Neuroscience 255 (2013) 255–264

RUMINATION MEDIATES THE RELATIONSHIP BETWEEN STRUCTURAL VARIATIONS IN VENTROLATERAL PREFRONTAL CORTEX AND SENSITIVITY TO NEGATIVE LIFE EVENTS

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Abstract—Individuals have different levels of stress sensitivity. An individual's predisposition to experience negative life events (NLEs) may make him/her more vulnerable to a series of psychopathological and physical diseases. However, the neuroanatomical correlates of individual differences in sensitivity to NLEs remain unknown. In this study, voxel-based morphometry was used to identify the gray matter (GM) associations of individual differences in sensitivity to NLEs measured by adolescent self-rating life events checklist. Results showed that there was a positive association between individual NLEs sensitivity and regional GM volume (rGMV) in the ventrolateral prefrontal cortex (VLPFC). GM was mostly evident in the left frontal operculum and a small part of the left middle frontal gyrus. This region was thought to play an important role in introception. Importantly, our study revealed that rumination served as a mediator between the rGMV of the VLPFC and individual NLEs sensitivity. These findings suggest that people with greater VLPFC might be more inclined to ruminate and the ruminative response style might make them more sensitive to NLEs.

Key words: individual differences, frontal operculum, stress sensitivity, coping style.

INTRODUCTION

Individual differences in sensitivity to negative life events (NLEs)

People exhibit different sensitivities in response to NLEs. Some people are more susceptible to daily hassles, while others are left unaffected. In the face of additional NLEs, some individuals become trapped in a chronic stressful life cycle; by contrast, others are strong enough to overcome adversity and even make positive changes in response to a situation (Park et al., 1996; McMillen et al., 1997). NLEs have a great influence on people, however, the degree to which NLEs affect humans depends on the individual experiencing them (Updegraff and Taylor, 2000). MacLeod and Hagan (1992) suggested that personality may play a role in determining this link. Through a longitudinal experiment, they found that there exists an automatic trait pattern of encoding selectivity among individuals with high levels of trait anxiety, which favors the process of emotionally threatening information. This processing bias moderates individual emotional responses to stressful life events. Meanwhile, the manner by which a person perceives a situation and the behavioral and lifestyle choices made by that person also play an important role in determining individual responses to potentially stressful situations (Flier et al., 1998). Numerous studies have suggested that genetic factors, such as the serotonin transporter (5-HTT) gene (Caspi et al., 2003), may determine one's reaction to stressful life events (Kendler et al., 1995, 1999, 2001; Straub et al., 1995; Kendler and Karkowski-Shuman, 1997; Risch et al., 2009).

Stressful life events and diseases

Stressful life events were reported to contribute to a variety of psychopathology and autoimmune diseases (McEwen, 2007; McLaughlin and Hatzenbuehler, 2009). Stressful life events especially affect the onset of depression. Kessler (1997) summarized research on the relationship between stressful experiences and depression, and made a couple of distinctions about the effects of the specific life stress on depression (i.e., overall stress effects and focused studies of particular events; acute stressful life events and chronic stress). Furthermore, Maes et al. (2001) investigated the effects of pre- and post-disaster stressful life events on post-traumatic stress disorder (PTSD) incidence rates by two man-made traumatic events. Their results showed that

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Abbreviations: ASLEC, adolescent self-rating life events checklist; CRT, combined Raven's test; CVD, cardiovascular disease; DV, dependent variable; FO, frontal operculum; GM, gray matter; IFG, inferior frontal gyrus; MNI, Montreal Neurological Institute; MR, magnetic resonance; MRI, magnetic resonance imaging; NLEs, negative life events; PTSD, post-traumatic stress disorder; rGMV, regional GM volume; ROI, region of interest; RRS, rumination (or ruminative) responses scale; RSQ, response style questionnaire; SAS, self-rating anxiety scale; SD, standard deviation; SDS, self-rating depression scale; s.e., standard error; SPM, statistical parametric mapping; VBM, voxel-based morphometry; VLPFC, ventrolateral prefrontal cortex; WM, white matter.

0306-4522/13 $36.00
http://dx.doi.org/10.1016/j.neuroscience.2013.09.053

the number and the severity of additional stressful events lead to greater PTSD development risks. Other than this fact, the avoidance–depression dimension of PTSD symptomatology is more severe. Moreover, Black and Garbutt (2002) reported that various stresses may induce cardiovascular disease (CVD). Besides, stress does not only affect immune functions but also predicts susceptibility to infectious diseases. Marsland et al. (2002) reported that individuals differ in the magnitude of their immune responses to stress. They suggested that such differences in immune responses indicate the extent of one's vulnerability to infectious diseases.

Rumination and effects of NLEs

A ruminative (also called rumination) response style refers to a series of thoughts and behaviors that occur in response to a sad or a negative mood, resulting in individuals focusing more on the causes and consequences of their emotions. And such response leaves them unable to focus on distracting activities that may alleviate their symptoms (Nolen-Hoeksema, 1991). In fact, rumination and the effects of NLEs are intimately related. For example, ruminative participants are more inclined to exhibit negative responses to stressful events or interpersonal difficulties. They also expressed a gloomier outcome about positive future events than those in a distracted condition (Lyubomirsky and Nolen-Hoeksema, 1995). Another study further demonstrated that dysphoric participants who underwent the rumination induction task recalled more negative autobiographical memories than those who underwent a distraction induction task (Lyubomirsky et al., 1998). Moreover, Gerin et al. (2006) explored the function of rumination and distraction in blood pressure recovery. Compared with the distraction group, they found that the rumination group expressed angrier thoughts and higher levels of rumination. The rumination group also exhibited the poorest blood pressure recovery. Meanwhile, (Brosschot et al., 2005, 2006; Brosschot, 2010) suggested that stressful events themselves might not cause prolonged physiological activity. Rather, this may be attributed to sustained cognitive representation (i.e., perseverative cognition), which refers to ruminations on past stressful events and worries about future events. Recent studies suggested that rumination mediates the association between stressors and individual sensitivity differences or stress reactions. For example, rumination has been found to significantly predict PTSD and depression 6 months after the occurrence of a traumatic event (Ehring et al., 2008), suggesting that rumination plays a mediatory role between the traumatic event and the trauma-related emotional disorders. Bennett and Wells (2010) revealed that rumination mediates the relationship between traumatic memory beliefs (positive/negative meta-memory beliefs) and the severity of PTSD symptoms. More recently, Radstaak et al. (2011) reported that the negative affect manipulation as well as rumination can hamper blood pressure recovery, thereby emphasizing the negative affect manipulation and rumination in stress recovery.

The present study

Previous studies have reported that individuals have different sensitivities to stress. However, the neural basis for such differences remains unknown. An individual's predisposition to experiencing NLEs may make him/her more vulnerable to a series of psychopathological and physical diseases. These diseases may manifest in depression, PTSD, CVD, infectious diseases, and cancer among other conditions. Hence, determining the neural basis behind these differences can help us gain a better understanding of stress-related disorders, which can also facilitate the development of preventive disease measures. Rumination has been reported to mediate the association between the stressor and the different reaction magnitudes in response to stress. Hence, high-level ruminators might be more influenced by stress than low-level ruminators. In the magnetic resonance imaging (MRI) studies of rumination as well as distraction, ventrolateral prefrontal cortex (VLPFC) was always identified and discussed. For instance, with the guidance to increase/decrease negative thought about the negative/neutral pictures or just look at it, VLPFC was found to show a greater magnitude of activation for the participants with a greater tendency to ruminate in the increase as well as passive look conditions (Ray et al., 2005). In addition, Hooker et al. (2010) found that lower inferior frontal gyrus (IFG) activity levels were associated with higher degrees of rumination. In recent literature, Kuhn et al. (2012) found that rumination is negatively correlated with gray matter (GM) volume in the bilateral IFG, the left anterior cingulate cortex (ACC), and the bilateral mid-cingulate cortex. Thus, in the current work, we speculated that the regional GM volume (rGMV) of the VLPFC may be correlated with rumination and NLEs sensitivity. This assumption is based on the causal and temporal relationships among rGMV, rumination, and individual differences in sensitivity to NLEs. Hence, rumination is not only a mediator between stressors and physiological reactions, but also a mediator between the rGMV of the VLPFC and individual NLEs sensitivities.

EXPERIMENTAL PROCEDURES

Subjects

311 right-handed, healthy adolescent volunteers took part in the study as part of our ongoing project exploring the relationship between brain image and mental health. However, a few participants were excluded because of unqualified images (nine participants) and lack of behavioral data (two participants). The eventual sample consisted of 175 (58.4%) females with a mean age of 19.78 years (standard deviation (SD) = 1.34) and 125 (41.6%) males with a mean age of 20.20 years (SD = 1.40). All the participants came from the local community of the Southwest University. All participants completed the adolescent self-rating life events checklist (ASLEC) (Liu et al., 1997). None of them had a history of neurological or psychiatric illness. The study was

approved by the Southwest University Brain Imaging Center Institutional Review Board. On the adherence to The Declaration of Helsinki (1991), we obtained written informed consent from all the volunteers.

Because our data was collected in several phases, the two scales of ASLEC and short form of rumination (or ruminative) responses scale (RRS) were collected in different phases. 311 subjects (with 300 validated) took part in the measurement of ASLEC. Voxel-based morphometry (VBM) analyses of our data were based on these subjects (300 validated subjects). Some participants did not engage in the behavior test under phase IV of the ongoing project, in which phase we collected our RRS data. There were 235 volunteers left who completed both of the two scales. Mediation analyses were based on these subjects (235 subjects). The conjunction sample of the two phases consisted of 130 (55.3%) females with a mean age of 19.73 years (SD = 1.23) and 105 (44.7%) males with a mean age of 20.07 years (SD = 1.30).

Assessment of sensitivity to NLEs

Sensitivity to NLEs was acquired by the ASLEC (Liu et al., 1997), which evaluated the impact of stressful life events experienced within the past 12 months. This scale consist of 26 NLEs collected from multiple stress domains: ''Criticized by teachers'' (school); ''Conflicts between parents'' (family); ''Break up with close friends'' (interpersonal); ''Personal serious illness/injury'' (physical diseases) and so on. For each event that occurred, participants have to report about the impact it had on their lives on a 5-point Likert scale with a response pattern ranging from 1 ''not at all'' to 5 ''extremely severe''. Scores were set to 0 for events that volunteers reported which did not occur in the past year. Cronbach's alpha coefficient for internal consistency in this sample was 0.85 and Spearman–Brown Split-Half coefficient was 0.74. As it is said in Nikolova et al. (2012), there are three main variables from the ASLEC: (1) Total number of events; (2) Total score, All the 26 items were summed up to acquire a total score; and (3) Average impact score, ASLEC total score divided by ASLEC total number of events that happened. We derived ASLEC average impact as a variable of interest because it reflected individual differences in sensitivity to NLEs.

Assessment of rumination

We used the short form of RRS, one of the subscales of the response style questionnaire (RSQ) (Nolen-Hoeksema and Morrow, 1991), to assess rumination response style. The SRRS is made up of 10 items, which are extracted from the original RRS (Treynor et al., 2003). The scale described ruminative responses to sad feelings and is made up of reflection response style (e.g. ''Go someplace alone to think about my feelings'') and brooding response style (e.g. ''Think 'Why do I always react this way?''). Volunteers have to respond on a 4-point Likert scale with a response pattern ranging from 1 ''almost never'' to 4 ''almost always''. Cronbach's alpha coefficient of the scale is 0.76. The translation to Chinese and adjustment to Chinese culture and language are depicted elsewhere (Zhang and Xu, 2010).

Assessment of general intelligence

The effect of general intelligence on brain structures (Jung et al., 2009; Takeuchi et al., 2010, 2011) was controlled by using the combined Raven's test-the rural in China (CRT-RC3) (revised by the Psychology Department of East China Normal University in 1994). This test is a widely used intelligence test with good reliability and validity (Wang, 2007). CRT contains the Raven's standard progressive matrix (C, D, E sets) and Raven's colored progressive matrix (A, B, AB sets). CRT consists of 72 nonverbal items and each item comprises a matrix with a missing piece that is to be completed by selecting the best answer from six or eight alternatives. The score of this test is equal to the number of correct answers in 40 min and used as a psychometric measure of individual intelligence.

Assessment of the self-report anxiety and depression

The self-rating depression scale (SDS) (Zung et al., 1965) and self-rating anxiety scale (SAS) (Zung, 1971) were used to measure depression and anxiety levels respectively. The SDS is a 20-item scale describing depressive symptoms and had demonstrated satisfactory reliability and validity (Zung, 1986). Each item could be rated on a 4-point Likert scale with a response pattern ranging from 1 ''a little of the time'' to 4 ''most of the time''. A higher SDS score is indicative of a greater level of depressive symptoms. The 20-item SAS is a self-report assessment tool to measure state anxiety (Zung, 1971) in the latest week. Each item used a 4-point scale from ''none of the time'' to ''most of the time.'' It consists of 15 somatic and five affective symptoms that were related to anxiety and had proved satisfactory internal consistency and test–retest reliability (Michelson and Mavissakalian, 1983; Olatunji et al., 2006). It contains items that assess both physiological and psychological symptoms commonly associated with anxiety. SAS is considered a sensitive and ecologically valid measure of subjective anxiety levels in patients as well as in nonclinical participants.

MRI data acquisition

Magnetic resonance (MR) images were acquired on a 3.0-T Siemens Trio MRI scanner (Siemens Medical, Erlangen, Bavaria, Germany). High-resolution T1-weighted anatomical images were acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (repetition time (TR) = 1900 ms; echo time (TE) = 2.52 ms; inversion time (TI) = 900 ms; flip angle = 9 degrees; resolution matrix = 256 × 256; slices = 176; thickness = 1.0 mm; voxel size = 1 × 1 × 1 mm).

Voxel-based morphometry analysis

The MR images were processed using the statistical parametric mapping-8 (SPM8, Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 2009b (MathWorks Inc., Natick, MA, USA). Each MR image was first displayed in SPM8 to screen for artifacts or gross anatomical abnormalities. For better registration, the coordinate origins of the images were manually set to the anterior commissure. Segmentation of the images into gray matter (GM), white matter (WM) and cerbrospinal fluid were implemented using the new segmentation in SPM8. Subsequently, we performed Diffeomorphic Anatomical Registration through Exponentiated Lie algebra in SPM8 for registration, normalization, and modulation (Ashburner, 2007). The warping to Montreal Neurological Institute (MNI) space was performed using linear transformations. To ensure that regional differences in the absolute amount of GM were conserved, the image intensity of each voxel was modulated by the Jacobian determinants using linear transformations. Finally, the normalized modulated images (GM and WM images) were smoothed with a 10-mm full-width at half-maximum Gaussian kernel to increase signal to noise ratio.

Statistical analysis

Statistical analysis of the rGMV data was performed using SPM8. We used whole brain analysis to examine the association between rGMV and average impact score of ASLEC (individual differences in sensitivity to NLEs). To control for possible confounding variables, participants' age, gender, general intelligence, and global volume of GM were entered as confounding covariates into the regression model. To avoid edge effects around the borders between GM and WM, an absolute threshold masking of 0.2 was used, meaning that voxels with GM values lower than 0.2 were excluded from the analyses. Statistical significance level of whole-brain analysis was set at $P < 0.05$ (corrected using the nonstationary correction) at cluster level with an underlying voxel level of $P < 0.001$ (Hayasaka et al., 2004). Using VBM8 Toolbox by Gaser (http://dbm.neuro.uni-jena.de/vbm/), the size of each cluster was corrected according to the local smoothness values (Worsley et al., 1999).

The behavioral data were analyzed using SPSS 16.0 software. As described above, we divided the total score of ASLEC by total number of events of ASLEC to generate the average impact score (NLEs sensitivity). Bivariate Pearson-correlation was calculated between the score of rumination and sensitivity to NLEs. In further analysis, we defined the significantly correlated region (left VLPFC) as a region of interest (ROI) using the xjview toolbox (http://www.alivelearn.net/xjview/). Then, Resting-State fMRI Data Analysis Toolkit software package (Song et al., 2011) was used to extract the rGMV of left VLPFC from each participant. Finally, the relationship between left VLPFC and rumination score were calculated.

To avoid the possibility that objective adversity and subjective response of an event are confounded and cannot be distinguished on the scale, we took a unique measure similar as Li et al. (2012). Specifically, several steps were taken to derive a new index of individual differences in sensitivity to NLEs that was relatively independent of the objective stress level of NLEs experienced. First, we calculated the *Z*-score of each event (the score of zero was not counted because it is an event that did not happen) from our sample. Then, we summed the *Z*-score of the 26 events of each subject. Finally, we divided the total *Z*-score by total number of events that happened to derive the average *Z*-score for each participant. This *Z*-score reflect individual differences in how strong and subjectively they respond to life events. A "0" average *Z*-score means that the individual had an average response (or impact) of NLEs. A positive average *Z*-score means that this individual was more sensitive than average, i.e., more easily affected when responding to the same NLEs as others. Alternatively, a negative average *Z*-score means that this individual was less sensitive than average, i.e., less easily affected when responding to the same NLEs as others.

RESULTS

Correlation of rGMV and sensitivity to NLEs

Tables 1 show the descriptive statistics of demographic data and the distribution of behavioral data.

We used VBM to explore the correlation between rGMV and individual differences in sensitivity to NLEs. After controlling for gender, general intelligence, age and GM global volume, we found that that regions indicating significantly positive associations ($P < 0.05$, corrected) between rGMV and NLEs sensitivity scores mainly included the left IFG and a small portion of the left middle frontal gyrus (Fig. 1).

NLEs sensitivity scores also showed a tendency to be positively correlated with rGMV in the right VLPFC as well, however, the cluster did not survive the correction. In addition, we split our sample into two extreme groups (50 subjects with the highest sensitivity scores and 50 subjects with the lowest ones) to check if there were bilateral findings. We performed a two-sample *t*-test using SPM8. Both of the left and right VLPFC became more conservative (left VLPFC: $x,y,z = -48,13,32$; $t = 3.87$; $P < 0.001$, uncorrected; right VLPFC: $x,y,z = 49,12,34$; $t = 2.60$, $P < 0.01$, uncorrected). Our data showed that at a less conservative threshold, there were bilateral findings, which suggested that

Table 1a. Participants' age as well as the mean and standard deviation (SD) of the sensitivity to NLEs score

Measure	Mean	SD	Range
Age	19.95	1.38	17–27
Sensitivity to NLEs score	2.50	0.50	1–4
Rumination score	21.11	4.55	12–37

Abbreviations: NLEs, negative life events.

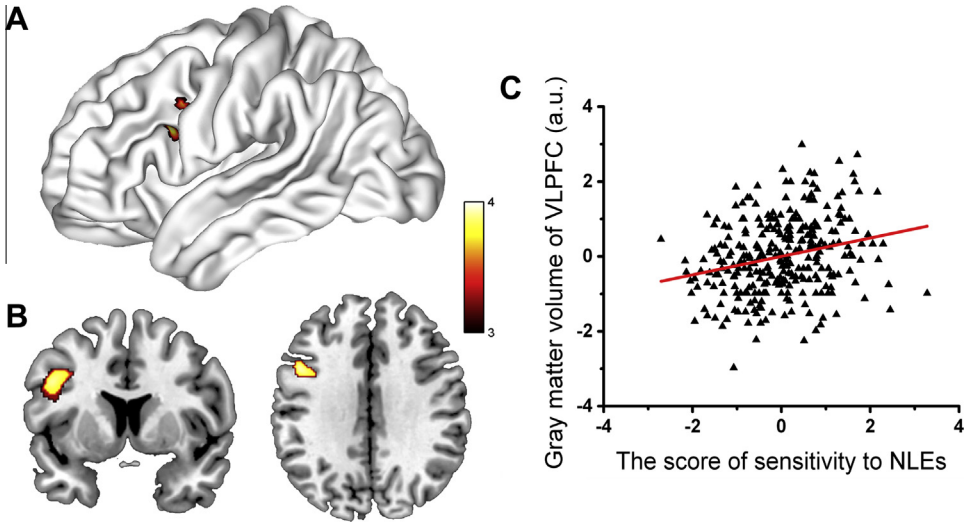

Fig. 1. Regions showed positive association between rGMV and sensitivity to NLEs. Results are shown with a threshold of $P < 0.05$, non-stationarity adjusted cluster-level. After controlling for gender, general intelligence, age and global volume of GM, regions showing significant association between rGMV and NLEs score mainly include left IFG and a small part of left middle frontal gyrus. (A) *T* statistical map was rendered using the BrainNet Viewer (Xia et al., 2013). (B) *T* statistical map was overlaid on an anatomical image (i.e., ch2better.nii) provided in the MRIcroN software (http://www.cabiatl.com/mricro/). The color bar represents the *T* score. (C) For display purpose, the association is shown in the scatterplot. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1b. The distribution of sensitivity to NLEs scores

	1–1.5	1.5–2	2–2.5	2.5–3	3–3.5	3.5 and above
Sensitivity to NLEs score	3	36	101	108	38	14

Abbreviations: NLEs, negative life events.

Table 1c. The distribution of rumination scores

	10–15	15–20	20–25	25–30	30 and above
Rumination score	21	103	124	59	13

sensitivity to NLEs is associated with GMV of VLPFC in a symmetric but not lateralized manner. No other significant correlated regions were found.

Analysis of covariance (ANCOVA) and interaction analysis were conducted to investigate whether the interaction between NLEs sensitivity scores and gender produced any effects on rGMV. However, we found no interaction between the two. We also investigated the association between WM volume (WMV) and individual differences in sensitivity to NLEs score and found no significantly correlated regions. The effects of the total number of events and the total score were not displayed, because we found no results when using the total number of events or the total score as a variable of interest. The Brodmann area, cluster size, peak *t* value, and peak coordinates (MNI) of the significant results (GMV) are shown in Table 2.

Next, we calculated the correlation coefficient between the average ASLEC impact score and the average *Z*-score, and found that the two variables were highly correlated ($r = 0.991$, $P < 10^{-6}$). When we used the average *Z*-score as a variable of interest to substitute the average ASLEC impact score in SPM8, we obtained the same results, with the average ASLEC impact score ($x, y, z = -48, 12, 28$; $t = 4.22$; $P < 0.001$, corrected).

In order to explore the possibility that the identified positive association between GMV of VLPFC and differential sensitivity to NLEs score might be driven by differences in similar behavioral measures such as depression and anxiety, we repeated the statistical analysis after including both of the two variables as covariate of no interest, the significant result was replicated ($P < 0.001$, corrected), thus indicating that the observed positive association did not depend on depression or anxiety.

Mediation analyses

Partial correlation statistics revealed a positive association between the rumination scores and NLEs sensitivity ($P < 0.001$) (Table 3). After controlling for gender, general intelligence, age and global volume of GM ($P < 0.001$, uncorrected), we also found a significantly positive correlation between rumination scores and the rGMV of the left VLPFC. The significant

Table 2. Brain areas for which gray matter volume positively correlated with sensitivity to NLEs score

Brain regions	Brodmann area	Cluster size	*T*-score	Peak coordinates (MNI)		
				X	*Y*	*Z*
Left FO/Left MFG	9/44/45	443	4.33*	−48	12	28

Note: MNI, Montreal Neurological Institute; FO, frontal operculum; MFG, middle frontal gyrus.
* $P < 0.05$, corrected.

Table 3. Partial correlation (two-tailed) for left VLPFC, sensitivity to NLEs score and rumination score

Partial correlations	Left VLPFC	Sensitivity to NLEs score	Rumination score
Left VLPFC		0.244**	0.232**
Sensitivity to NLEs score			0.338**

Note: $N = 235$ (105 males, 135 females). *Abbreviations:* VLPFC, ventrolateral prefrontal cortex; NLEs, negative life events; GM, gray matter.
** $P < 0.001$. Partial correlations: the relationship among left VLPFC, sensitivity to NLEs score and rumination score was calculated after controlling for age, gender, general intelligence and global volume of GM.

associations found among the rGMV of the left VLPFC, rumination, and NLEs sensitivity suggested that rumination may mediate the relationships among these variables. We tested whether or not rumination mediated the correlation of the rGMV of the VLPFC and different individual sensitivities to NLEs. This was done using the script written by Andrew F. Hayes (The Ohio State University, http://www.comm.ohio-state.edu/ahayes) in SPSS 16.0. For details, see Preacher and Hayes (2008). We chose the GMV of the ROI (left VLPFC), NLEs sensitivity, and rumination as the independent variable, the dependent variable (DV) and the proposed mediator, respectively.

As expected, mediation analyses revealed that the rGMV of the VLPFC had a significant indirect effect on NLEs sensitivity levels via rumination [bias corrected confidence intervals = (0.30, 1.28); sample size = 235; model summary for DV Model: $R^2 = 0.14$, $F = 7.67$, $P < 10^{-4}$). Greater rGMV of the VLPFC was associated with higher levels of rumination [$a = 0.18$, standard error (s.e.) = 0.06, t (232) = 2.91, $P < 0.005$]. Higher levels of rumination were also associated with increased NLEs sensitivity [$b = 0.31$, s.e. = 0.06, t (232) = 4.90, $P < 10^{-4}$]. More importantly, the direct pathway between the sensitivity to NLEs score and rGMV of the VLPFC became non-significant [$c' = 0.12$, s.e. = 0.27, t (232) = 1.90, $P = 0.06$ (n.s.)] when rumination mediated these two factors. The results showed a moderate mediation effect (Fig. 2). We cannot thoroughly rule out the possibility that the rGMV size of the VLPFC results from increased NLEs responses or increased levels of rumination. When we substituted the independent variable, the DV and the proposed mediator with one another, the model became insignificant. In addition, we repeated the statistical analysis after including the total number of events as covariates of no interest. This was done because of the possibility that plastic changes in the brain may occur when people experience NLEs. The significant result was replicated ($P < 0.001$, corrected), indicating that the observed positive association did not depend on the number of events that occurred.

DISCUSSION

The aim of the present study was to use VBM to explore the association between rGMV and NLEs sensitivity in young healthy subjects. Our results showed that the rGMV of the left VLPFC was positively correlated with NLEs sensitivity. We further investigated the assumption that rumination plays a mediating role in the relationship between the rGMV of VLPFC and NLEs sensitivity. And our data yielded positive results.

After controlling for gender, general intelligence, age and GM global volume variables, we have found that the rGMV of the left VLPFC was positively correlated with NLEs sensitivity, that is, people with greater VLPFC were more sensitive to NLEs. This confirms our first hypothesis. The neural activity of the anterior insular cortex and frontal operculum (FO) correlates with the accuracy of participants' performance in the heartbeat detection task (Critchley et al., 2004). Moreover, the rGMV of the same region is associated with both interoceptive accuracy and subjective visceral awareness assessment. Previous studies reported evidence that the accuracy of interoception is intimately correlated with subjective emotion (intensity and arousal) (Pollatos et al., 2005). Zaki et al. (2012) revealed that the anterior insular cortex and the FO are commonly activated during interoception and emotional awareness. People with greater IFG may be more sensitive to subtle endogenous or exogenous changes. As a result, our daily stressful experiences may cause different levels of physiological reaction, giving rise to individual differences in sensitivity to NLEs. In line with our idea, Aron et al. (2012) proposed that there is a genetically determined trait in the ''sensory processing sensitivity'' model, and this model involves a deeper cognitive stimuli processing procedure driven by higher emotional reactivity. They suggested that sensitive individuals might use more responsive strategies that are partly characterized by ''being more prone to 'pause to check' in a novel situation, being more sensitive to subtle stimuli, and employing deeper or more complex processing strategies for planning effective action and

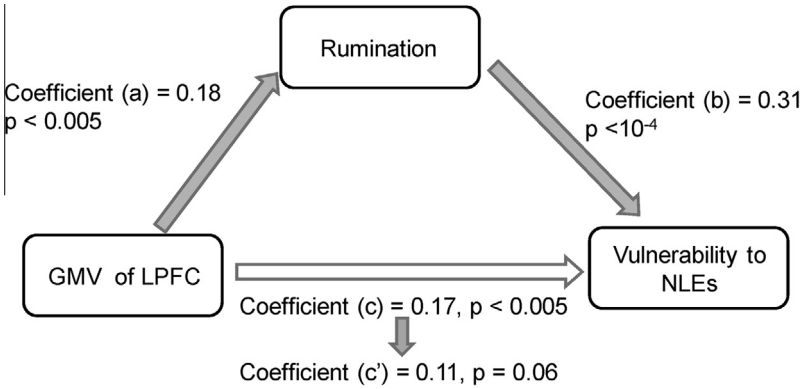

Fig. 2. Mediational effects of rumination on the relationship between GMV of VLPFC and sensitivity to NLEs score.

later revising cognitive maps, all of which are driven by stronger emotional reactions, positive and negative.

In addition, our results showed that rumination mediated the relationship between the rGMV of VLPFC and NLEs sensitivities, hence confirming our second hypothesis. As described in the introduction, rumination is associated with the rGMV of the left VLPFC, such that individuals with greater VLPFC are more inclined to ruminate. This, in turn, makes such individuals more sensitive to NLEs. Thus, the identified positive relationship between the rGMV of the VLPFC and different individual NLEs sensitivities may partly be induced by the indirect effect of rumination. However, we obtained contrary results with those from previous research (Kuhn et al., 2012). They suggested that rumination was negatively correlated with GM volume in bilateral IFG. This gap can be attributed to the fairly small sample size used in the previous research (38 participants). In addition, the research excluded two participants with moderate depression (BDI measure with scores of 23 and 25, respectively). Doing this, their results may be affected. In our work, we did not exclude such participants for that reason. Finally, brain regions identified in the two studies did not exactly overlap.

Based on the previous findings, aside from its role in exerting control over behavior that needs to be stopped (Aron et al., 2004), the VLPFC is also responsible for inhibiting unwanted memories (Anderson et al., 2004; Depue et al., 2007). These two studies used the think/no-think paradigm to explore the neural associations of the suppression of unwanted memories and found increased VLPFC activation was associated with impaired retention of those memories. Furthermore, the VLPFC can also suppress or stop the ceaseless ruminations. For example, Hamilton et al. (2011) found that compared to healthy controls, depressed patients showed an over-activity of the default-mode network, which was associated with higher levels of maladaptive rumination. At the same time, the adaptive engagement of the right IFG and the insular cortex stop maladaptive rumination has been found in healthy controls. In addition, Dieler et al. (2013) found that voluntary thought suppression is influenced by anxious and ruminative tendencies in healthy volunteers.

Our results also showed that people with smaller VLPFC are more efficient at suppressing or stopping constant rumination. One proposed interpretation behind the negative association between rumination suppression and the rGMV of VLPFC lies in the pruning process, which is related to the improvement of processing efficacy in that region during early development. As a result, a mature cortical area might be associated with smaller GM volume and better behavioral performance (Kanai et al., 2011). In summary, the present results showed that people with greater rGMV of the VLPFC are more inclined to deploy a ruminative response style upon encountering NLEs and the ruminative response style makes them more sensitive to NLEs.

Our findings provide new insight into the mental well-being of healthy subjects. One such particular new insight is that the tendency to ruminate may be a trait marker of NLEs sensitivity. Given that coping styles can affect the perceived life stresses experienced by individual, maladaptive coping styles may be a trait marker for mood disorders (Vinberg et al., 2010). In addition, the tendency to adopt a ruminative response style when faced with a depressed mood is a stable individual difference across time (Nolen-Hoeksema, 1991). Furthermore, test–retest correlations of the RSQ, the principal measure of the ruminative response style, over a period of one year is typically greater than 0.60 (Nolen-Hoeksema and Davis, 1999; Nolen-Hoeksema, 2000), showing a reasonable degree of stability, thereby indicating that the tendency to ruminate may be a trait marker of sensitivity to NLEs.

Moreover, we revealed a positive association between rGMV and NLEs sensitivity. Specifically, increased rGMV goes with an enhanced sensitivity to NLEs (i.e., less GM volume might indicate protection against NLEs). At first glance, the results may seem counter-intuitive. However, upon further examination, these results are in agreement with those studies reporting reduced GM volume in the somatosensory-motor network associated with ballet dance expertise (Hänggi et al., 2010) or increased GM volume in the putamen associated with focal hand dystonia in musicians (Granert et al., 2011) or increased cortical thickness in congenital amusia (Hyde et al., 2007) and in migraine (DaSilva et al., 2007).

There are several limitations in this study. First, the predominant use of life event questionnaires poses two problems: one refers to the retrospective quality resulting from data gathered by life events checklists, that is, the results of such lists may contain recall biases; and the other refers to the tendency that people often interpret life event descriptors in highly personal ways (Dohrenwend, 2006). Depending on how a particular individual interprets the question, the same life event descriptor can represent a range of life events—from trivial to catastrophic (Monroe, 2008). However, Duggal et al. (2000) recommended that the self-report checklists represent a summary index of "overall levels of subjectively experienced stress". In addition, interview-based life stress measurement procedures are more expensive and time consuming; hence, these measures are less suitable for investigations that require large samples (Hammen, 2005; Dohrenwend, 2006). Second, our sample is limited to adolescent college students. Whether these results apply to the full range of the population remains to be seen. Hence, we suggest that future research should obtain more representative samples. Third, we only used the VBM method to test our hypotheses. As mentioned in Giuliani et al. (2011), using only VBM methods may obscure crucial results. Future works should employ both ROI and VBM methods to verify whether other results may found. Finally, we did not use longitudinal design in this study. The interpretation of the results of mediation analysis on cross-sectional data must always proceed with caution. Further studies should develop longitudinal or other better designs in order to examine causation and investigate the related questions in a more comprehensive manner.

Acknowledgements—We thank the participants, the experimenters for the ongoing project, and all our other colleagues for their support. The study was supported by the National Natural Science Foundation of China (31070900; 30970892; 31170983), the Program for New Century Excellent Talents in University (2011) by the Ministry of Education, the Fundamental Research Funds for the Central Universities (SWU1209101), China Postdoctoral Science Foundation funded project (2012M510098), the Research Funds for Southwest University (SWU09103), the Key Discipline Fund of National 211 Project (NSKD11007), and the postgraduate Innovation Foundation of Science and Technology of Southwest University (kb2011002).

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(Accepted 27 September 2013)
(Available online 10 October 2013)