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Does resting-state connectivity reflect depressive rumination? A tale of two analyses

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ABSTRACT

Major Depressive Disorder (MDD) is characterized by rumination. Prior research suggests that resting-state brain activation reflects rumination when depressed individuals are not task engaged. However, no study has directly tested this. Here we investigated whether resting-state epochs differ from induced ruminative states for healthy and depressed individuals. Most previous research on resting-state networks comes from seed-based analyses with the posterior cingulate cortex (PCC). By contrast, we examined resting state connectivity by using the complete multivariate connectivity profile (i.e., connections across all brain nodes) and by comparing these results to seeded analyses. We find that unconstrained resting-state intervals differ from active rumination states in strength of connectivity and that overall connectivity was higher for healthy vs. depressed individuals. Relationships between connectivity and subjective mood (i.e., behavior) were strongly observed during induced rumination epochs. Furthermore, connectivity patterns that related to subjective mood were strikingly different for MDD and healthy control (HC) groups suggesting different mood regulation mechanisms.

Introduction

Many researchers have found differences in brain connectivity during unconstrained "resting-state" intervals between healthy persons and individuals diagnosed with Major Depressive Disorder (Berman et al., 2011; Bohr et al., 2012; Broyd et al., 2009; Greicius et al., 2007; Sheline et al., 2010; Zeng et al., 2012; Zhang et al., 2011). These differences in brain connectivity are often interpreted as being a neural mechanism reflecting depressive rumination (Berman et al., 2011; Greicius et al., 2007; Hamilton et al., 2011; Whitfield-Gabrieli and Ford, 2012), a negative repetitive thought process that characterizes depression (Nolen-Hoeksema et al., 2008; Treynor et al., 2003). No research, however, has directly tested whether the thinking during "rest" is the same as that of directly induced rumination for participants with depression compared to non-depressed participants. The first goal of the present study was to investigate whether patterns of functional connectivity during unconstrained resting-state epochs differed from active rumination in depressed and healthy individuals. Uncovering this would greatly aid our understanding of the neural processes associated with depressive rumination. To do so, we designed an experimental paradigm to assess baseline resting-states and compared those intervals to induced ruminative states and resting-states that occurred after induced rumination. The baseline resting-states were first tested so as not to be contaminated by our induced-rumination procedure.

The second goal of the present study was to investigate whether different results would be uncovered from seed-based analyses compared to analyses of the full connectivity profile (i.e., how all brain areas are connected to all other areas) for healthy controls (HCs) and individuals diagnosed with depression. There has been some debate in the literature where many studies report hyper-connectivity or hyper-activation in the default-mode network in MDD (Berman et al., 2011; Broyd et al., 2009; Greicius et al., 2007; Sheline et al., 2010), whereas other studies find decreased connectivity in MDD in a few different resting-state networks (Veer et al., 2010). Recent studies have found that the full connectivity profile was highly sensitive in discriminating healthy vs. depressed individuals at rest (Veer et al., 2010; Zeng et al., 2012). We sought to investigate whether hyper- or hypo-connectivity results depended on whether analyses were based on singular brain networks or all brain networks in their totality. To this end, we implemented a seed-based analysis with the Posterior Cingulate Cortex (PCC) to focus our analysis on a single network; the "default-mode" network and compared those results to an analysis where we explored connectivity between all brain nodes.

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To identify global patterns of functional connectivity and how those patterns differed across groups and cognitive states (resting states and induced rumination states) we implemented a partial-least squares analysis (PLS; Krishnan et al., 2011; McIntosh and Lobaugh, 2004; McIntosh and Misic, 2013). As a multivariate statistical framework, PLS determines the combination of groups and experimental conditions that is optimally related to a spatiotemporal pattern of neural activity. We used PLS in a novel way, by entering functional connections between all possible pairs of brain regions as dependent variables, rather than activation contrasts or singular seed correlations, which are typically used. For the present study, this application of PLS offered a few important advantages. First, we were able to capture patterns of functional connections that covary together. Thus, these patterns are naturally interpretable as coherent functional networks. Second, PLS offers a framework to examine how these changes in functional connectivity were related to changes in subjective mood, which is rarely performed when examining functional connectivity. Lastly, we were able to investigate the dominant functional connectivity patterns without having to specify a priori hypotheses about the differentiation of groups and experimental conditions. Thus, we used the analysis to determine the similarities and differences between resting-states and induced rumination in a completely data-driven way.

In summary, we set out to achieve two goals in this study. The first was to examine whether resting-state epochs differed from induced rumination states for participants diagnosed with major depression compared to non-depressed controls. We assessed these potential differences both behaviorally and with multivariate measures of functional connectivity. The second goal of the study was to assess how different measures of functional connectivity, i.e. seed-based vs. global connectivity, could help to distinguish the groups during rest vs. induced rumination.

Materials and methods

Note: These fMRI parameters, task parameters and analysis parameters are similar to those from Misic et al. (in press).

Participants

Seventeen participants diagnosed with clinical depression [mean age = 26.6 years, SD = 5.94; 12 female, mean Beck Depressive Inventory (Beck et al., 1996) (BDI) = 29.8] and seventeen non-depressed controls (mean age = 24.2 years, SD = 5.95; 12 female, mean BDI = 1.4) participated in our study. Participants' diagnosis of MDD vs. a non-diagnosis was determined by a trained clinician administering the Structured Clinical Interview Diagnostic (SCID) IV (Williams et al., 1992). Five MDD participants were taking antidepressants during scanning. These medications included: Zoloft, Prozac, Levothyroxine, Renlafaxin, Trazadone, Effexor and Wellbutrin. Three of the five participants that were on medications were on more than one medication. In addition, 14 of the 17 MDD participants were suffering a recurrent episode. Seven of the 17 MDD participants had a co-morbid diagnosis of anxiety, panic or social phobia, one participant had co-morbid diagnosis of an eating disorder, one participant had co-morbid diagnosis of PTSD and one participant had co-morbid diagnosis of schizophrenia. One MDD participant was excluded from the fMRI analysis because of poor segmented normalization (i.e., part of cortex was segmented off).

The Institutional Review Board of the University of Michigan approved this study and all participants provided informed consent as administered by the Institutional Review Board of the University of Michigan. Participants had to refrain from marijuana use for at least 6 months prior to participation and had to refrain from alcohol consumption at least 24 h prior to participation. Participants were also excluded if they had every used illicit drugs (i.e., cocaine, LSD). Participants were compensated $25/h for their participation.

fMRI acquisition and preprocessing parameters

Images were acquired on a GE Signa 3-Tesla scanner equipped with a standard quadrature head coil. Functional T2* weighted images were acquired using a spiral sequence with 40 contiguous slices with 3.44 × 3.44 × 3 mm voxels (repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; flip angle = 90°; field of view (FOV) = 22 cm). A T1-weighted gradient echo anatomical overlay was acquired using the same FOV and slices (TR = 250 ms, TE = 5.7 ms, flip angle = 90°). Additionally, a 124-slice high-resolution T1-weighted anatomical image was collected using spoiled-gradient-recalled acquisition (SPGR) in steady-state imaging (TR = 9 ms, TE = 1.8 ms, flip angle = 15°, FOV = 25–26 cm, slice thickness = 1.2 mm).

Functional images were corrected for differences in slice timing using 4-point sinc-interpolation (Oppenheim et al., 1999) and were corrected for head movement using MCFLIRT (Jenkinson et al., 2002). To reduce noise from spike artifacts, the data were winsorized prior to normalization (Lazar et al., 2001) by exploring time courses for each voxel and finding values that were 3 standard deviations (SDs) away from the mean of that voxel's time course. Spikes that were above 3 SDs from the mean were made equal to the mean + 3 SDs and spikes that were 3 SDs below the mean were made equal to the mean − 3 SDs.

Each SPGR anatomical image was corrected for signal in-homogeneity and skull-stripped using FSL's Brain Extraction Tool (Smith et al., 2004). These images were then segmented with SPM5 (Wellcome Department of Cognitive Neurology, London) into gray matter, white matter and cerebrospinal fluid and normalization parameters for warping into MNI space were recorded. These normalization parameters were applied to the functional images maintaining their original 3.44 × 3.44 × 3 mm resolution, and then the functional images were spatially smoothed with a Gaussian kernel of 8 mm.

To correct for physiological artifacts all of our functional data underwent PHYCAA correction, which removes some known sources of physiological noise from the data (Churchill et al., 2012). This model estimates physiological noise components that originate from consistent brain regions, and have strong temporal autocorrelations. PHYCAA controls for both global sources of noise present in brain tissue (e.g. gray and white matters), and noise that is concentrated in the ventricles and major blood vessels (Churchill et al., 2012). This provides a more conservative approach to removing global noise in the brain, unlike standard mean regression (Fox et al., 2009), which may have a partly neuronal basis (Schölvinck, et al., 2010) and can distort connectivity patterns (Saad et al., 2012) particularly when comparing groups (Gotts et al., 2013). Lastly, corrections based on physiological models have been previously shown to reduce global confounds while simultaneously preserving functional connectivity relationships (Chang and Glover, 2009).

Furthermore, 24 motion parameters were calculated, which included the linear, squared, derivative, and squared derivative of the six rigid-body movement parameters (Lund et al., 2005). A principal component analysis was performed on these 24 motion parameters and only the first principal component, which accounted for nearly 90% of the motion variance, was covaried out from each voxel's time course to remove any signal that could be attributed to motion. Lastly, functional images were parceled into 116 different ROIs based on the AAL template for analysis.

Task parameters

Participants initially performed two resting-state scans back-to-back that were 8 min in length. Participants were instructed to look at a fixation cross at the center of the screen and were told not to think about anything in particular (i.e., they could think about whatever they wanted to). After acquiring anatomical images of the brain, participants were then taken out of the scanner and were asked to generate four negative autobiographical memories. In order to facilitate the