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

Yina Ma[1,3], Bingfeng Li[2,3], Chenbo Wang[1,3], Zhenhao Shi[1,3], Yun Sun[2,3], Feng Sheng[1,3], Yifan Zhang[1,3], Wenxia Zhang[2,3], Yi Rao[2,3] and Shihui Han[1,3]

[1]Department of Psychology, [2]Peking-Tsinghua Center for Life Sciences at School of Life Sciences, [3]PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing 100871, China

Address correspondence to S. Han, Department of Psychology, Peking University, Beijing 100871, China. Email: shan@pku.edu.cn;

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:

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 reflection on negative traits of a close friend. If the 5-HTTLPR effect is not specific to negative reflection on the self, we would expect a similar effect on negative reflection on a close other.

Materials and Methods

Participants

Experiment 1 recruited Chinese college students homozygous for the s allele ($n = 30$, 24 males, mean age = 20.3 ± 1.7 years) and those homozygous for the l allele ($n = 30$, 24 males, mean age = 19.8 ± 1.3 years) as paid volunteers. Experiment 2 recruited an independent group of 20 s/s (16 males, mean age = 20.3 ± 1.4 years) and 20 l/l genotype participants (16 males, mean age = 19.8 ± 1.2 years). Informed consents approved by a local ethics committee were obtained. All participants were right-handed, reported no history of neurological or psychiatric diagnoses, and had normal or corrected-to-normal vision. All participants completed the HA subscale, which consists of 34 yes/no items, from the Tridimensional Personality Questionnaire (Cloninger et al. 1993) and the Rosenberg Self-esteem scale (Rosenberg 1965) prior to fMRI scanning. Gender, age, self-esteem, and HA scores did not differ significantly between s/s and l/l groups in each experiment (Table 1).

DNA Isolation and Analysis

We used a PCR method (Ota et al. 2007) to determine the genotypes of 5-HTTLPR. In a total volume of 50 µL, about 25 ng of genomic DNA were amplified in the presence of 1 × TransStart FastPfu DNA Polymerase (TransGen Biotech) reaction system and oligonucleotide primers (forward 5′-GCATCCCCCATTATCCCCCCCT-3′ and reverse

Table 1
Information of participants in Experiments 1 and 2

Variables	Mean (SD)		Independent *t*-test	
	s/s	l/l	*T*-value	*P*
Experiment 1				
Gender	24 males, 6 females	24 males, 6 females	—	—
Age (years)	20.3 (1.7)	19.8 (1.3)	1.466	0.100
Self-esteem	28.9 (2.6)	29.3 (3.8)	−0.514	0.609
HA scores	14.4 (6.1)	15.9 (6.5)	−0.928	0.357
Self-distress	7.4 (1.6)	6.5 (1.9)	2.095	0.041
Friend-distress	4.0 (2.2)	4.4 (1.8)	0.697	0.489
Experiment 2				
Gender	16 males, 4 females	16 males, 4 females	—	—
Age (years)	20.3 (1.4)	19.8 (1.2)	1.362	0.181
Self-esteem	28.9 (2.7)	29.1 (4.7)	−0.123	0.903
HA scores	13.9 (5.8)	15.9 (6.2)	−1.054	0.299
Self-distress	7.8 (1.3)	6.3 (2.1)	2.721	0.010
Friend-distress	4.2 (2.2)	4.1 (2.1)	0.147	0.884

Note: Self-distress = rating scores of personal distress during reflection on one's own weakness; Friend-distress = rating scores of personal distress during reflection on a friend's weakness. Self-esteem was measured by the Rosenberg Self-esteem scale (Rosenberg 1965), which consists of 10 items describing subjective feeling about oneself on a Likert scale from 1 (strongly disagree) to 4 (strongly agree).

5′-AGGCTTGGAGGCCGGGATGC-3′) at final concentration of 200 nM. Thermal cycling consisted of a 15 min of initial denaturation at 95 °C followed by 35 cycles of 95 °C (20 s), 69 °C (20 s) and 72 °C (15 s) each with a final extension step of 10 min at 72 °C. Subsequently, the PCR product was loaded onto a 3% agarose gel (BioWest G-10) to perform electrophoresis to distinguish genotypes of s/s, s/l and l/l. All genotyping was performed in duplicate.

Stimuli and Procedure

One hundred eighty trait adjectives (half-positive and half-negative) were selected from established personality trait adjective pools (Liu 1990). Each word consisted of 2 Chinese characters. Each Chinese character subtended a visual angle of 0.34° × 0.45° (width × height) at a viewing distance of 80 cm during scanning.

In Experiment 1, participants were scanned in an event-related fMRI design while they judged if a positive (e.g., smart, friendly) or negative (e.g., lazy, greedy) trait adjective was able to describe oneself. Participants responded by key press on one of 4 buttons that were associated with a 4-point Likert scale that indexed the self-relevance of each item (1 = not at all like me, 4 = very much like me). Three functional scans of 248 s were obtained from each participant. Each functional scan started with a 6-s instruction, followed by 60 trials. Each word was presented for 1250 ms, followed by a fixation cross for 750 ms. Fifty-six null events consisting of a fixation cross for 2000 ms were pseudorandomly interspersed in each scan to introduce jitter into the fMRI time series.

After scanning, participants rated the valence and arousal of each trait used during scanning. The results of the valence ratings confirmed our precategorization of the words, and the valence rating did not differ between s/s and l/l genotype groups ($F_{1,\ 58} = 1.015$, $P = 0.318$). Participants also rated their personal distress on an 11-point Likert scale (0 = not distressed at all, 10 = extremely distressed) when thinking about the negative traits of their own and of an age-/gender-matched friend, respectively.

In experiment 2, participants were first asked to provide the name of a close friend who is of similar age and the same gender with the participant. All aspects of stimuli and procedure in Experiment 2 were identical to those in Experiment 1 except that participants judged whether a positive or negative trait adjective described his/her friend. Participants responded by key press on 1 of 4 buttons that were associated with a 4-point Likert scale that indexed the friend-relevance of each item (1 = not at all like my friend Allen, 4 = very much like my friend Allen).

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 ($64 \times 64 \times 32$ matrix with $3.44 \times 3.44 \times 5.0$-mm

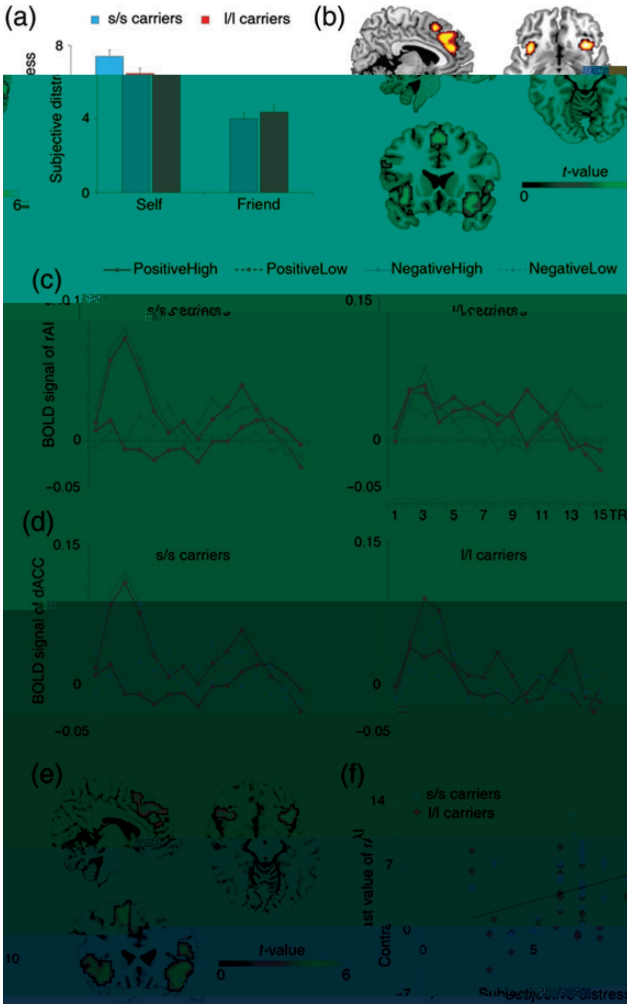

Figure 1. Behavioral and whole-brain fMRI results in Experiment 1. (*a*) Participants rated distressed feelings induced by thinking about weakness of oneself and a friend (0 = do not feel distressed at all, 10 = feel extremely distressed). The s/s genotype individuals (n = 30) reported greater distress associated with reflection on one's own negative traits compared with the l/l genotype individuals (n = 30). However, thinking about a friend

(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. 1e). 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. 1f; 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**	0.128
Mediator: Left AI/IF activity				
Regression Model 3				
Independent: Genotype (dummy code)	0.590	0.464	0.168	0.136
Mediator: Left AI/IF activity	0.146	0.070	0.273*	
Dependent: Subjective distress				
Right 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)	2.832	0.586	0.536***	0.287
Mediator: Right AI/IF activity				
Regression Model 3				
Independent: Genotype (dummy code)	0.194	0.500	0.055	0.180
Mediator: Right AI/IF activity	0.261	0.095	0.392**	
Dependent: Subjective distress				

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

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 ($Ps > 0.2$). Response ratio and RTs did not significantly differ between s/s and l/l genotype groups ($Fs < 1$, Supplementary Fig. 5).

fMRI data analysis focused on a 2-sample t-test of the contrast of Negative$_{\text{(high – low friend-relevance)}}$ minus Positive$_{\text{(high – low friend-relevance)}}$, 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), our 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 our 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

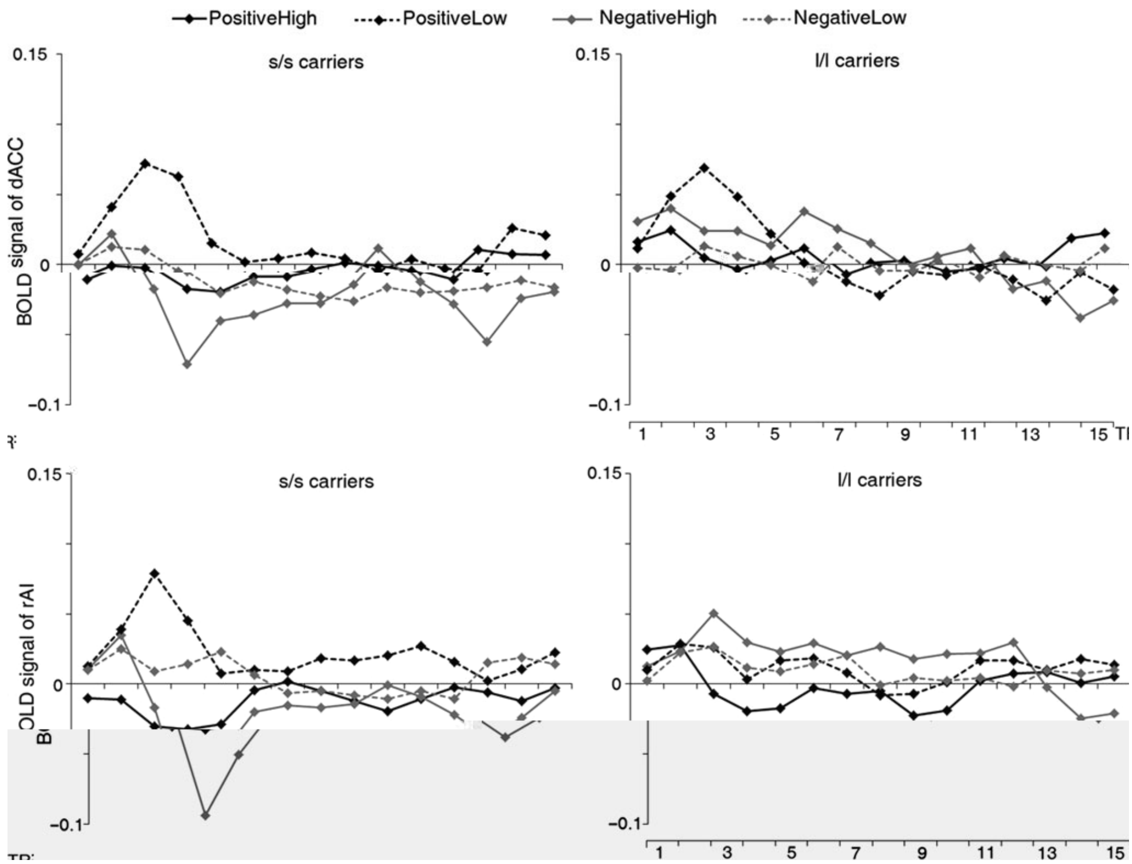

Figure 2. Time courses of BOLD signals in the dACC and Right AI during reflection on negative traits of a friend in Experiment 2. As the whole-brain analyses in Experiment 2 did not show any significant activation, the dACC and AI were defined in the activated brain regions observed in Experiment 1.

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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