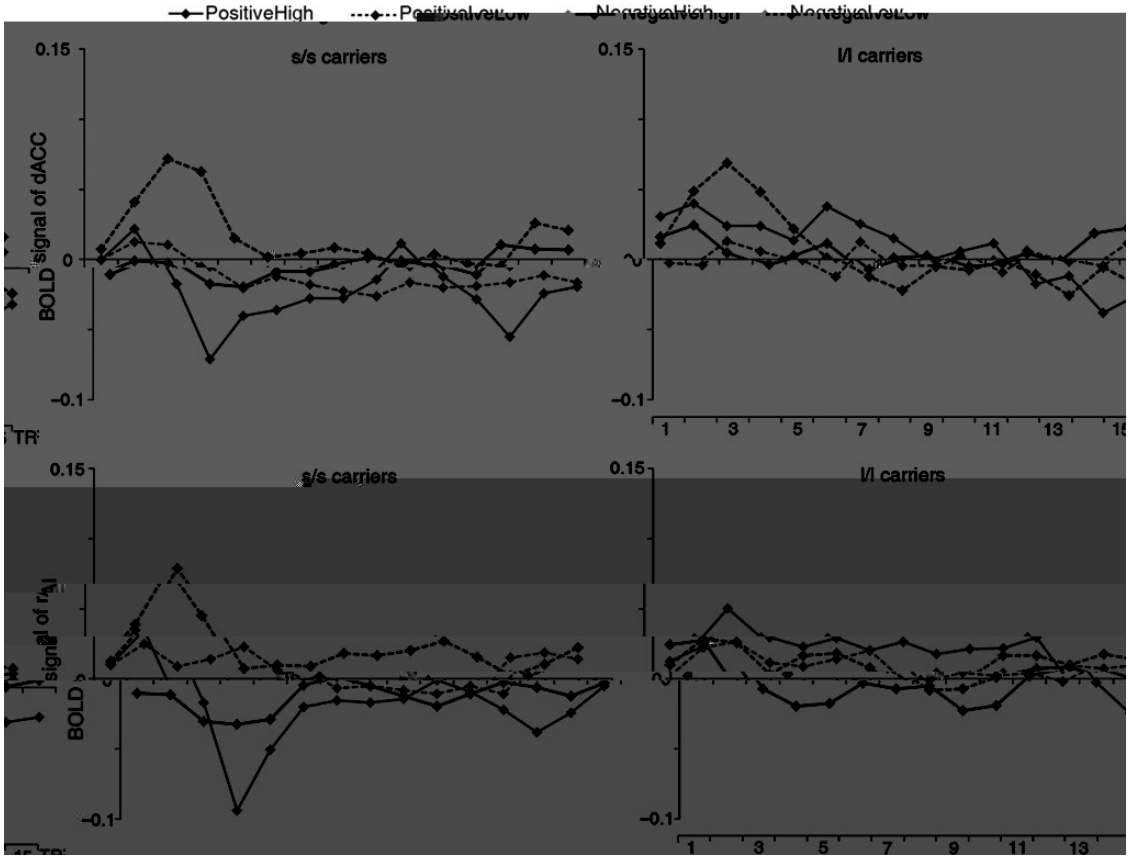

Figure 2. Time courses of BOLD signals in the dACC and Right AI during reflection on negative traits of a friend in Experiment 2. As the whole-brain analyses in Experiment 2 did not show any significant activation, the dACC and AI were defined in the activated brain regions observed in Experiment 1.

precuneus during self-referential processing (Northoff et al. 2006; Schmitz and Johnson 2007), and the mPFC is hypothesized to encode stimulus self-relevance (Kelley et al. 2002; Macrae et al. 2004; Han and Northoff 2009; Ma and Han 2011). Depressed patients showed increased activations in the mPFC and ACC during self-referential processing of negative personality traits (Lemogne et al. 2009; Yoshimura et al. 2010), suggesting enhanced self-focus on and increased self-relevance encoding of the negative stimuli (Northoff 2007; Wagner et al. in press). The increased dmPFC/dACC activity during negative self-reflection observed in s/s genotype individuals in the current study may reflect enhanced self-focus and increased association between the self and negative stimuli in individuals with the risk allele for depression. Therefore, our current findings suggest a potential neurogenetic mechanism for depression that helps to clarify the previous findings of increased negative self-focus in depressed patients (Ingram 1990; Grunebaum et al. 2005; Northoff 2007) and high risk for depression in the short 5-HTTLPR variant (Bellivier et al. 1998; Lotrich and Pollock 2004; Lasky-Su et al. 2005; Uher and McGuffin 2008).

The current study also demonstrated that negative self-reflection provokes stronger personal distress in s/s compared with l/l genotype group. The neural responses to negative self-reflection in the AI/IF predicted self-report personal distress induced by negative self-reflection. More importantly, the AI/IF activity fully mediated the 5-HTTLPR genotype effect on the subjective distress. Thus, the AI/IF may serve as the neural substrate of the personal distress induced by negative thoughts about the self. Consistent with the current findings, previous research has shown that thinking about one's own negative traits threatens self-concept (Ma and Han 2010) and produces personal distress (Bénabou and Tirole 2002). Feelings of distress are associated with a neural circuit consisting of the dACC and AI that encode negative affect during physical pain (Tölle et al. 1999; Price 2000) and social pain (Eisenberger et al. 2003; Singer et al. 2004). Given that depressed patients showed increased personal distress and experience of negative affect (Watson et al. 1988; Clark and Watson 1991; Roiser et al. 2012), it may be proposed that the hyperactivity in the dACC/AI related to negative self-reflection in the s/s variant of 5-HTTLPR provides another potential neurogenetic mechanism for vulnerability for depression in s/s genotype individuals.

Taken together, the current and previous studies (Hariri et al. 2002; Canli et al. 2005; Heinz et al. 2005) indicate that 5-HTTLPR influences the neural substrates underlying negative information-processing bias toward both environment and oneself. The neural mechanisms involved in the negative schemas of environment and the self are respectively characterized by hyperresponsiveness in the subcortical (i.e., amygdale) and cortical (mPFC/ACC, AI/IF) structures in the s carriers versus l/l genotype individuals. The enhanced amygdala responses to negative environmental stimuli may serve as an endophenotype of mood disorder such as depression (Hariri et al. 2002; Pezawas et al. 2005). Our current findings of enhanced dmPFC/dACC and AI/IF activity implicate another intermediate phenotype of depression linked to

negative self-schema. In contemporary societies, people are often confronted with negative social feedback and social comparisons in daily life, both of which may provoke negative self-view (Swallow and Kuiper 1988; Swann et al. 1992) and may in turn lead to the core symptom of depression—negative schema of the self (Kuiper and Olinger 1986; Haaga et al. 1991; McIntosh and Fischer 2000).

Our findings may have implications for treatment of depression. Established treatments for depression include medications and psychotherapy. Antidepressant medication acts on information-processing bias directly, such as normalization emotional reactivity (Roiser et al. 2012). Chronic SSRI treatment can improve depression symptoms (Richardson et al. 1994; Levkovitz et al. 2002) and normalize the hyperactivity in amygdala in depressed patients (Sheline et al. 2001; Fu et al. 2004; Anand et al. 2007). However, psychotherapies such as cognitive-behavioral therapy aim at cognitive control, that is, to train patients to separate their internal representation from negative external stimuli (Roiser et al. 2012). As the increased mPFC/ACC activity to encode self-relevance of negative stimuli has been observed in depressed patients (Lemogne et al. 2009; Yoshimura et al. 2010) and in individuals carrying the risk allele for depression (the current study), the neural activity in response to negative self-reflection may be used for depression detection and a measurement of depression treatment efficiency, especially for depressed patients with suicide attempts, as suicide is an escape from aversive self-awareness (Baumeister 1990). Moreover, our findings implicate that individuals' genetic makeup may affect treatment efficacy and contribute to depression risk detection. It has been suggested that SSRI efficacy differs between s and l/l allele genotype individuals (Smeraldi et al. 1998; Serretti et al. 2005). The current study demonstrated that individuals with different 5-HTTLPR polymorphisms were characterized by distinct personal distress and neural responses to negative self-reflection and distinct patterns of the association between the harm-avoidance tendency and dmPFC/dACC activity to negative self-reflection. Thus, individuals' genetic makeup may affect the efficiency of medication and psychotherapy treatment and should be considered in future treatment of depression.

Finally, our findings raise a few important questions for future research. For example, as the current work only examined the 5-HTTLPR effects on the neural correlates of negative self-reflection on personality traits, it remains unclear whether the neural correlates underlying self-reflection on other attributes such as social status are similarly modulated by 5-HTTLPR. Our recent study has shown that reflection on one's social attributes engages the temporoparietal junction besides the mPFC in Chinese (Ma et al. in press). Future research may investigate whether thinking about one's own low social status induces similar distressed feelings and dACC/AI activations so as to clarify whether the 5-HTTLPR effect on negative self-reflection can be generalized to other domains of personal attributes. Another question arising from the current study is whether 5-HTTLPR modulates the dACC/AI activity involved in negative self-reflection in other ethnic groups. The s allele frequency is higher in Asian than Caucasian populations (Kunugi et al. 1997) and the association between s allele and amygdala hyperactivity in responses to negative environmental stimuli shows different patterns in Asian and Caucasian populations (e.g., Hariri et al. 2002; Heinz et al. 2005; Lee and Ham 2008; Li et al. 2012). In addition, the neural activity involved in self-reflection is significantly different between Asians and Westerns (Zhu et al. 2007; Ma et al. in press). Thus, future research should address whether 5-HTTLPR similarly modulates the dACC/AI activity underlying negative self-reflection in other ethnic groups. This may help to understand whether and how culture interacts with individual's genetic makeup to shape the effect of 5-HTTLPR on the neural activity related to mental disorders.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

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