

Individual differences in rumination in healthy and depressive samples: association with brain structure, functional connectivity and depression

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Background. Rumination is an important cognitive risk factor for onset and relapse of depression. However, no studies have employed a dimensional approach in investigating the neural correlates of rumination and the relationship with depression.

Method. Non-clinical healthy subjects ($n=306$), who completed the classical rumination and depression scales, were studied using voxel-based morphometry and regional homogeneity (ReHo). Subsequently, mediation analysis was conducted to examine the influence of rumination on the relationship between brain structure and depression. Moreover, depressive patients ($n=60$) and a control group ($n=63$) of comparable age and education were studied with regions of interest that were identified in the healthy individuals.

Results. For healthy individuals, regional grey-matter volume (rGMV) of dorsolateral prefrontal cortex (DLPFC) and parahippocampal gyrus (PHG) were positively correlated with rumination. In addition, rumination had a mediating effect on the relationship between the DLPFC and PHG and depression. Moreover, ReHo analysis showed that rumination had a significantly negative correlation with functional homogeneity of DLPFC. However, compared to the control group, depressed patients showed significant decrease of rGMV in the DLPFC and PHG and there was a significant negative correlation between DLPFC volume and depressive rumination.

Conclusions. Increased DLPFC volume (decreased ReHo) in healthy individuals while decreased in depression indicated the trend of DLPFC from inefficient inhibition ('overload state') to impaired regulatory mechanism ('paralysis state'). This finding might elucidate when and why healthy individuals would develop sustained negative mood and depression eventually.

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Introduction

Rumination (repetitive thought) was one of the important cognitive risk factors of mood-related diseases (Ekkers *et al.* 2011; Huffziger *et al.* 2012) and could predict the onset, duration, severity and relapse of depression (Lyubomirsky & Nolen-Hoeksema, 1995; Kuehner & Weber, 1999; Nolen-Hoeksema, 2000; Roelofs *et al.* 2006). According to previous studies, defect in cognitive control poses a difficulty for vulnerable people to avoid negative rumination, which in turn enhances depressive symptoms (De Raedt & Koster, 2010;

Demeyer *et al.* 2012). Thus, rumination might be a behavioural predictor for depression.

Previous studies have reported that depressed subjects showed decreases in regional grey-matter volume (rGMV), including bilateral medial and left superior frontal gyri, bilateral inferior frontal gyrus (IFG), right anterior cingulate cortex (ACC), left parahippocampal gyrus (PHG), left caudate, left inferior parietal lobe and amygdala (Putnam & McSweeney, 2008; Denson *et al.* 2009; Kross *et al.* 2009; Hooker *et al.* 2010). Recently, Kühn *et al.* (2012) reported that rumination in healthy subjects was negatively correlated with rGMV in bilateral IFG, left ACC and bilateral mid-cingulate cortex, which might be related to inhibition control and thought suppression. In addition, there was much evidence on establishing a link between rumination and alterations of the task-related control network comprising such brain regions as

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lateral prefrontal cortex and parietal cortex (Putnam & McSweeney, 2008; Hooker *et al.* 2010). However, major depressive disorder (MDD) is characterized by a failure of dorsal areas [e.g. dorsolateral prefrontal cortex (DLPFC)] to regulate affective processing systems (Phillips *et al.* 2003; Vanderhasselt *et al.* 2013).
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As is the case with the bulk of previous research, which typically employed a categorical rather than dimensional approach to conceptualizing rumination (Joormann *et al.* 2007; Kuhn *et al.* 2012; Vanderhasselt *et al.* 2013), few studies have focused on the development from the normal individual to high risk of depression and eventually to clinical depression. In addition, the National Institute of Mental Health (NIMH), had encouraged a dimensional approach to investigate the neural correlates of psychopathology (Webb *et al.* 2014). Indeed, in a sample of healthy never-depressed individuals, inter-individual differences in rumination might reveal specific brain structural correlates of rumination (Joormann *et al.* 2007; Vanderhasselt *et al.* 2013). Moreover, rumination is a relatively stable trait, independent of ongoing depression level (Nolen-Hoeksema, 1991). This state of never-depressed healthy individuals scoring high on rumination is thought to be prodromal to depressive disorders, and a precise understanding of it is important to predict clinical depression (Cuijpers & Smit, 2004; Hayakawa *et al.* 2013). Thus, it remain to be elucidated whether there is a continuum with clinical depression in healthy individuals with high rumination, and whether the same brain alterations are present in healthy and depressive rumination.

Recently, voxel-based morphometry (VBM) analysis has been widely used in normal subjects over other neuroimaging methods to investigate the neuroanatomical correlates of inter-individual differences in human cognition and behaviour. Previous studies have demonstrated that the networks underlying personality can be identified by measuring rGMV/white-matter volume. Thus, this analysis can allow us to reveal the brain structures underlying rumination. Admittedly, structural alteration in the brain leads to neural functional changes. Previous studies on normal subjects or patients have revealed that the brain structure does determine and influence the neural functions to some extent (Greicius *et al.* 2009; Honey *et al.* 2009, 2010; de Kwaasteniet *et al.* 2013).

Thereby, investigation into functional connectome of the individual differences in rumination is of significance and is necessary to verify the reliability of the structural results on the one hand, and to better understand the nature of functional anatomy of rumination on the other. Among the indexes of functional connectome, regional homogeneity (ReHo) is the most widely used analysis and shows high test-retest reliability. It measures the local synchronization of low-frequency spontaneous activity in regions, showing overlap with the previously reported structural, functional and metabolic 'backbones' of the human brain connectome (Hagmann *et al.* 2008; Buckner *et al.* 2009).

Therefore, VBM and ReHo were used in the present study to identify the neural correlates of individual ruminative thinking style in healthy subjects and depressive patients. It is well-documented that there is close relationship among rumination, structure of the DLPFC and limbic regions, and depression (Spasojević & Alloy, 2001; Robinson & Alloy, 2003; Lo *et al.* 2008; Vanderhasselt *et al.* 2013). Nevertheless, little empirical evidence is available to support the mediational model in which the structure of these brain regions is associated with the early cognitive risk factor of rumination, which in turn might be related to depression. In addition, little is known as to whether the alteration of brain structure associated with rumination in healthy subjects and depressive patients show a similar trend. Thus, the specific aim of the current study was to examine whether rumination predicts self-rating depressed status in healthy subjects and depressive patients and has a mediating effect on the relationship between the structure of DLPFC and limbic regions and depressed status. We hypothesized that (1) rumination would correlate positively with symptoms of depression both in healthy individuals and in depressive patients; (2) individual differences in rumination would be associated with rGMV variations within the DLPFC and limbic regions, which are associated with negative mood inhibition; (3) functional homogeneity of DLPFC and limbic regions would be associated with rumination; and (4) the structure of DLPFC and limbic regions would interact with rumination and influence depression both in healthy subjects and in depressive patients.

Method

Subjects

Three hundred and six (146 males, 160 females) non-clinical healthy subjects (dataset 1) participated in the study, which is part of an ongoing project to examine the association among brain imaging, creativity and mental health (Li *et al.* 2014; Wei *et al.* 2014). No subject

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had history of neurological conditions, or of mental disorders in first-degree relatives. In addition, 60 (16 males, 44 females) depressive patients and 63 (31 males, 32 females) age-matched non-clinical control subjects (dataset 2) were selected from another ongoing project, which examined the occurrence and development of depression.

Assessment

To assess the level of rumination, we used the 10-item Chinese Short Ruminative Responses Scale (SRRS) (Zhang & Xu, 2010), which was revised from the Ruminative Responses Scale (RRS) developed by Nolen-Hoeksema and has excellent reliability and validity (Nolen-Hoeksema, 1991; Treynor *et al.* 2003). It is composed of two different factors (sensitive rumination and assessment rumination), which are similar to brooding and reflection. Rumination was a common mechanism relating depressive risk factors to depression. The SRRS is a self-report assessment scale which measures the response of self-focus and symptoms-focus, guess of reason and thought of result to depressive mood. Exemplar items are 'I think about my tired and painful feelings' and 'I think about how often I feel sad'. The SRRS uses a 4-point Likert-type scale (1 = almost never, 2 = sometimes, 3 = often, 4 = almost always). The internal consistency (Cronbach's α) of the SRRS was 0.767 (Zhang & Xu, 2010). The convergent validity for the SRRS scale was confirmed by significant correlation with measure of depression (CES-D; Radloff, 1977). Results showed that rumination had a significant positive correlation with depression ($r=0.594$, $p<0.001$). In our sample (dataset 1), the scale had a high level of internal consistency (Cronbach's $\alpha=0.829$), constructing validity with the Self-rating Depression Scale (SDS) and Beck Depression Inventory (BDI) ($r=0.45$, $p=0.000$; $r=0.43$, $p<0.000$) and test-retest reliability ($r=0.577$, $p=0.000$).

All subjects was required to complete classical depression scales (SDS, BDI). In addition, 3D-T1 weighted and resting-state functional MRI data were acquired. For detailed information, see online Supplementary material.

Anatomic imaging preprocessing (datasets 1 and 2)

VBM is a procedure that not only characterizes differences of GMV between two groups but also neuroanatomical correlates of cognitive performance across participants (Ashburner & Friston, 2000). In this study, 3D-T1 structural images for datasets 1 and 2 with the same parameters were independently preprocessed to avoid the influence mutually. Preprocessing was performed using SPM8 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging,

UK). For better registration, all T1-weighted structural images were manually co-registered to the anterior commissure-posterior commissure (AC-PC). Next, using the unified segmentation procedure, the co-registered images from each participant were segmented into grey matter (GM), white matter and cerebrospinal fluid (Ashburner & Friston, 2005). Then, GM images of each participant were spatially normalized to a study-specific T1-weighted template using a diffeomorphic nonlinear registration algorithm (DARTEL; diffeomorphic anatomical registration through exponentiated lie algebra). The DARTEL registration involves, first computing the specific template using the average tissue probability maps from all the participants, and then warping each participant's segmented maps into a specific template. In order to improve the alignment and achieve a more accurate inter-subject registration, the procedure was repetitively conducted until a best study-specific template was generated. Subsequently, a further modulation was conducted to preserve the volume of GM. The following inference about correlation with cognitive performance was based on measures of volume rather than density after using the modulated images. Then a 10-mm full width at half maximum was applied to smooth the modulated GM images.

Relationship between rumination and rGMV (dataset 1)

Statistical analysis of rGMV data for healthy subjects was performed using multiple regression analysis with SPM8. In the whole-brain analysis, we investigated the neuroanatomical correlates of individual differences in rumination measured by SRRS and treated age, sex and total GM brain volumes (TGM) as covariates in order to control for possible confounding variables. For the regression analysis, we used the family-wise error (FWE) of $p<0.05$ at the whole brain level and ≥ 15 contiguous voxels as a threshold to correct for multiple comparisons. Then, two regions of interest (ROIs) (DLPFC and PHG, see dataset 1 results) were created by thresholding (at $p<0.05$, FWE corrected) the peak of significance from the rGMV correlation of rumination.

Mediation analyses (dataset 1)

Mediation analyses were used to understand a relationship by exploring its underlying mechanism. An exploratory mediation analysis, in the present study, was performed for rGMV, rumination and depression. We examined whether the trait of rumination would mediate the relationship between DLPFC volume or PHG and depression.

The present study used the script written by Preacher & Hayes (2008) to conduct mediation analysis

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Q10 in SPSS 16.0 (SPSS Inc., USA). We chose the GMV of the ROIs (DLPFC and PHG, separately), rumination score (SRRS), and depression score (SDS) as the independent variable, the proposed mediator and the dependent variable, respectively. In addition, age, sex and TGM were entered as a control variable to avoid the influence of irrelevant factors.

ReHo analysis (dataset 1)

ReHo measured functional homogeneity of resting-state fMRI signals within a small region (Zang et al. 2004). Previous studies suggested that surface-based fMRI processing would reflect the functional organization more naturally and achieve more accurate cross-subject matching of functional regions (Argall et al. 2006; Fischl et al. 2008). Thus, in the present study, a 2-dimensional variant ReHo (2dReHo), which was proposed by Zuo et al. (2013), was used to investigate the neural mechanism of individual differences of rumination. The 2dReHo computation procedure, which was similar to previous ReHo computation, was repeated for all vertices in surfaces to produce vertex-wise Kendall's coefficient of concordance (KCC) ReHo maps for both hemispheres separately. KCC ReHo measures Kendall's coefficients which correlate the signal of one vertex with its neighbours. Finally, all ReHo maps for each subject were transformed to Z scores for subsequent analysis.

Relationship between rumination and ReHo (dataset 1)

At the group-level analysis, we tested the individual differences in the relationship between rumination and functional homogeneity. Statistical analyses were performed using the General Linear Model method. We used a multiple regression analyses to look for regions where functional homogeneity was significantly related to individual differences in rumination. The effects of age and sex were included as regressors of no interest. Gaussian random field theory was used to correct for multiple comparisons at the cluster-level (min $Z > 2.3$, cluster significance: $p < 0.05$, corrected).

Relationship between brain structure and rumination in depressive patients (dataset 2)

To test whether the same brain structural alterations are present in depressive or healthy rumination, and whether there is a continuum between clinical depressive patients and healthy individuals with high rumination, we first extracted the rGMV of ROIs (DLPFC and PHG) determined by dataset 1 results for depressive patients and control groups. Then, two-sample t test was performed to compare GMV of ROIs between the depressed and control groups.

Subsequently, partial correlation analysis was conducted between rGMV and rumination score for depressive patients and control groups, respectively. As the sample of dataset 1 was from healthy college subjects and might have low ecological validity, we first conducted the correlation analysis for the control group which had high ecological validity to verify the result of dataset 1. Similar to the partial correlation analysis in dataset 1 (healthy college individuals), we included age, sex, education and TGM as covariates of no interest. Then, partial correlation analyses between depressive rumination and rGMV of ROIs were performed on depressive patients to check the developmental trend between rumination and brain structure, with age, sex, education and TGM as covariates of no interest.

Finally, we performed mediation analysis to investigate whether rumination would mediate the relationship between rGMV and depression in the depressed patients. Similar to the analysis in dataset 1 (healthy college individuals), the rGMV of the ROIs (DLPFC and PHG, separately), rumination score (SRRS), and depression score (SDS) were respectively selected as the IV, the proposed mediator and the DV. In addition, age, sex, education and TGM were entered as a control variable to avoid the influence of irrelevant factors.

Results

Subjects

In dataset 1, 306 non-clinical healthy subjects were included. Kurtosis (-0.02) and skewness (0.38) of SRRS scores were within the range between -1 and $+1$, indicating the normality of the data (Marcoulides & Hershberger, 1997). Demographic characteristics for dataset 1 are given in the Table 1. The results show that a significant positive correlation between rumination and depression score (SDS and BDI) was found ($r = 0.45$, $p = 0.000$; $r = 0.43$, $p < 0.000$, respectively). For each component of ruminative scale, sensitive rumination and assessment rumination were also positively correlated with depression score: sensitive rumination (correlation with SDS, $r = 0.438$, $p < 0.000$; correlation with BDI, $r = 0.421$, $p < 0.000$); assessment rumination (correlation with SDS, $r = 0.336$, $p < 0.000$; correlation with BDI, $r = 0.347$, $p < 0.000$). According to the descriptive standard in SDS, subjects with a normalized score > 53 were defined as individuals having a high risk of depression; and in BDI, subjects with a score > 13 as having a high risk of depression. In our study, about 15% of subjects might be subjects with a high risk of depression (SDS: 47 subjects, 15.36%; BDI: 45 subjects, 14.71%).

Table 1. Demographic characteristics of non-clinical healthy individuals (dataset 1)

Characteristics	Males (N = 146)		Females (N = 160)	
	Mean	S.D.	Mean	S.D.
Age (years)	20.09	1.19	19.77	1.23
SRRS score	21.46	4.92	20.75	4.25
SDS score	43.36	8.70	43.75	8.51
BDI score	7.19	5.90	6.93	5.10

SRRS, Short Ruminative Responses Scale; SDS, Self-rating Depression Scale; BDI, Beck Depression Inventory.

In dataset 2, 123 subjects (60 depressive patients, 63 control subjects) were included. Groups did not differ significantly in age (MDD: mean = 36.07, S.D. = 11.57; control: mean = 32.40, S.D. = 11.95; $t = 1.73$, $p = 0.086$) and education (MDD: mean = 12.13, S.D. = 3.72; control: mean = 12.76, S.D. = 3.33; $t = 0.99$, $p = 0.325$). However, two-sample t test showed that depressive patients had higher ruminative scores compared to the control group (MDD: mean = 23.07, S.D. = 4.73; control: mean = 18.14, S.D. = 4.35; $t = 6.01$, $p = 0.000$). For each component of rumination, depressive patients had higher scores compared to the control group in sensitive rumination, which corresponds to brooding (MDD: mean = 11.12, S.D. = 2.66; control: mean = 7.46, S.D. = 2.19; $t = 8.33$, $p = 0.000$) and assessment rumination, which was corresponds to reflection (MDD: mean = 11.95, S.D. = 3.03; control: mean = 10.87, S.D. = 2.86; $t = 2.03$, $p = 0.045$).

Dataset 1 results

Multiple regression analysis showed that rumination was positively correlated with rGMV in DLPFC ($Z = 6.22$, MNI coordinates: $x = -39$, $y = 8$, $z = 27$) and PHG ($Z = 4.41$, MNI coordinates: $x = 29$, $y = 2$, $z = -35$) (see Fig. 1). There was significant positive correlation between DLPFC and depression severity (BDI and SDS) ($r = 0.12$, $p = 0.041$; $r = 0.16$, $p = 0.006$, respectively). Moreover, correlation between PHG and depression severity (BDI and SDS) were also significantly positive ($r = 0.11$, $p = 0.067$; $r = 0.21$, $p = 0.000$, respectively).

To verify the results of structural neural correlates of rumination and further elucidate functional neural correlates, we also tested the relationship between individual differences in rumination and ReHo. Multiple regression analysis revealed that left DLPFC was significantly negatively correlated with rumination score (see Fig. 2) after controlling for age and sex.

In the exploratory analysis and model we proposed above, it is assumed that rumination has influence on the relationship between the occurrence of depressive

mood and DLPFC or PHG. As expected, mediation analyses revealed that the rGMV of the DLPFC had a significant indirect effect on depression via rumination (total ruminative score and each component). For detailed information, see online Supplementary material.

Dataset 2 result

First, the volumes of DLPFC and PHG were extracted from depressed patients and control groups. Compared with control group, depressed patients showed significantly decreased volume in DLPFC ($t = 5.06$, $p = 0.000$) and PHG ($t = 4.89$, $p = 0.000$).

Next, the partial correlation analysis for control group revealed that rumination score was positively associated with DLPFC volume ($r = 0.24$, $p = 0.064$) and PHG ($r = 0.26$, $p = 0.041$), after adjusting for variation attributable to age, sex, education and TGM. However, the partial correlation analysis for depressed patient group showed that rumination score was negatively associated with DLPFC volume ($r = -0.31$, $p = 0.015$), but not with PHG ($r = 0.21$, $p = 0.112$), with age, sex, education and TGM as controlling variables.

Mediation analyses, however, revealed that neither the rGMV of DLPFC nor that of PHG had a significant indirect effect on depression via rumination. For detailed information, see online Supplementary material.

Discussion

To the best of our knowledge, this is the first study to investigate the neural correlates of inter-individual differences in rumination which explores whether rumination mediates the relationship between brain structure and self-rating depressed status in healthy individuals and depressive patients. For the healthy individuals, the VBM results show that DLPFC and PHG volumes are significantly positively correlated with individual differences in rumination, and ReHo analysis provided evidence that functional homogeneity of DLPFC was negatively correlated with individual differences in rumination. In addition, both DLPFC and PHG volumes had a significant indirect effect on depression via rumination in healthy individuals. However, for depressive patients, there was a significantly negative correlation between DLPFC volume and rumination. These results indicated that there was a contrary tendency of rGMV variations within DLPFC associated with rumination in healthy individuals and depressive disorders. This interesting finding might provide an early risk biomarker of subtle differences in brain structural alterations associated with depressive rumination indicating when and why healthy

Table 2. Demographic and clinical characteristics of depressive patients and control subjects (dataset 2)

Characteristics	Depressive patients (N = 60)		Control subjects (N = 63)		Analysis	
	Mean	S.D.	Mean	S.D.	<i>t</i>	<i>P</i>
Age (years)	36.07	11.57	32.40	11.95	1.73	0.086
Education (years)	12.13	3.72	12.76	3.33	0.99	0.325
SRRS score	23.07	4.73	18.14	4.35	6.01	0.000
SDS score	61.35	10.54	38.84	7.92	13.43	0.000
HAMD score	23.93	5.32	1.89	1.81	27.71	0.000
BDI score	20.38	8.15	4.21	3.94	13.90	0.000
	<i>N</i>	%	<i>N</i>	%		
Female	43	71.67	32	50.79		
Family history of psychiatric disorder ^a	9	15.00	N.A.	N.A.		
Taking antidepressants ^b	24	40.00	N.A.	N.A.		
Co-morbid anxiety disorder	18	30.00	N.A.	N.A.		

SRRS, Short Ruminative Responses Scale; SDS, Self-rating Depression Scale; HAMD, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; N.A., not applicable.

^a Family history of depressive disorder up to second-degree relatives.

^b The information for two patients was missing.

individuals would develop sustained negative mood which in turn results in depression.

First, we found that increased rGMV in the DLPFC and the PHG may contribute to higher rumination through 'inhibition compensation dysfunction' that is associated with these regions in healthy individuals. There has been evidence that MDD patients compared to healthy subjects showed increased brain activity within cognitive control-related regions (e.g. DLPFC) along with preserved behavioural performance (Harvey *et al.* 2005; Wagner *et al.* 2006; Langenecker *et al.* 2007). Moreover, to behaviourally perform as well as low brooders, healthy individuals with higher brooding over negative information were found to recruit more brain activity in the dorsal pathway when they had to suppress a response to negative information (Vanderhasselt *et al.* 2013), and consequently down-regulated activation of limbic regions which is related to the processing of negative information (Derakshan *et al.* 2009; Vanderhasselt *et al.* 2013). That is to say, in normal individuals with higher rumination, the ACC monitors increased negative self-focused conflicts (e.g. dealing with a job loss, and receiving criticism will elicit thoughts about the causes), and then increased volume of DLPFC was needed to inhibit these increased monitoring conflicts (increased attentional control and cognitive reappraisal) (MacDonald *et al.* 2000; Botvinick *et al.* 2004; Mansouri *et al.* 2007). However, our behavioural data showed that rumination scores correlated positively with self-rating depressed status in these healthy

subjects. Moreover, our study also found that decreased ReHo of the DLPFC was associated with higher rumination during resting state, which might be related to abnormal neural activity of the DLPFC (less efficient inhibitory control). Therefore, we thought that this neural compensation (increased volume of DLPFC) to inhibit a dominant/habitual response to negative information might not be enough to effectively evade negative vicious cycles for higher rumination brooders (De Raedt & Koster, 2010; Vanderhasselt *et al.* 2013).

The present study found that volumes of DLPFC and PHG had an indirect effect on self-rating depressed status in healthy individuals via rumination. Although we cannot determine the direction of causation between rumination, self-rating depressed status and brain structure, it might be hypothesized that higher rumination (which is stable in healthy adults) interacted with increased DLPFC and PHG volume (increased self-focused conflicts and less efficient inhibitory control associated with decreased ReHo of the DLPFC), which in turn develops sustained negative mood, and then enhances depression (self-rating depressed status). By contrast to previous studies by Kühn *et al.* (2012), which found that rumination was negatively correlated with IFG (triangularis), the result of a positive correlation in the present study might be due to the difference in sample size, VBM analysis and culture. In sum, higher rumination associated with increased DLPFC volume (decreased ReHo of the DLPFC) might be qualified as one of behavioural and

Fig. 1 - Colour online, Colour in print

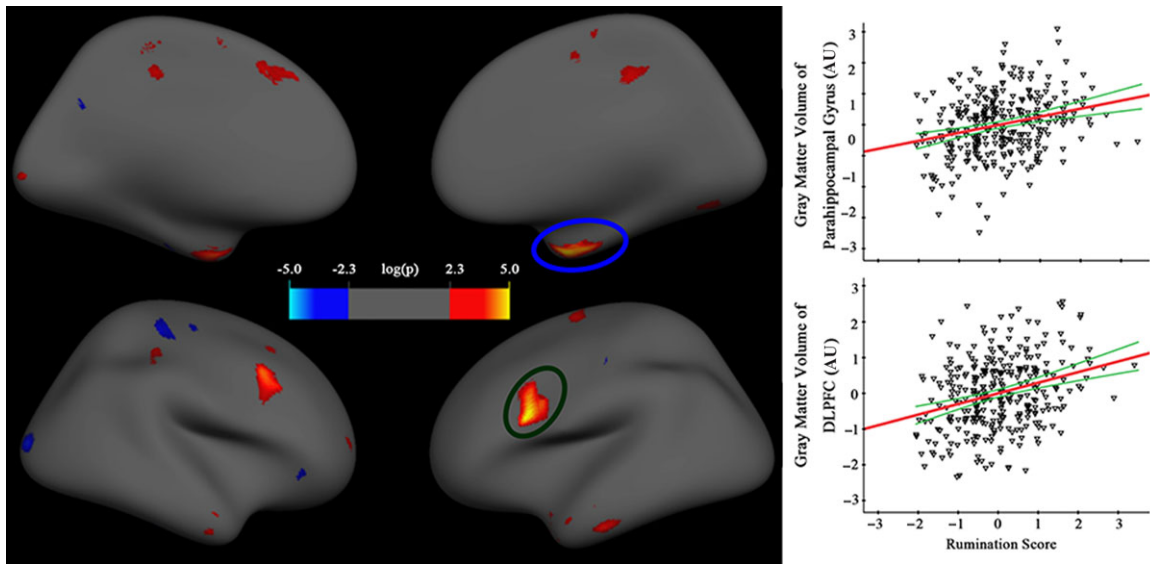


Fig. 1. Regions of grey-matter volume (GMV) significantly correlated with Rumination Scale (dataset 1). The parahippocampal gyrus (blue oval) and dorsolateral prefrontal cortex (green oval) in which variability in GMV exhibited significant positive correlation with rumination score. The significant cluster is shown at $p < 0.01$ for visualization purpose. Scatterplots between rumination score and GMV of parahippocampal gyrus (top right) and DLPFC (bottom right) are shown for illustration purpose only, with age, gender and total GMV as controlling variables. AU, ???????.

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Fig. 2 - Colour online, Colour in print

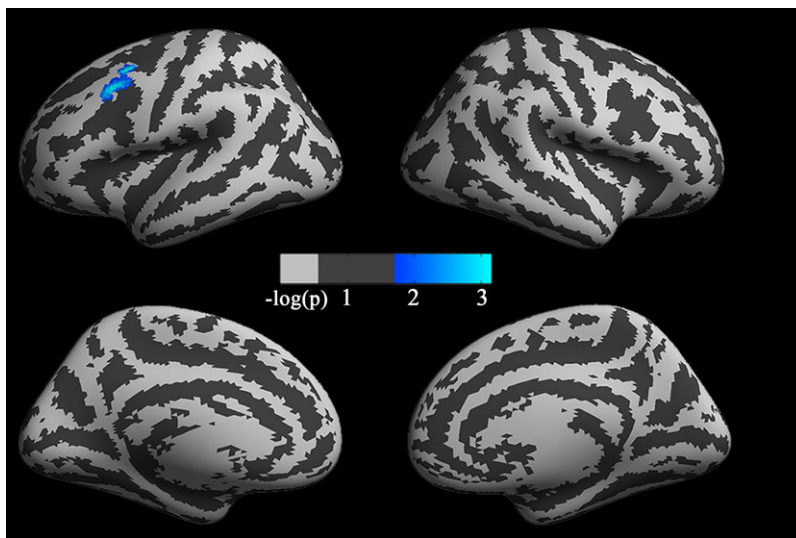


Fig. 2. Rumination was negatively correlated with regional homogeneity of the dorsolateral prefrontal cortex. The significant cluster was shown at cluster level of multiple comparisons with $p < 0.05$.

neuroanatomical predictors of serious self-rating depressed status in healthy individuals.

Taken together, in healthy subjects, the DLPFC volume was significantly positively correlated with individual differences in rumination, while there was a significantly negative correlation between DLPFC volume and rumination in depressive patients. In addition, mediating effects of rumination on the

relationship between DLPFC and depression imply the different potentially influential role of DLPFC towards the occurring depression (increased DLPFC volume in healthy individuals while DLPFC atrophy in depressive disorders with higher rumination). These results indicate that it might not be reasonable to regard healthy individuals as a homogeneous group (Joormann *et al.* 2007; Kuhn *et al.* 2012; Vanderhasselt

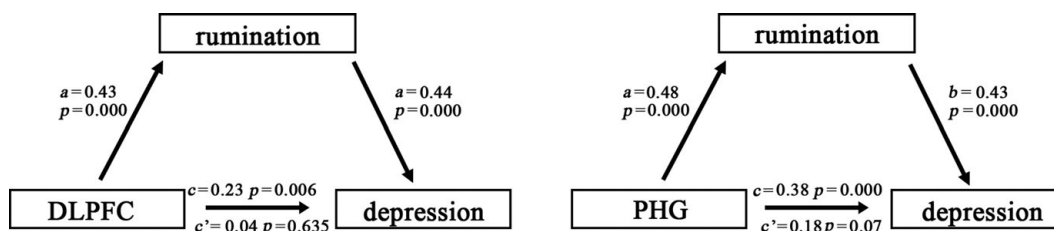


Fig. 3. Mediation effects of rumination on the relationship between dorsolateral prefrontal cortex (DLPFC) and depression (left), and between parahippocampal gyrus (PHG) and depression (right). Severity of depression was measured by the Self-rating Depression Scale.

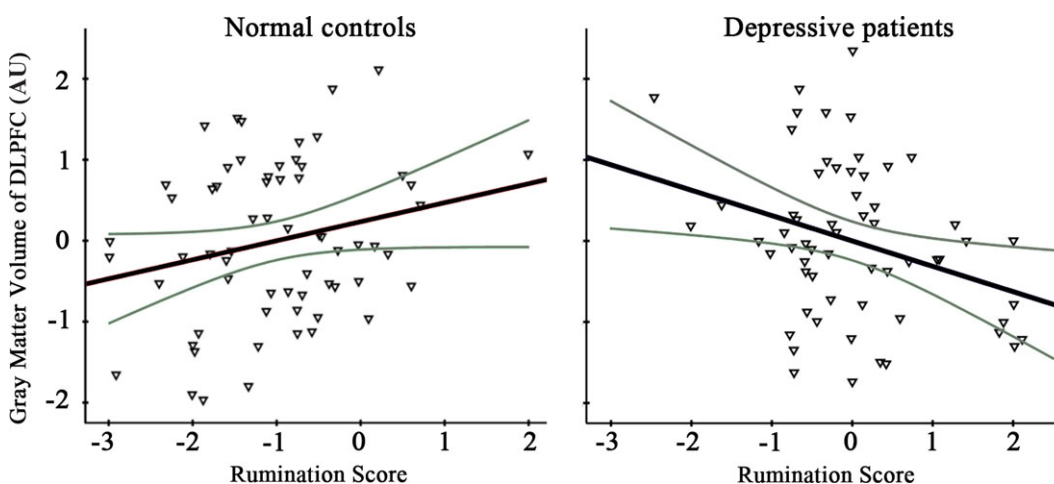


Fig. 4. Scatterplots of the association between score of rumination and volume of dorsolateral prefrontal cortex (DLPFC) in control individuals (left) and depressive patients (right). AU, ???????.

et al. 2013). In our sample of healthy never-depressed individuals, inter-individual differences in rumination revealed that increased DLPFC volume (decreased ReHo of the DLPFC) correlated with rumination, which might be insufficient and inefficient inhibition ('overload state' function of DLPFC) over increased monitoring conflicts, resulting in sustained negative vicious cycles to enhance the individual's depressive rumination. On the contrary, there was a clear association between the DLPFC and hippocampal atrophy and the severity of depressive rumination. The DLPFC atrophy in depressive disorders might reflect an impaired regulatory mechanism ('paralysis state' function of DLPFC). However, the stage at which DLPFC atrophy begins in depressive rumination is still unclear (from 'overload state' to 'paralysis state'). Recently, the incidence of 'minor depression' or 'subclinical depression' has aroused much concern (Hayakawa *et al.* 2013). Therefore, in the future, it is important to explore and compare the brain structural alterations among non-clinical healthy individuals, subclinical depressive patients and clinical depressive patients with higher rumination in order to prevent dynamic effects of

rumination interacting with brain structures on depression.

Conclusion

In the present study, we employed VBM to identify the rGMV correlates of individual ruminative thinking style as measured by the SRRS in healthy individuals and depressive patients. Our results showed that rumination, which correlated with the structure of DLPFC and PHG, could predict self-rating depressed status in healthy individuals and depressive patients. In our sample of healthy never-depressed individuals, increased DLPFC volume (decreased ReHo of the DLPFC) associated with higher rumination might be inefficient inhibition ('overload state' of DLPFC). In our sample of depressive patients, there was a clear association between the DLPFC and PHG atrophy and severity of depressive rumination, and DLPFC atrophy might reflect an impaired regulatory mechanism ('paralysis state' of DLPFC). This interesting finding might provide an early risk biomarker of subtle differences in brain structural alterations associated with

depressive rumination indicating when and why healthy individuals would develop sustained negative mood which in turn enhances depressive symptoms. However, we cannot determine the direction of causation between rumination, depression and DLPFC volume. In the future, the implementation of longitudinal or intervention studies (transcranial direct-current stimulation, transcranial magnetic stimulation or electroconvulsive therapy) may help elucidate the complex relationships between rumination, depression and brain structure.

Supplementary material

For supplementary material accompanying this paper visit <http://dx.doi.org/10.1017/S0033291715000938>.

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Declaration of Interest

None.

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