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

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**Supplemental material**

**Subjects of Dataset 2**

Sixty (16 males and 44 females; mean age = 36.06, SD = 11.60) depressive patients and sixty-three (31 males and 32 females; mean age = 32.40, SD = 11.95) age-matched nonclinical control subjects (Dataset 2) were selected from the same ongoing project, which examine the occurrence and development of depression. All depressive patients were diagnosed according to DSM-IV criteria ([All 1995](#_ENREF_1)) by experienced psychiatrists from The First Affiliated Hospital of Chongqing Medical University. Hamilton Depression Rating Scale (HAM-D) (17 items) ([Hamilton 1960](#_ENREF_5)) was used to rate the depression severity. In this study, inclusion criteria of patients were: 1) no history of major medical or neurological abnormalities (e.g.: head trauma with loss of consciousness, migraine, cyst, or unusually large ventricles); 2) no presence of alcohol or substance abuse; 3) diagnosed as depressive disorder, but not bipolar disorder. Control subjects were recruited through advertisements distributed in residential areas. Inclusion criteria for control subjects were: 1) no history of psychotic or mood disorders in first-degree relatives; 2) no history of medical or neurological conditions; 3) no current or lifetime Axis I psychiatric disorder and 4) no gross anatomical abnormalities or extraordinary motion artifacts.

**MRI Acquisition (Dataset 1 and Dataset 2)**

All MRI data acquisition was conducted with a 3.0-T Siemens Trio MRI scanner (Siemens Medical, Germany). MRI structural images were acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (repetition time [TR] = 1900ms; echo time [TE] = 2.52ms; flip angle = 9o; field of view [FOV] = 256 mm ×256 mm; slices = 176; slice thickness = 1.0 mm).

In addition, thirty-two transaxial gradient-echo images (TR = 2000 ms; TE = 30 ms; flip angle = 90°, slice thickness = 3.0 mm, slice gap = 1.0 mm, matrix = 64 × 64, FOV = 220 mm × 220 mm) were acquired using an echo planar sequence. For this scan, a total of 242 volumes were acquired while subjects were resting. Before scanning, the subject was positioned carefully in the coil with a comfortable support and fitted with soft earplugs to limit the effects of noise on brain activity. During scanning, subjects were instructed to relax with their eyes closed, remain awake, lie still, and try not to think of anything, as has been done similarly ([Damoiseaux *et al.* 2006](#_ENREF_4); [Takeuchi *et al.* 2012](#_ENREF_7)) . After scanning, all subjects were requested to confirm that they had not fallen asleep.

**Regional** **homogeneity (ReHo) Preprocessing**

In order to verify the reliability of the structural result, ReHo analysis was performed with the Connectome Computation System (CCS: http://lfcd.psych.ac.cn/ccs.html). The functional images were corrected for slice timing, motion correction, normalization and realigned to individual’s anatomical T1 image. In order to obtain more accurate results for functional data, registration was conducted by registering functional images to MNI152 standard template, using boundary-based co-registration (bbregister) and FNIRT. Then several sources of spurious variances were regressed out (i) twenty-four motion parameters, (ii) white matter and cerebrospinal fluid mean signals which were derived from the WM/CSF masks output by the segmentation routine of FreeSurfer. Finally, band-pass temporal filtering (0.01–0.10 Hz) was used to remove magnetic field drifts of the scanner and to minimize physiologic noise of high-frequency components.

**Depression assessment** (Dataset 1 and Dataset 2)

Self-Rating Depression Scale (SDS) was used to quantify the depressed status of all participants ([Zung *et al.* 1965](#_ENREF_8)). It is a widely used self-rating depression scale and consists of 20 items. All participants selected one out of four differently labeled 4-point Likert-type response scales (1 = a little of the time, 4 = most of the time) according to their condition of past week. SDS of Chinese version had a satisfactory reliability and validity ([Biggs *et al.* 1978](#_ENREF_3); [Zung *et al.* 1965](#_ENREF_8)).

 Further, Beck Depression Inventory (BDI) of Chinese version was used to quantify the depressed status of all participants ([Beck *et al.* 1988](#_ENREF_2); [Shek 1990](#_ENREF_6)). This inventory consists of 21 items. Participants were asked to select one out of four options according to their condition of past week. The Chinese-versioned BDI had a satisfactory reliability and validity ([Shek 1990](#_ENREF_6)).

**Mediation analyses result of Dataset 1**

Mediation analyses first revealed that the rGMV of the DLPFC had a significant indirect effect on depression via rumination (model summary for DV Model: R2 = 0.22, F= 16.58, P<104). Greater rGMV of the DLPFC was associated with higher levels of rumination [a paths: coeff = 0.43, standard error (s.e.) = 0.08, t (306) = 5.41, P< 104]. Higher levels of rumination were also associated with depression [b paths: coeff = 0.44, s.e. = 0.05, t (306) = 8.27, P<104]. Moreover, the direct pathway between rGMV of the DLPFC and depression became non-significant [c’ paths: coeff = 0.04, s.e. = 0.08, t (306) = 0.48, P= 0.635] when rumination mediated these two factors [c paths: coeff = 0.23, s.e. = 0.08, t (306) = 2.78, P= 0.006].

Moreover, mediation analyses revealed that the rGMV of the DLPFC had a significant indirect effect on depression via each component of ruminative score. First, sensitive rumination mediate the relationship between DLPFC and depression (model summary for DV Model: R2 = 0.21, F= 15.82, P<104). Greater rGMV of the DLPFC was associated with higher levels of sensitive rumination [a paths: coeff = 0.98, standard error (s.e.) = 0.19, t (306) = 5.26, P< 104]. Higher levels of sensitive rumination were also associated with depression [b paths: coeff = 0.18, s.e. = 0.02, t (306) = 8.05, P<104]. Moreover, the direct pathway between rGMV of the DLPFC and depression became non-significant [c’ paths: coeff = 0.05, s.e. = 0.08, t (306) = 0.59, P= 0.553] when sensitive rumination mediated these two factors [c paths: coeff = 0.23, s.e. = 0.08, t (306) = 2.78, P= 0.006]. Then, assessment rumination mediate the relationship between DLPFC and depression (model summary for DV Model: R2 = 0.14, F= 9.74, P<104). Greater rGMV of the DLPFC was associated with higher levels of assessment rumination [a paths: coeff = 1.03, standard error (s.e.) = 0.23, t (306) = 4.52, P< 104]. Higher levels of assessment rumination were also associated with depression [b paths: coeff = 0.12, s.e. = 0.02, t (306) = 5.96, P<104]. Moreover, the direct pathway between rGMV of the DLPFC and depression became non-significant [c’ paths: coeff = 0.11, s.e. = 0.08, t (306) = 1.34, P= 0.182] when assessment rumination mediated these two factors [c paths: coeff = 0.23, s.e. = 0.08, t (306) = 2.78, P= 0.006].

In addition, mediation analyses also revealed that the rGMV of the parahippocampal gyrus had a significant indirect effect on depression via rumination [model summary for DV Model: R2 = 0.22, F= 17.35, P<104). There was association between greater rGMV of the parahippocampal gyrus and higher levels of rumination [a paths: coeff = 0.47, s.e. = 0.10, t (306) = 4.66, P< 104], and between higher levels of rumination and depression [b paths: coeff = 0.43, s.e. = 0.05, t (306) = 8.09, P<104]. More importantly, there was marginal significance in the direct pathway between rGMV of the parahippocampal gyrus and depression [c’ paths: coeff = 0.17, s.e. = 0.10, t (306) = 1.80, P= 0.07] when rumination mediated these two factors [c paths: coeff = 0.38, s.e. = 0.10, t (306) =3.66, P= 0.000].

**Mediation analyses result of Dataset 2**

Mediation analyses revealed that neither the rGMV of the DLPFC nor that of parahippocampal gyrus had a significant indirect effect on depression via rumination (model summary for DV Model: R2 = 0.25, F= 2.96, P = 0.015 ; model summary for DV Model: R2 = 0.25,F= 2.93, P=0.015). First, when rGMV of DLPFC was selected as the proposed mediator, lower rGMV of the DLPFC was associated with higher levels of rumination [a paths: coeff = -0.33, s.e. = 0.14,t (63) = -2.42, P=0.019]. Higher levels of rumination were also associated with depression [b paths: coeff = 0.44, s.e. = 0.13,t (60) = 3.33, P=0.001 ]. However, the direct pathway between rGMV of the DLPFC and depression were non-significant [c’ paths: coeff = 0.09, s.e. = 0.14, t (60) = 0.66, P= 0.509] when rumination mediated these two factors [c paths: coeff = -0.05, s.e. = 0.14, t (60) = -0.37, P= 0.716 ]. Morever, in mediation analysis with parahippocampal gyrus as the proposed mediator, rGMV of the parahippocampal gyrus was not associated with higher levels of rumination [a paths: coeff = 0.27, s.e. = 0.17,t (60) = -2.42, P=0.019] although higher levels of rumination were also associated with depression [b paths: coeff = 0.43, s.e. = 0.13,t (60) = 3.33, P=0.002 ]. However, the direct pathway between rGMV of the DLPFC and depression were non-significant [c’ paths: coeff = -0.09, s.e. = 0.17, t (60) = -0.55, P= 0.584] when rumination mediated these two factors [c paths: coeff = 0.02, s.e. = 0.18, t (60) = 0.13, P= 0.897 ].

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