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Rumination in bipolar disorder associated with brain network and behavioural measures of inhibitory executive control

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Original Article

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Abstract

Objective: Rumination is a passive form of negative self-focused cognition that predicts depressive episodes for individuals with bipolar disorder (BD). Individuals with BD also have impaired inhibitory executive control; rumination in BD may therefore reflect executive dysfunction. We investigated the relationship between a neural measure of executive functioning (functional connectivity between the frontoparietal control network [FPCN] and the default mode network [DMN] during an effortful task), behavioural measures of executive functioning (the Behavior Rating Inventory of Executive Function) and rumination (the Ruminative Responses Scale). *Methods:* Fifteen individuals with BD and fifteen healthy controls underwent MRI scans during mental distraction. Using CONN toolbox, between-network FPCN-DMN connectivity values were calculated. We conducted Pearson's *r* bivariate correlations between connectivity values, BRIEF and RRS scores. *Results:* RRS scores were positively correlated with BRIEF Behavioral Regulation Index (BRI) scores. In individuals with BD, there was a positive correlation between FPCN-DMN functional connectivity during distraction and BRIEF BRI scores. FPCN-DMN functional connectivity was also positively correlated with RRS ruminative brooding scores. Healthy controls did not show significant correlations between these behavioural and neural measures of executive functioning and rumination. *Conclusion:* For individuals with BD, the greater the tendency to ruminate and the higher the executive dysfunction, the stronger the connectivity between an executive control network and a network involved in rumination during an unrelated cognitive task. This could reflect continual attempts to inhibit ruminative thinking and shift back to the distraction task. Therefore, engagement in rumination may reflect failed inhibitory executive control.

Significant outcomes

- A neural measure of executive functioning, functional connectivity between the FPCN and DMN during a distraction task was significantly correlated with a behavioural measure of rumination only in individuals with BD, not healthy controls.
- Since rumination can predict future depressive episodes, targeting executive functioning and/or FPCN-DMN connectivity could decrease the tendency to ruminate, and reduce the risk of future depressive episodes.

Limitations

- This study had a small sample size of BD individuals ($n = 15$) and healthy controls ($n = 15$).
- Behavioural tasks assessing inhibitory executive functioning were not included, only self-report measures.
- Executive functioning was assessed as a general trait variable in BD individuals, who were euthymic, and thus does not have the sensitivity to distinguish between impairments in executive functioning outside of mood episodes versus during mood episodes.

Introduction

When something goes wrong, or we find ourselves in an unpleasant circumstance, most of us tend to think about the actions we took and choices we made that led to our current situation in the hopes of alleviating our current circumstances and possibly preventing such outcomes in the future. Not surprisingly, patients with bipolar disorder (BD), when depressed, do so as well,

except that their self-reflection often takes a negative, persistent, sometimes all-encompassing form, defined as rumination, a vicious cycle of going over past errors and blaming themselves for their current distress. The tendency to engage in negative rumination can predict the onset or relapse of depressive episodes (Nolen-Hoeksema, 2000).

This raises the question of why individuals get stuck in the cycle of this kind of thinking. One possibility is the inability to inhibit the processes set in motion. Indeed, individuals with a tendency to engage in negative rumination have been found to exhibit perseverative errors (Davis and Nolen-Hoeksema, 2000) and failures to inhibit task demands from a previous task (Whitmer and Banich, 2007). Additionally, patients with Major Depressive Disorder, who underwent a rumination induction, showed failures to inhibit on a random number generation task (Watkins and Brown, 2002). Individuals with BD have been found to have impaired executive dysfunction, particularly inhibitory executive control (e.g., Larson *et al.*, 2005; Cotrena *et al.*, 2020), and so the tendency to ruminate in individuals with BD in response to depressed mood may reflect impaired executive functioning (Ghaznavi and Deckersbach, 2012).

In the brain, executive control is regulated through the relationship between the frontoparietal control network (FPCN) and the default mode network (DMN; Fox *et al.*, 2005; Spreng *et al.*, 2010). The FPCN includes the dorsolateral prefrontal cortex and the dorsal anterior cingulate cortex, whereas the DMN includes the posterior cingulate cortex, medial prefrontal cortex, and inferior parietal lobule. The DMN is a network that is active during internally focused tasks such as self-referential cognition (e.g., Buckner *et al.*, 2008; Qin and Northoff, 2011). Activation in specific DMN regions is associated with both positive and negative rumination in individuals with BD (Ghaznavi *et al.*, 2023). The FPCN is involved in overall cognitive control and may shift the focus of attention (i.e. modulate DMN activity) when engaging in specific goal-related behaviour and inhibiting irrelevant information (Spreng *et al.*, 2010). Therefore, the relationship between the FPCN and DMN is crucial when shifting between internal and external attention demands, which may be impaired in those who engage in excessive internal self-focus, i.e. rumination.

We investigated the relationship between rumination and executive functioning using behavioural and neural measures in euthymic individuals with BD and healthy controls (HC). By selecting patients with BD who were euthymic, we could eliminate the possible confounding effects of mood states on executive dysfunction. Specifically, we investigated whether the tendency to ruminate, measured with the Ruminative Responses Scale (RRS) of the Response Styles Questionnaire (RSQ; Nolen-Hoeksema and Morrow, 1991), is correlated with inhibitory executive functioning, measured with the Behavior Rating Inventory of Executive Function (BRIEF-A; Gioia *et al.*, 2000). We hypothesised that the tendency to ruminate would be positively correlated with the Behavioral Regulation Index subscale of the BRIEF consistent with the tendency to ruminate reflecting difficulty with inhibitory executive function in individuals with BD compared to HC. We also examined whether functional connectivity in brain networks implicated in executive functioning during a task requiring external focus, 'mental distraction' (i.e. periods requiring executive control to focus externally as opposed to internally) in individuals with BD is associated with the tendency to ruminate. Specifically, we hypothesised that FPCN-DMN functional connectivity during distraction would be positively correlated with the tendency to ruminate in individuals with BD compared to HC. We also hypothesised that functional connectivity between the FPCN and DMN during mental distraction would be positively correlated with scores on the BRIEF subscale, reflecting the greater effort necessary to shift, inhibit, and regulate rumination (the Behavioral Regulation Index; described in further detail in the Methods section) in individuals with BD compared to HC.

Materials and methods

Sample

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The Mass General Brigham Human Research Committee approved this research study. Individuals with DSM-V Bipolar Disorder (BD; $n = 15$, 8 female) were recruited from the Dauten Family Center for Bipolar Treatment Innovation at Massachusetts General Hospital. The BD group had mean Young Mania Rating Scale (YMRS; Young *et al.*, 1978) scores = 1.57 ($SD = 1.99$) and mean Hamilton Depression Scale (HAM-D; Hamilton, 1960) scores = 3.83 ($SD = 3.79$). Healthy controls ($n = 15$, 9 female) were also recruited; a trained clinician administered the Mini International Neuropsychiatric Interview (MINI; Sheehan *et al.*, 1998) to confirm group membership. The HC and BP group did not significantly differ in age (BD $M = 36.07$, $SD = 10.45$; HC $M = 33.33$, $SD = 10.74$; $t(28) = -0.71$, $p = 0.49$), years of education (BD $M = 17.75$ years, $SD = 1.67$ years; HC $M = 16.58$ years, $SD = 2.51$ years; $t(28) = 2.67$, $p = 0.75$), or scores on the Wechsler Test of Adult Reading (Wechsler, 2001) (BD $M = 116.40$, $SD = 8.28$; HC $M = 116.80$, $SD = 13.78$, $t(28) = 0.096$, $p = 0.92$), a measure of intellectual functioning. After written informed consent, participants completed the questionnaires and MRI scans (described below).

Questionnaires

Behaviour Rating Inventory of Executive Function (BRIEF)

The Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A; Gioia *et al.*, 2000) is a 75-item self-report measure of executive dysfunction. Participants were asked to rate the frequency (never, sometimes, or often) with which they engage in specific behaviours or thoughts. It consisted of two indices, the Behavioral Regulation Index (BRI) and the Metacognition Index (MI), as well as an overall score, the Global Executive Composite. The BRI is a sum of scores on the subscales inhibit (e.g. 'I tap my fingers or bounce my legs'), shift (e.g. 'I have trouble changing from one activity or task to another'), emotional control (e.g., 'I have angry outbursts'), and self-monitor (e.g. 'I don't notice when I cause others to feel bad or get mad until it is too late'). The MI is a sum of scores on the subscales initiate ('I need to be reminded to begin a task even when I am willing'), working memory (e.g. 'I have trouble concentrating on tasks [such as chores, reading, or work]'), plan/organise (e.g. 'I get overwhelmed by large tasks'), task monitor (e.g. 'I make careless errors when completing tasks'), and organisation of materials (e.g. 'I am disorganised'). Raw scores were converted to *T*-scores based on age-normed data. Higher scales signify higher levels of executive dysfunction. The BRIEF has shown high internal consistency (Cronbach's $\alpha = 0.96$) and convergent validity (Ciszewski *et al.*, 2014). Since we hypothesised that individuals with BD had to inhibit ruminative thinking to shift to an effortful mental task, and the BRI measures these specific constructs, we focused on the BRI scores in our analyses.

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Ruminative Responses Scale

The Ruminative Responses Scale (RRS) of the Response Styles Questionnaire (RSQ; Nolen-Hoeksema and Morrow, 1991) is a 22-item self-report measure that assesses the frequency of ruminative thinking. Participants were asked to rate how often (almost never, sometimes, often, and almost always) they endorse a specific statement when they are feeling sad, down, or depressed. This scale has three different subscales: brooding (e.g. '[how often do you] think "why do I have problems other people don't have?"'), depression (e.g. '[how often do you] think about how sad you feel'), and self-reflection (e.g. '[how often do you] go someplace alone to think about your feelings'; Treynor *et al.*, 2003). This measure has high internal consistency, good test-retest reliability and has acceptable convergent and predictive validity (Butler and Nolen-Hoeksema, 1994).

MRI scans

Participants underwent MRI scans with a 1.5 T Siemens Skyra MRI scanner at Massachusetts General Hospital's Athinoula A. Martinos Center for Biomedical Imaging. A high-resolution 3D MPRAGE sequence (TR/flip angle = 2530 ms/7°), with an in-plane resolution and slice thickness of 1 mm, was collected to be used for co-registration with fMRI data. BOLD images were acquired (TR/TE/flip angle = 3000 ms/30 ms/85°) with an in-plane resolution and slice thickness of 3 mm.

During fMRI scanning, participants completed a mental distraction task. They were presented with 10 different phrases and asked to think about and imagine the content of the phrases for 30 s blocks. These phrases were neutral and not related to the self (i.e. externally focused; e.g. 'Imagine the color of leaves in the fall'). We investigated functional connectivity between the FPCN and DMN during this 5 min task (described in further detail below).

fMRI data analyses

Functional data were preprocessed using SPM8 software (Wellcome Department of Cognitive Neurology, London, UK). For each individual subject, fMRI images were realigned to a reference image, coregistered, normalised to the standardisd normalised space established by the Montreal Neurological Institute (MNI; http://www.bic.mni.mcgill.ca), and smoothed/convolved with a three-dimensional Gaussian filter of 6 mm full-width at half maximum (FWHM). Images from the different scan sequences were realigned to each other. Segmentation was performed to produce grey matter, white matter, and cerebrospinal images for each subject's structural scans.

These preprocessed images were entered into CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012; www.nitrc.org/projects/conn). BOLD signal from white matter and cerebrospinal fluid and realignment parameters were identified as confounders and their effects were removed. A set of ROIs were defined and mapped to the FPCN and DMN (Yeo *et al.*, 2011). Fisher's *z*-transformed values were extracted, and FPCN-DMN connectivity strength values were then calculated for each individual subject.

Behavioural data analyses

All behavioural data analyses were conducted in SPSS Version 24. Independent samples t-tests were run to identify potential group differences in age, years of education, and WTAR scores. Generalised linear models were run to determine the effect of group on BRIEF and RRS scores. We ran Pearson's *r* bivariate correlations between the connectivity strength values and our behavioural measures.

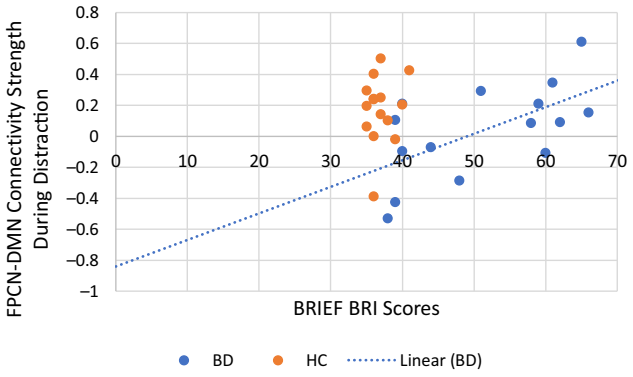

Figure 1. Functional connectivity between the frontoparietal control network (FPCN) and default mode network (DMN) during distraction was significantly correlated with Behavior Rating Inventory of Executive Function (BRIEF) Behavioral Regulation Index (BRI) scores (Pearson's $r(15) = 0.608$, $p = 0.016$) in individuals with bipolar disorder (BD), not healthy controls (HC).

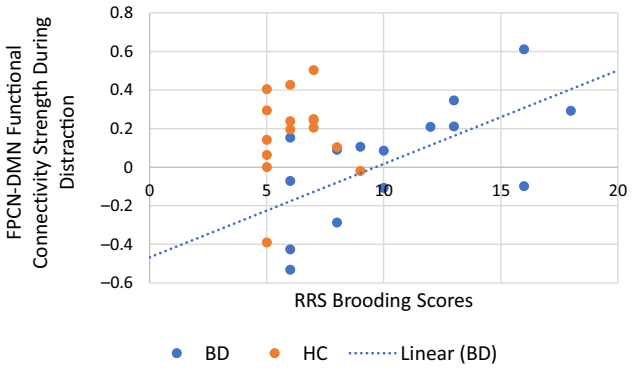

Figure 2. Functional connectivity between the frontoparietal control network (FPCN) and default mode network (DMN) during distraction was also correlated with scores on the Ruminative Responses Scale (RRS) ruminative brooding subscale (Pearson's $r(15) = 0.649$, $p = 0.009$) in individuals with bipolar disorder (BD), not healthy controls (HC).

Results

Individuals with BD had significantly higher RRS ruminative brooding ($F(1,30) = 15.284$, $p = 0.001$) and depressive rumination ($F(1,30) = 46.032$, $p < 0.001$) subscale scores than healthy controls. There was a group difference at a trending level of significance in the RRS reflective rumination subscale ($F(1,30) = 4.087$, $p = 0.053$). Individuals with BD also had higher BRIEF BRI scores compared to healthy controls ($F(1,30) = 26.580$, $p < 0.001$). RRS total scores were significantly positively correlated with the BRIEF BRI (Pearson's $r(30) = 0.506$, $p = 0.004$).

In individuals with BD, functional connectivity strength between the FPCN and DMN during distraction was significantly correlated with the BRIEF BRI (Pearson's $r(15) = 0.608$, $p = 0.016$; Fig. 1). This was not the case for the healthy controls (Pearson's $r(15) = 0.173$, $p = 0.538$).

Connectivity between the DMN and FPCN was also specifically correlated with RRS ruminative brooding (Pearson's $r(15) = 0.649$, $p = 0.009$) in individuals with BD (Fig. 2). Ruminative brooding

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was not significantly correlated with FPCN-DMN connectivity in healthy controls (Pearson's $r(15) = 0.079$, $p = 0.781$).

Discussion

In this study, we sought to investigate whether rumination in BD reflects inhibitory executive dysfunction. First, we found that individuals with BD had a tendency to engage in negative forms of rumination as measured by the RRS, relative to HC. Second, individuals with BD had higher scores on a self-report behavioural measure of executive dysfunction, the BRIEF BRI, which is specific for inhibitory executive dysfunction, consistent with previous studies (Larson *et al.*, 2005; Cotrena *et al.*, 2020). Third, we found that scores on the BRIEF BRI were correlated with ruminative brooding (namely passive and perseverative self-focus). That is, the greater the level of executive dysfunction, the greater the tendency to ruminate with a negative focus in a perseverative manner. Fourth, we found that functional connectivity between two brain networks involved in dynamic executive control (i.e. the FPCN and DMN) during an effortful distraction task, requiring inhibiting negative self-focus, was significantly correlated with ruminative brooding in individuals with BD, but not in HC. The greater the level of ruminative brooding, the greater the connectivity between the FPCN and DMN during distraction, possibly reflecting greater need for FPCN inhibition of DMN activity underlying self-focus. Thus, we have behavioural and neural evidence which suggests that rumination reflects inhibitory executive dysfunction in individuals with BD.

Our finding with FPCN and DMN resting state functional connectivity builds upon previous studies investigating the relationship between rumination and specific DMN regions at rest in individuals with MDD (Berman *et al.*, 2011; Zhu *et al.*, 2017), by showing that DMN connectivity across the whole network, and its interaction with the FPCN, is correlated with rumination, especially during a task requiring attention to be directed externally, and not on self. We have also extended the results from a previous study showing that DMN activity during rest, relative to activity in task-positive networks, was positively correlated with depressive rumination and negatively correlated with reflective rumination in individuals with unipolar depression (Hamilton *et al.*, 2011). Our study shows that there is a relationship between rumination and DMN-executive control network connectivity in individuals with bipolar depression.

During distraction, there was a significant positive correlation between FPCN-DMN functional connectivity and BRIEF BRI scores in individuals with BD; the greater the executive dysfunction, the greater the between FPCN-DMN connectivity. Importantly, healthy controls did not show this relationship. This BD-specific finding may represent the increased effort with which individuals with BD are engaging these networks in order to perform the distraction task. This increased effort may reflect attempts to inhibit ruminative thinking and shift back or maintain focus on the distraction task. This is consistent with a previous study showing that increases in attentional awareness after mindfulness-based cognitive therapy in individuals with BD was associated with increased connectivity between regions of the DMN and task-positive networks such as FPCN (i.e. brain networks active during effortful tasks; Chou *et al.*, 2022).

Limitations of this study include not having a measure of successful task engagement (i.e. the degree to which participants were engaged in the distraction task). The sample size was also small, and we did not include tasks assessing inhibitory executive functioning. Future studies could include tests of executive functioning in larger samples as well as investigate whether interventions specifically targeting rumination (e.g. Rumination Focused Cognitive Behavioral Therapy; Watkins *et al.*, 2011) or FPCN-DMN connectivity (e.g. brain stimulation targeting the dorsolateral prefrontal cortex or posterior cingulate cortex) can reduce inhibitory executive dysfunction and in turn, rumination.

Finally, our findings not only support the idea that rumination in BD reflects executive dysfunction but also presents a possibility for intervening and preventing mood episodes. The findings presented here are in *euthymic* individuals with BD (i.e. in between manic or depressive episodes), thus individuals outside of a mood episode. Given that negative rumination predicts the likelihood of a depressive episode, targeting executive functioning in BD might help decrease rumination, and thus prevent future depressive episodes.

Author contribution. Dr. Chou analysed the data and prepared the initial draft of the manuscript. Dr. Dougherty and Dr. Nierenberg contributed to the interpretation of the data and critically revised the manuscript. Dr. Ghaznavi conceptualised the study design, acquired and analyzed the data, and critically revised the manuscript. All authors approved the final version of the manuscript.

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