

# 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. © 2013 IBRO. Published by Elsevier Ltd. All rights reserved.

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

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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.

## 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

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

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