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Research paper

Medial prefrontal disengagement during self-focus in formerly depressed patients prone to rumination

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ABSTRACT

Background: Medial prefrontal cortex (MPFC) activity during self-referential processing has been associated with rumination and found aberrant in depression. We investigated whether this aberrant activity reflects a trait marker that persists in remitted patients.

Methods: Twenty-five patients fully remitted from major depression for at least 6 months, and 29 matched healthy controls were scanned with fMRI while presented with personality trait words in two conditions: Self condition asked whether the trait described themselves; General condition asked whether the trait was generally desirable. Contrasts-of-interest were examined in a factorial model and rumination correlates were examined in 2-sample t-tests with Ruminative Response Style score as covariate. All findings were reported at a conservative $p < 0.05$, with whole-brain peak-level family-wise error correction.

Results: Self-referential processing increased anterior cortical midline activity to a similar extent in both groups. Dorsal anterior cingulate cortex (MNI(x,y,z) = -12,20,26) and dorsal MPFC (MNI(x,y,z) = -6,46,40) activity during self-referential processing was positively associated with rumination in healthy control subjects and negatively associated with rumination in remitted patients.

Limitations: A longitudinal design tracking the relationship between rumination and MPFC activity would have aided the interpretation of our findings as to whether high ruminators are exhibiting an adaptive process to maintain remission or whether it represents a maladaptive process considering that high ruminators have an increased vulnerability for relapse.

Conclusions: The association between increased anterior cortical midline activity during self-referential processing and rumination differentiated healthy controls from formerly depressed patients. Self-referential neural processing during remission from depression may depend on the cognitive tendencies to ruminate.

1. Introduction

Past findings have linked abnormal function of the medial prefrontal cortex (MPFC) to acute depression (Grimm et al., 2009; Johnson et al., 2009; Lemogne et al., 2009; Yoshimura et al., 2010; Kessler et al., 2011; Sarsam et al., 2013; Delaveau et al., 2016; Renner

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et al., 2015; Cooney et al., 2010) and to groups at high-risk for developing major depressive disorder (Lemogne et al., 2011; Ma et al., 2014), making MPFC dysfunction a potential candidate for a trait biomarker of vulnerability for depression. However, studies which examine patients in remission are needed to address whether abnormal MPFC activity is a stable feature of depression vulnerability or reflects the depressive state (Lemogne et al., 2012; Nejad et al., 2013). Identifying such vulnerability biomarkers might be of crucial interest in developing personalized medicine in psychiatry (Prendes-Alvarez and Nemeroff, 2018).

Depression is associated with increased attention to the self (Mor and Winquist, 2002). Self-focus in depression is not only quantitatively increased, but also qualitatively distinct (Watkins, 2008), characterized by repetitive thinking on negative aspects of one's self. This negative self-focus, or rumination, is strongly associated with vulnerability for depression (Figueroa et al., 2015). In healthy subjects, self-referential processing involves several brain regions within the cortical midline structures, including both dorsal and ventral parts of the MPFC (Johnson et al., 2006; van der Meer et al., 2010), which are also parts of the default mode brain network involved in the resting, mind-wandering brain state – a state mostly consisting of self-referential thoughts (Gusnard et al., 2001). Among currently depressed patients, self-referential processing has been generally associated with increased activity of the MPFC (Lemogne et al., 2009; Yoshimura et al., 2010; Kessler et al., 2011; Sarsam et al., 2013). Studies have also reported brain functional connectivity differences of the MPFC to posterior midline regions (Philippi et al., 2018; Satyshur et al., 2018) which might have a modulatory effect that increases self-directed thoughts (Davey et al., 2017), as well as MPFC dysconnectivity to the subgenual anterior cingulate cortex which has been suggested to assign negative affect to self-directed thought (Hamilton et al., 2015). However, it is unclear whether dysfunctional activity is associated with a greater vulnerability for depression or increased ruminative thinking at the time of data acquisition (Lemogne et al., 2012; Nejad et al., 2013); in other words, whether it reflects proneness to ruminate or the act of ruminating. Data from remitted patients, who presumably display high levels of proneness to ruminate but low levels of current negative affect, are thus needed to disentangle the role of MPFC function in vulnerability for depression (Lemogne et al., 2010; Liotti et al., 2002; Mocking et al., 2016). In the present study, fully-remitted formerly depressed patients were compared to healthy subjects while performing a self-referential task during functional magnetic resonance imaging (fMRI). In line with the idea that MPFC activity is a trait marker for depression, our main hypothesis was that during a self-referential task remitted patients will display increased MPFC activity compared to healthy subjects. We also hypothesized that MPFC activity will be positively associated with proneness to ruminate and we explored whether this association differed between remitted patients and healthy subjects.

2. Methods and materials

2.1. Participants

To be included in the study, patients had to have been in remission for at least 6 months but no more than 48 months. The rationale of including healthy never-depressed subjects and formerly depressed subjects was to compare low versus high vulnerability groups. Since one half of recurrent depressive episodes occur within 48 months after remission (Furukawa et al., 2008), those with a duration of remission exceeding 48 months were considered at low risk of recurrence and likely to display low levels of vulnerability, and were thus not included. Remission was defined as the absence of current depressive episode assessed by the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), a score of 10 or less on the Beck's Depression Inventory (BDI) and a score of 7 or less on the Montgomery–Asberg Depression Rating Scale (MADRS). Duration of remission was ascertained by the consulting psychiatrist of the patient. Remitted patients were not included if their first depressive episode occurred after the age of 50, if their last depressive episode was treated with electroconvulsive therapy, if they had a history of depressive episode with psychotic features or a current comorbid psychiatric condition (assessed with the MINI), including borderline personality disorder (assessed with the Structured Clinical Interview for DSM-IV Axis II Disorders (First et al., 1997)) but not generalized anxiety disorder, or have any first-degree relatives with bipolar disorder (assessed with the Family Interview for Genetic Studies (Maxwell, 1992)). The MINI assesses current and past major depressive episode, dysthymia, manic episode, panic disorder, social anxiety, obsessive-compulsive disorder, post-traumatic stress disorder, substance use disorders, psychotic disorders, anorexia nervosa, bulimia and generalized anxiety disorder (Sheehan et al., 1998). Control subjects were not included if they had a history of psychiatric disorders or a first-degree relative with a diagnosed mood disorder (assessed with the same aforementioned structured interviews). All participants ranged between 25–65 years of age, were native French speakers, met MRI compatibility criteria, had no known neurological afflictions and gave written informed consent for study participation.

Twenty-five fully-remitted patients (4 males) with major depressive disorder and 29 healthy control subjects (4 males) were included in the study. Originally, the study recruited 35 remitted patients from the psychiatry department of four university hospitals of the Paris area who were matched in age, sex and education level with 40 healthy control subjects who were recruited from the research volunteer list of the Brain and Spine Institute, Paris. Seven patients were not included in the current study due to an unforeseen sampling bias of former patients in long term remission of 5–20 years (mean duration of remission = 127 months (SD = 54.4); mean number of past episodes = 1.57 (SD = 0.49)). Two participants (one control subject) did not complete the scan, seven participants (six control subjects) were excluded due to excessive movement (more than two volumes of framewise displacement > 3 mm (Power et al., 2014)), and five participants (four control subjects) were excluded due to poor fMRI data quality: One participant had the field of view misplaced, one participant acquired fMRI in the opposite phase encoding direction, and three participants' fMRI data were tainted with spiking or radio frequency interferences. Of the remaining 25 patients, three were not currently taking any psychotropic medication. Seven were taking serotonin and norepinephrine reuptake inhibitors (three with medium dosage, four with high dosage; mean duration = 19.9 months; SD = 13.6), 14 were taking selective serotonin reuptake inhibitors (two with low dosage, 11 with medium dosage, one with high dosage; mean duration = 46.6 months; SD = 73.6), and one was taking agomelatine (medium dosage) for the past 24 months. The study was approved by the Ethics Committee for Biomedical Research “Ile-de-France III” .

2.2. Assessment of rumination

Proneness to ruminate was assessed with the French translation of the 22-item Ruminative Response Style (RRS) scale (Guimpel et al., 2012; Treynor et al., 2003). Participants were asked to indicate how often they engaged in each of the 22 ruminative thoughts or behaviors (e.g. “Think “Why can't I handle things better?” ”) when they feel sad, blue or depressed. One might thus have a high RRS score while not being currently depressed nor even ruminating at the time of assessment. The French translation of RRS has strong internal consistency (Cronbach's coefficient of 0.90) that allows the use of its total score as a first approach (Guimpel et al., 2012). Additional exploratory analyses were based on RRS subscales of brooding and self-reflection, which are thought to underlie maladaptive and adaptive aspects of self-focused thoughts, respectively.

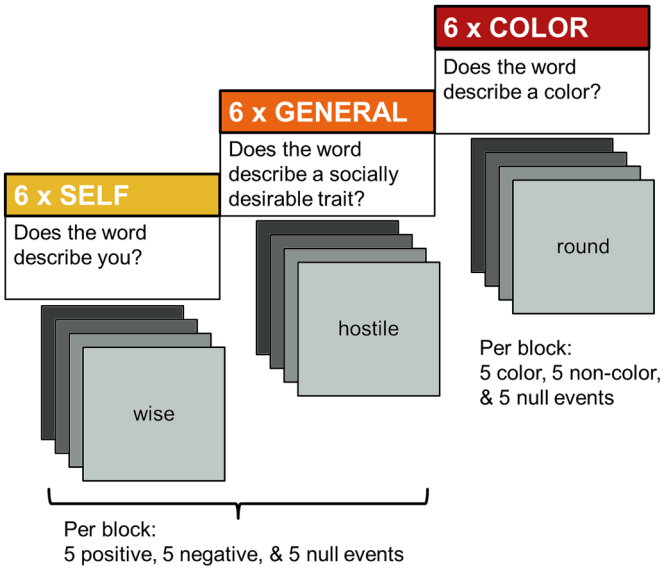

Fig. 1. The self-referential fMRI task. The Self, General and Color conditions were presented in 6 blocks each with 10 word trials and 5 null events in each block. Words were presented for 500 ms followed by a fixation cross for 3500 + /- 500 ms.

2.3. FMRI task design

All tasks were presented and responses recorded using E-Prime v2.0 (Psychology Software Tools, Pittsburgh, PA). Fig. 1 illustrates the general setup of the fMRI self-referential task. A total of 120 personality trait words were identified as reliably positive or negative and their meanings commonly understood by the surveying of 60 independent subjects. The words were divided into two lists matched for valence, word length of orthographic discriminability and frequency in spoken French (Ferrand et al., 2010). One list (30 positive words, 30 negative words) was presented to subjects under a "Self" condition where they were asked whether the word described themselves, and the other list (30 positive words, 30 negative words) were presented under a "General" condition where they were asked whether the word was generally socially desirable. The presentation of the lists in either the Self or General conditions was counterbalanced across subjects. The task also included a "Color" condition where 60 color and non-color words were presented and subjects were asked whether the word described a color. Each word was presented for 500 ms followed by a jittered inter-stimulus period of 3500 + / − 500 ms consisting of a fixation cross during which subjects were expected to respond with a button press 'yes' with the index finger or 'no' with the middle finger. 90 null events were randomly presented throughout and consisted of a continuous fixation cross. There were six blocks of each condition and each block consisted of a 4 s instruction screen followed by a randomized order of five positive (or color) words, five negative (or non-color) words, and 5 null events. Subjects performed a practice run using a separate set of words immediately before functional scanning.

2.4. Postscan assessment

Deeper encoding is thought to occur with items processed self-referentially leading to better recall compared to non-self referentially processed items (Symons and Johnson, 1997). To ensure that subjects adequately performed the task, we tested for this so-called "self-referential memory effect" with an unexpected recognition task introduced after the scan session. Subjects were shown words in a randomized order sequentially on a computer screen. Twenty-four positive and 24 negative words were included, half of which had been shown during the Self condition and the other half had been shown during the General condition of the fMRI task. Sixteen positive and 16 negative filler words previously unseen were also included. Subjects were asked to respond 'yes' or 'no' with right-hand button presses on a keyboard whether they had previously seen the words in the scanner. We hypothesized that more of the words shown in the Self condition would be remembered than words shown in the General condition (Symons and Johnson, 1997).

2.5. MRI acquisition and preprocessing

MRI data were acquired on a Siemens Trio 3T scanner (Siemens Medical Solutions, Erlangen, Germany). The task was presented during imaging of blood oxygen level-dependent changes using an echo-planar imaging (EPI) sequence with a resolution of 3 mm isovoxel size, TR of 2020 ms, 27 ms echo time, flip angle of 78°, and 40 slices interleaved over a field of view of 198 mm. The task was performed for 19.5 mins resulting in 586 EPI volumes. A high-resolution three-dimensional T1-weighted image was also acquired with a resolution of 1 mm isovoxel size, repetition time of 2300 ms, echo time of 4.18 ms, and a field of view of 256 mm. We also acquired a B0 field map (TR = 396 ms; TE1 = 5.19 ms, TE2 = 7.65 ms; flip angle = 60°; distance factor = 10%; FOV = 204 mm; 40 slices; slice thickness = 3 mm).

SPM8 was used to preprocess and analyse the imaging data. With the VBM8 toolbox, the anatomical image was segmented and normalized into MNI space using DARTEL's high dimensional iterative warping procedure with the standard template included in the VBM8 toolbox. The resulting deformation field was used to normalize the functional data after B0 gradient unwarping, rigid-body realignment to the first acquired functional volume, and coregistration to the raw anatomical image. As a last step, functional images were smoothed with an 8 mm FWHM Gaussian kernel.

2.6. Behavioral data analysis

Statistical analyses were performed with IBM SPSS statistical software package v22 (IBM Corp., Armonk, NY). Demographic data were analysed for between-group differences with a two-sample *t*-test for age, and chi-square test for sex ratio and education level. Responses in the fMRI task were divided into negative self-assessments (i.e., 'yes' to negative words or 'no' to positive words during the Self condition) and positive self-assessments (i.e., 'no' to negative words or 'yes' to positive words during the Self condition). RRS and negative self-assessments were tested for between-group differences with two-sample t-tests. Within-group, between-group and interaction effects were tested for in a 2 (Group: remitted patients vs. controls) by 2 (Recall: Self words vs. General words) by 2 (Valence: Positive words vs. Negative words) general linear model. The self-referential memory effect was verified by a within-group difference between the number of remembered words for words shown in the Self condition compared to those shown in the General condition. Between-group differences of motion during scanning was tested with a two-sample *t*-test of the mean framewise displacement during scanning (Power et al., 2014). For all tests, statistical significance was evaluated using a two-tailed alpha set at 0.05, Bonferroni-corrected to 0.00625.

2.7. FMRI analysis

A general linear model specifying the onset of events in each condition separated according to valence (positive or negative) or color (color word or non-color word), as well as a regressor indicating the onset of the instruction screens, were modelled as task regressors. Each individual's movement realignment parameters and their derivatives were modelled to account for head movement and subsequent spin effects (Andersson et al., 2001). A high-pass filter of 128 s was applied to the data.

First-level contrasts of relevant task regressors were entered in a 2

(Between-group factor, Group: patient or control) by 2 (Within-group factor, Conditions: Self or General) by 2 (Within-group factor, Valence: positive or negative) factorial model at the second-level. We used the General condition as a control condition since the same words were counterbalanced across the subjects for the Self and General conditions. The color condition was included in the task to potentially disentangle whether any group differences were specific to Self or General condition or a general difference. We firstly performed within-group analyses for each group to look for regions displaying a condition main effect (Self > General). We then tested a group main effect (patients vs. controls) across both conditions (Self and General). Thirdly, we tested for significant interactions between factors (i.e. group, condition and valence). In each case, we first computed an F-contrast. Post hoc t-contrasts followed whenever a significant effect was found.

Additionally, we looked at the RRS score as a covariate-of-interest in two-sample *t*-test of the Self contrast. We lacked RRS for one control subject who was excluded from this analysis. Associations between brain activity in the Self condition and proneness to ruminate were examined for within-group and between-group effects (i.e. group by RRS score interactions). Analyses were repeated in an identical fashion for RRS associations with brain activity in the General condition to determine whether findings were specific to the Self condition. Significant findings were analysed *post hoc* for associations with the brooding and self-reflection subscales of the RRS. Peak beta values were extracted per significant cluster and introduced as the dependent variable in general linear models including Group, RRS subscores (total, brooding or self-reflection) and Group by RRS subscore interaction as explanatory variables.

In all tests except for the *post hoc* associations with RRS subscales, results are reported at the whole-brain level with the significance threshold set to $p < 0.05$, corrected for multiple comparisons with family-wise error (FWE).

3. Results

3.1. Clinical and behavioral data

A summary of the participants' clinical and behavioral data is displayed in Table 1. Groups did not differ in any demographic variable or movement during scanning (all $p > 0.3$). The remitted patient group scored significantly higher than the control group on the RRS score ($t(52) = 5.2$; $p < 0.001$). Furthermore, remitted patients made significantly more negative self-assessments in the self-referential fMRI task ($t(52) = 3.6$; $p < 0.001$). For the post-scan recall task, results from six controls and six patients had to be omitted due to computer malfunction or misunderstanding the task instructions. Participants recalled significantly more words that were previously presented to them in the Self condition than those presented in the General condition ($F(1,52) = 48.9$; $p < 0.001$). There was a Valence effect where both groups exhibited a strong positive bias ($F(1,52) = 20.6$; $p < 0.001$). Groups did not differ in the number of positive or negative words recalled ($F(1,52) = 1.65$; $p = 0.205$) nor was there an interaction between group, valence and condition ($F(1,52) = 0.09$; $p = 0.77$). Groups did not differ in the number of words recalled ($F(1,52) = 0.8$; $p = 0.37$) nor was there an interaction with condition ($F(1,52) = 0.07$; $p = 0.79$).

Table 1
Descriptive and behavioral statistics of the control and patient groups [a].

	Controls	Patients
N	29	25
Age (years)	41.4(12.8)	38.8(12.0)
Sex (n subjects; F:M)	25:4	21:4
Education level (n subjects; basic/low/middle/high)	11/10/4/4	8/14/2/1
Age at first episode (years)		27.7(9.5)
Number of episodes		3.2(2.4)
Duration of last episode (months)		10.1(10.0)
Duration of remission (months)		11.2(7.1)
Medication (n subjects; SSRI/SNRI/atypical/none)		14/7/1/3
Ruminative Response Style score	30.7(10.1)	45.9(11.3) [b]
Negative self-assessments (n words)	6.1(4.3)	11.0(5.9) [b]
Positive self-assessments (n words)	53.9(4.2)	49.0(5.9) [b]
Recalled, Self condition (n words)	19.2(3.5)	19.1(3.5)
Positive words	10.5(1.8)	10.4(1.7)
Negative words	7.3(3.8)	7(3.8)
Recalled, General condition (n words)	17.3(4.4)	15.3(5.5)
Positive words	9.9(2.3)	9.2(2.7)
Negative words	6.3(3.6)	5.2(3.6)

[a] Values are mean(SD) unless otherwise stated
[b] Significant between-group difference, $p < 0.001$

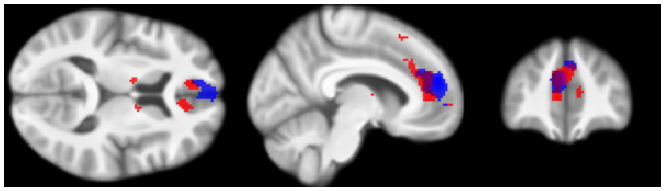

Fig. 2. The Self > General within-group contrasts of the remitted patient group (red) and the healthy control group (blue). Map is thresholded at a whole-brain FWE corrected, peak-level, $p < 0.05$.

3.2. FMRI results

3.1.1. Main effects

There were no significant between-group or interaction effects over the Self and General conditions or over word valence. The Self > General contrast for each group revealed significantly increased activity in the pregenual ACC, dorsal/rostral MPFC and the left anterior insula during the Self condition compared with the General condition (Fig. 2; Table 2). Although remitted patients recruited an extended prefrontal and insular network as well as the thalamus and cerebellum, activity was not significantly different from the control group.

3.1.2. Associations with proneness to ruminate (RRS score)

The dorsal mPFC ($MNI_{x,y,z}$: 0, 58, 22; $t_{(1,\ 49)} = 5.40$, $p_{FWE} = 0.037$) and dorsal ACC ($MNI_{x,y,z}$: −4, 18, 22; $t_{(1,\ 49)} = 5.34$, $p_{FWE} = 0.044$) showed significant between-group differences in the neural correlates of proneness to ruminate during the Self condition (Table 3, Fig. 3). In other words, the dorsal MPFC and dorsal ACC showed a significant group by RRS score interaction. The right superior temporal gyrus ($MNI_{x,y,z}$: 52, −16, 4; $t_{(1,\ 49)} = 5.29$, $p_{FWE} = 0.051$), and left posterior superior temporal gyrus ($MNI_{x,y,z}$: −42, −30, 4; $t_{(1,\ 49)} = 4.62$, $p_{FWE} = 0.064$) showed trend-wise significance toward the same interaction pattern.

When looking at associations with proneness to ruminate in the whole sample, we did not find any cluster whose activity was significantly associated with RRS score. However, in the whole-brain test of the control group, we found that with greater level of RRS score there was increased dorsal ACC ($MNI_{x,y,z}$: −12, 20, 26; $t_{(1,\ 49)} = 5.68$, $p_{FWE} = 0.016$) activity during the Self condition (Table 3). Activity in the dorsal MPFC ($MNI_{x,y,z}$: −6, 46, 40; $t_{(1,\ 49)} = 5.24$, $p_{FWE} = 0.059$), and right dorsolateral PFC ($MNI_{x,y,z}$: 28, 40, 28; $t_{(1,\ 49)} = 5.22$, $p_{FWE} = 0.062$) showed a trend-wise positive association with RRS score.

In contrast, there were no significant positive associations in the remitted patient group but a significant negative association was found between proneness to ruminate and activity in the left posterior superior temporal gyrus ($MNI_{x,y,z}$: −48, −34, 8; $t_{(1,\ 49)} = 5.71$, $p_{FWE} = 0.015$) (Table 3), whereas activity in the right thalamus ($MNI_{x,y,z}$: 26, −32, 2; $t_{(1,\ 49)} = 5.19$, $p_{FWE} = 0.067$), right superior temporal gyrus ($MNI_{x,y,z}$: 64, −6, 14; $t_{(1,\ 49)} = 5.19$, $p_{FWE} = 0.067$), and dorsal mPFC ($MNI_{x,y,z}$: 0, 58, 22; $t_{(1,\ 49)} = 5.08$, $p_{FWE} = 0.091$) showed trend-wise significance for a negative association with RRS score.

Table 2
MNI coordinates and statistics of factorial model analysis with word valence regressors*.

Contrast	Anatomical region	Cluster size (2 mm isovoxels)	x	y	z	Peak T	Peak Z	Peak-level P_{FWE}
Remitted patients' within- group effect: Self > General	Left pregenual ACC	781	−6	40	22	6.44	6.15	2.9288e-05
	Left pregenual ACC		−4	42	6	6.02	5.77	2.4104e-04
	Right superior medial gyrus (dorsal MPFC)		8	52	28	5.81	5.59	6.3550e-04
	Right pregenual ACC	73	10	36	8	5.95	5.71	3.3599e-04
	Left insula lobe	140	−28	20	−10	5.63	5.42	0.0015
	Left inferior frontal gyrus (par Triangularis)		−42	22	0	5.45	5.26	0.0032
	Right posterior medial frontal sulcus	32	12	16	58	5.60	5.40	0.0017
	Right superior frontal gyrus	19	20	54	16	5.40	5.22	0.0040
	Right cerebellum (Lobule VIIa)	31	22	−74	−28	5.33	5.16	0.0054
	Right inferior frontal gyrus (par Orbitalis)	9	42	22	−16	5.17	5.01	0.0109
	Left thalamus	11	−10	−4	8	5.15	4.99	0.0117
	Left posterior medial frontal sulcus	15	−8	20	54	5.06	4.91	0.0167
	Right inferior frontal gyrus (par Orbitalis)	3	44	30	−6	4.96	4.82	0.0253
	Right thalamus	10	12	−2	8	4.96	4.81	0.0255
Control subjects' within- group effect: Self > General	Left insula lobe	43	−28	20	−14	6.68	6.35	8.6321e-06
	Left superior medial gyrus (rostral MPFC)	1023	−8	50	20	6.57	6.26	1.5111e-05
	Left pregenual ACC		−4	40	22	6.16	5.90	1.1813e-04
	Right superior medial gyrus (dorsal MPFC)		6	50	28	5.82	5.59	6.1931e-04
	Right pregenual ACC	3	4	34	8	4.88	4.74	0.0350

ACC, anterior cingulate cortex; MPFC, medial prefrontal cortex
* At whole-brain threshold $P_{FWE} < 0.05$

Moreover, no correlation was found between proneness to ruminate and activity during the General condition in either group.

Table 4 shows the results of *post hoc* general linear models testing the interactions between Group and RRS scores (total, self-reflection or brooding) in predicting Self-related activity in the dorsal MPFC and dorsal ACC, and whether these associations differed between groups. Although the Group by RRS score interaction was significant for both regions and all scores, the results seem to suggest a greater loading on the brooding subscale that can explain the Group by RRS total score interaction in the dorsal MPFC, whereas the Group by RRS total score in the dorsal ACC seems to be explained equally by brooding and self-reflection. For one control subject, both the RRS total and brooding scores, as well as the Self-related activity in the dorsal ACC, were 3 SD above the mean of the control group. However, replacing the values of these variables with the second highest value of the control group (Dixon, 1960) yielded similar results, with a significant group by RRS score interaction for both regions and all scores (Supplementary Table 1). Exploratory whole-brain analyses based on the fMRI data and RRS subscales are displayed in Supplementary Tables 2 and 3.

4. Discussion

The present study aimed to examine differential activity of the MPFC during self-referential processing between fully remitted patients with major depressive disorder and healthy control subjects. Although the increased activity of anterior cortical midline structures during self-referential processing did not differ between remitted patients and controls, the two groups differed in their associations between proneness to ruminate and self-related activity in both the dorsal MPFC and dorsal ACC. More specifically, proneness to ruminate tends to be positively correlated with the activity of the dorsal MPFC and dorsal ACC during self-referential processing in controls whereas the opposite pattern was observed in remitted patients. The present discussion will focus on these two regions since other regions showing within-group associations were neither significantly different between-group nor *a priori* hypothesized.

The lack of between-group differences regarding dorsal MPFC activity during self-referential processing is at odds with previous findings in currently depressed patients (Grimm et al., 2009; Johnson et al., 2009; Lemogne et al., 2009; Renner et al., 2015; Sarsam et al., 2013; Yoshimura et al., 2010), including those from three independent teams using similar methodology to the present study (Lemogne et al., 2009; Sarsam et al., 2013; Yoshimura et al., 2010). At the behavioral level, the confirmation of a self-referential memory effect suggests that both remitted patients and controls were committed to the task (Symons and Johnson, 1997). At the neural level, we found increased activity with self-referential processing in expected regions of the anterior cortical midline in both groups (van der Meer et al., 2010). We are thus confident in the validity of the task in eliciting self-referential processing and reluctant to attribute the lack of expected differences between patients and controls to methodological differences. Therefore, the main reason why the present results are at odds with previous findings in currently depressed patients might be precisely because the patients in the present study were not currently depressed.

As regards other studies of remitted patients, several have been conducted looking at fMRI response to various tasks or during resting state, with many implicating dorsal MPFC. In one study remitted patients displayed distinct and increased brain activity during an autobiographical memory retrieval task specifically in the dorsal MPFC compared to healthy control subjects and current major depressive disorder patients (Young et al., 2014). Thomas et al. used an emotional face task and found that brain activity during positive stimuli viewing in dorsal MPFC, amongst other regions, was negatively correlated to trait rumination in predominately antidepressant-free remitted patients (Thomas et al., 2011). During negative stimuli viewing, activity in other brains regions, e.g. insula and middle cingulate gyrus, were positively

Table 3
MNI coordinates and statistics of rumination covariate analysis in two-sample t-tests of Self Contrast: Healthy controls vs. Remitted patients*.

Contrast	Anatomical region	Cluster size (2 mm isovoxels)	x	y	z	Peak T	Peak Z	Peak-level P_{FWE}
Positive association in Healthy controls	Left dorsal ACC	6	−12	20	26	5.68	4.95	0.0162
	Left superior medial gyrus (dorsal MPFC)	3	−6	46	40	5.44	4.85	0.0585
	Right middle frontal gyrus	1	28	40	28	5.22	4.63	0.0615
Negative association in Remitted patients	Left superior temporal gyrus	3	−48	−34	8	5.71	4.98	0.0148
	Right thalamus	2	26	−32	2	5.19	4.61	0.0666
	Right precentral gyrus	4	64	−6	14	5.19	4.61	0.0669
	Right superior temporal gyrus	2	64	−14	2	5.12	4.56	0.0830
	Left superior medial gyrus (dorsal MPFC)	1	0	58	22	5.08	4.53	0.0913
Between-group difference of trait association, Healthy controls > Remitted patients	Left superior medial gyrus (dorsal MPFC)	1	0	58	22	5.40	4.76	0.0371
	Left dorsal ACC	1	−4	18	22	5.34	4.72	0.0439
	Right superior temporal gyrus	3	52	−16	4	5.29	4.68	0.0509
	Left superior temporal gyrus	2	−42	−30	4	5.21	4.62	0.0645

ACC, anterior cingulate cortex; MPFC, medial prefrontal cortex
* At whole-brain threshold $P_{FWE} < 0.1$ to report clusters reaching trend-level significance

associated with trait rumination. In a reward task, Schiller et al. found that dorsal MPFC was attenuated in response to loss in remitted depression patients compared to healthy control subjects and, similar to our findings, that this activity correlated negatively with RRS score in the remitted patients (Schiller et al., 2013). Although these studies suggest that dorsal MPFC plays an important part in distinguishing patients in remission, the MPFC has not been found important in other studies. For example, in a study by Burkhouse et al., a rumination induction task was used and activity in several regions, but not the MPFC, was found increased in remitted adolescent patients compared to age-matched control subjects (Burkhouse et al., 2017). Additionally, activity in these brain regions was positively correlated with trait rumination scores in both the remitted patient and control groups.

Remitted patients have also been examined with resting state fMRI which measures brain connectivity amongst brain regions rather than activity within specific regions. Lois and Wessa found that the relationship between strength of connectivity within the anterior default mode network regions and levels of self-reported rumination had inversed associations in remitted patients than in healthy controls subjects (Lois and Wessa, 2016). Although the metric of measurement is different from the present study, this previous result also suggests that an inversed relationship exists between the level of tendency to ruminate and the function of the MPFC in remitted patients versus healthy control subjects. Although Lois and Wessa's study did not have a currently depressed patient group, previous resting state studies have found a positive association between rumination and increased anterior default mode network connectivity in healthy controls and currently depressed, drug-naïve patients (Berman et al., 2011; Zhu et al., 2017). This suggests that, as what we found with dorsal MPFC activity, dorsal MPFC connectivity also seems to have a unique relationship with rumination in remitted depression.

Interestingly, one study which examined the effect of agomelatine found that dorsal MPFC activity was predictive of remission at 24 weeks with future remitters displaying decreased activity compared to non-remitters (Delaveau et al., 2016) and that the level of activity remained stable weeks into treatment. In a cohort of patients with major

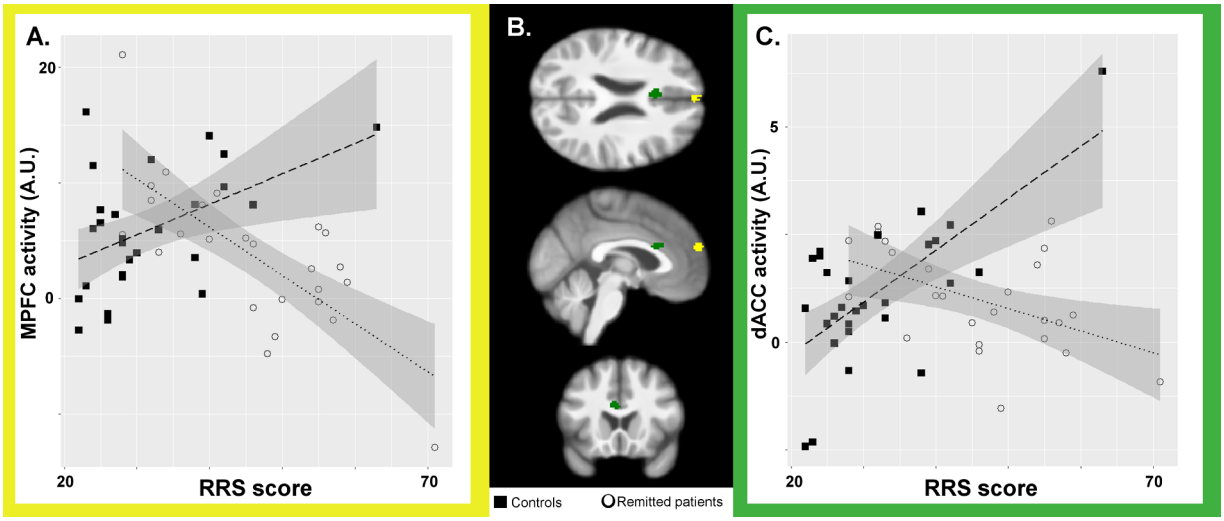

Fig. 3. Summary figure of the main findings. A) Scatter plot displaying significant negative association in remitted patients (hollow circles) and positive association in control subjects (filled squares) between rumination and Self-related activity in the dorsal medial prefrontal cortex (MPFC ; $MNI_{x,y,z} = 0,58,22$) corresponding to the yellow cluster in the brain maps of panel B. B) Brain regions showing significant between-group differences of trait association. The yellow cluster is of the dorsal MPFC ($MNI_{x,y,z} = -0,58,22$) at t-value > 4 in order to increase cluster size for visualization. The green cluster shows the finding of dorsal anterior cingulate cortex (ACC; $MNI_{x,y,z} = -4,18,22$) at t-value > 4 in order to increase cluster size for visualisation. C) Scatter plot displaying significant negative association in remitted patients (hollow circles) and positive association in healthy controls (filled squares) between rumination and Self-related activity in the dorsal ACC ($MNI_{x,y,z} = -4,18,22$) corresponding to the green cluster in the brain maps of panel B.

Table 4
Results of general linear models testing the interactions between the group and the RRS scores (total, self-reflection and brooding) in predicting brain activity in Self condition in the dorsal MPFC and dorsal ACC.

		Ruminative Response Style scale		
		Total	Self-reflection	Brooding
Dorsal MPFC	Group (controls vs. patients)	−25.193***	−9.897	−17.919***
	RRS score	−0.416***	−1.257*	−1.166**
	Group by RRS score	0.680***	1.942*	2.281***
Dorsal ACC	Group (controls vs. patients)	−6.030***	−4.657***	−4.461***
	RRS score	−0.051*	−0.266*	−0.129
	Group by RRS score	0.172***	0.862***	0.585***

Figures are the unstandardized estimated parameters.
All models included the group (controls vs. patients), one of the RRS scores (i.e. total, self-reflection or brooding) and the group by RRS score interaction.
* $p < 0.05$;
** $p < 0.01$;
*** $p < 0.001$

depressive disorder at 6 months remission, Farb et al. (Farb et al., 2011) found that both ventral and dorsal MPFC activity during sad versus neutral film viewing was predictive of relapse during the subsequent 18-month period, with those relapsing showing increased MPFC activity during sad film viewing. These findings suggest the possibility that our cohort of successful remitters already had reduced MPFC activity before remission.

The present findings in healthy controls where higher RRS scores were associated with increased self-referential activity in the dorsal anterior cortical midline structures are in line with past findings obtained in healthy individuals scoring high on risk factors for depression other than proneness to ruminate (e.g. genetic or other psychological risk factors) (Lemogne et al., 2011; Ma et al., 2014). Therefore, one could interpret the increased self-related dorsal MPFC activity levels as the neural substrate of vulnerability for depression. The association between increased MPFC activity and proneness to ruminate in healthy control subjects seems to suggest that increased MPFC activity confers risk for depression. However, in formerly depressed, yet fully-remitted patients, our data revealed that those scoring *lower* on RRS tended to show *greater* MPFC activity. Since vulnerability for depression is arguably higher in formerly depressed patients than in never-depressed individuals, and ruminative tendencies are associated with increased risk of relapse (Figueroa et al., 2015), decreased, rather than increased, dorsal MPFC activity during self-referential processing might thus reflect a maladaptive process associated with high levels of proneness to ruminate.

This 'maladaptive' interpretation of the negative relationship between proneness to ruminate and anterior midline cortical activity among formerly depressed patients is also consistent with the observation that dorsal MPFC and dorsal ACC, as well as dorsolateral PFC, have reliably been involved in emotion regulation (Frank et al., 2014), so the negative correlation observed in formerly depressed patients might suggest a failure of emotion regulation. From a broader perspective, the dorsal ACC plays a key role in conflict monitoring (Shackman et al., 2011), while the dorsolateral PFC is thought to implement subsequent cognitive control (Mansouri et al., 2009). Self-referential processing is generally conceptualized as a particular instance of conflict monitoring between one's current self and one's own standard (Carver and Scheier, 2001). Since increased proneness to ruminate is likely to increase such conflict, it might result in increased dorsal ACC activation and subsequent dorsal MPFC and dorsolateral PFC activity (Lemogne et al., 2012).

Alternatively, the negative association between anterior midline cortical activity and proneness to ruminate can be interpreted as an adaptive mechanism. Remitted patients could still be in active remission with less dorsal MPFC activity signaling avoidance of self-referential activity to keep ruminative thoughts at bay which might be a particularly effective coping mechanism for those more prone to rumination.

It is noteworthy that these results were specific to the Self condition and not observed in the General condition. Therefore, they are unlikely to be explained by a relationship between proneness to ruminate and general MPFC function, which would have yielded similar findings across the two conditions (Freton et al., 2014; Ray et al., 2005).

The present study has several strengths, including its novelty, being the first to explore the neural bases of self-referential processing in fully remitted patients in remission for more than 6 months. The validity of the task was ascertained by behavioral and fMRI within-group results (Symons and Johnson, 1997; van der Meer et al., 2010) and the sample size was large enough to conduct whole-brain analyses that demonstrated the specificity of dorsal MPFC and ACC function between groups. However, some limitations should also be mentioned. First, the results are a cross-sectional snapshot that does not allow us to determine whether the disengagement of anterior cortical midline areas is an adaptive process to maintain remission or a maladaptive process contributing to a greater risk of relapse. Alternatively, the disengagement of the anterior cortical midline regions with increased proneness to ruminate might not be either an adaptive or maladaptive process but rather a marker in those able to achieve sustained remission. As Delaveau et al.'s study showed, activity of the MPFC during a depressive episode distinguished those who went on to remission from those who did not (Delaveau et al., 2016). Longitudinal studies are warranted to go beyond these speculative interpretations and to verify whether anterior midline cortical activity changes or remains stable in remission. Ideally, such studies should measure the level of rumination during a depressive period and follow the patients until remission to track changes in both ruminative thoughts and proneness to ruminate, and their neural correlates. Furthermore, remitted patients were prescribed antidepressant medication which could have contributed to the differences, as well as the lack of differences, we found between remitted patients and control subjects. A recent fMRI study examined the effect of escitalopram on depressed patients' neural responses to a similar self-referential task and found that one-week escitalopram use had selective effects on positive self-referential stimuli (Komulainen et al., 2018). Indeed, most studies of antidepressant acute effects on self-referential processing have shown either a decreased activity to negative self-referent stimuli (Di Simplicio et al., 2012) or an increased activity to positive self-referent stimuli (Miskowiak et al., 2007; Norbury et al., 2008), although no antidepressant effect on self-referential brain activity has also been reported (Lemogne et al., 2010). These previous studies suggest potential ways antidepressants could affect self-referential-related brain activity, however, none had studied long-term treatment with antidepressants. In the present sample, most of the remitted patients had been on antidepressants for at least a year. Moreover, previous reports of MPFC hyperactivity in self-related cognition in major depressive disorder included patient samples medicated with antidepressants (Lemogne et al., 2009; Yoshimura et al., 2010). We, nonetheless, cannot delineate the effect of antidepressants on our findings and further studies elucidating the long-term effects of antidepressant medications is warranted. Lastly, although the present study did not find activity differences in the remitted group, this does not preclude differences in the functional connectivity of the anterior midline regions to the rest of the brain.

In conclusion, we did not find evidence of MPFC self-referential activity as a trait marker for vulnerability for depression, although we did find that anterior cortical midline activity was distinctive in the remitted patient group in how it associates with proneness to ruminate. These results suggest that the combination of both biological and psychological measures, as well as their interplay in a relevant context (i.e. self-referential processing, as in the present study), might provide new opportunities to understand the mechanisms of vulnerability for

depression. Future studies should investigate anterior midline cortical function's relationship with proneness to ruminate longitudinally (during depressive episode and remission) to determine how a negative association between the two variables during remission should be interpreted.

Author statement

ABN, PF and CL designed the study and wrote the protocol. RV set up the appropriate MR imaging sequences. JR and ABN carried out the data collection. CGL, NH, PG, CD, and FL assisted in the recruitment of participants. ABN and CL managed the literature searches and analyses, undertook the statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Supplementary materials

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