Aberrant default-mode network-hippocampus connectivity after sad memory-recall in remitted-depression

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Abstract

Rumination and cognitive reactivity (dysfunctional cognitions after sad mood-induction) remain high in remitted Major Depressive Disorder (MDD) and can contribute to new episodes. These factors have been linked to increased fMRI resting-state functional-connectivity within the Default-Mode Network (DMN). It remains unclear whether (I) increased DMN-connectivity persists during MDD-remission, and (II) whether sad mood-induction differentially affects DMN-connectivity in remitted-MDD vs controls. Moreover, DMN-connectivity studies in remitted-MDD were previously confounded by antidepressant-use. Sixty-two MDD-patients remitted from ≥2 episodes, psychotropic-medication free, and 41 controls, participated in two 5-min neutral and sad mood-inductions by autobiographical-recall and neutral/sad music, each followed by 8-min resting-state fMRI-scanning. We identified DMN-components using Independent Component Analysis and entered subject- and sessions-specific components into a repeated measures analysis of variance. Connectivity-differences were extracted and correlated with baseline cognitive reactivity and rumination as measures of vulnerability for recurrence. After sad vs neutral mood-induction, controls, but not remitted-MDD, showed an increase in connectivity between the posterior-DMN and a cluster consisting mostly of the hippocampus (P = 0.006). Less posterior-DMN-hippocampal connectivity was associated with higher cognitive reactivity (r = −0.21, P = 0.046) and rumination (r = −0.27, P = 0.017). After recalling sad autobiographical-memories, aberrant posterior-DMN-hippocampal connectivity, associated with cognitive reactivity and rumination, remains a neural vulnerability in MDD-remission.

Key words: depression; mood; autobiographical memory; cognitive reactivity; remission

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Introduction

One of the reasons that Major Depressive Disorder (MDD) is a highly disabling disease is its recurrent nature (Krij Balls, et al., 2012). After a first episode, MDD becomes recurrent in at least one third of patients (Eaton et al., 2008) and the risk of recurrence increases after each subsequent episode (Solomon et al., 2000). Investigation of remitted-recurrent-MDD (rrMDD), a vulnerable group at high risk of developing new episodes, might improve our knowledge about the pathophysiology of MDD vulnerability (Hetrick et al., 2008). Theory of cognitive reactivity (CR) states that, during MDD remission, sadness and stress easily activate dysfunctional cognitive schemas that further induce depressive processing-styles (Lau et al., 2004). An example of such a style is rumination, a repetitively focusing of attention to one’s sad mood, its possible causes and its negative consequences (Koster et al., 2011). Rumination has been regarded as a sub-category of CR (Raes et al., 2012) and both have been identified as risk-factors for recurrence in MDD (Segal et al., 1999, Watkins, 2008; Michaela et al., 2011; Figueroa et al., 2015).

The neurobiological mechanisms underlying persistent CR and rumination to sad mood during remission of recurrent MDD have not been well examined. It has been suggested that the Default-Mode Network (DMN) is important in processes as CR and rumination (Marchetti et al., 2012). The DMN is involved in spontaneous introspective thoughts during rest and becomes deactivated when tasks require external attention (Andrews-Hanna et al., 2014). The DMN is divided in anterior (aDMN) and posterior (pDMN) parts with the medial prefrontal cortex (MPC) and posterior cingulate cortex (PCC) as main hubs, respectively (Greicius, 2007). Additional DMN-nodes include the anterior cingulate cortex, hippocampus, lateral temporal cortex and inferior parietal cortex (Mulders et al., 2015).

The aDMN is involved in self-referential processing and emotion regulation, whereas the pDMN is implicated in episodic memory retrieval through its connection with temporal structures including the hippocampus (Andrews-Hanna et al., 2010). DMN resting-state connectivity aberrations are frequently identified in depression, (Zhang et al., 2011; Daviey et al., 2012; Zhu et al., 2012; Guo et al., 2013; Li et al., 2013a; Sambataro et al., 2014; Dutta et al., 2014) with most evidence pointing to increased resting-state connectivity within the aDMN and pDMN (Kaiser et al., 2015; Mulders et al., 2015). However, decreased connectivity within only the pDMN has been observed in MDD and has been suggested to underlie episodic memory retrieval impairments (Greicius, 2007; Zhu et al., 2012). Furthermore, studies have shown altered connectivity between the a/pDMN, though directions of effects are inconsistent (Mulders et al., 2015). In addition to changes of within DMN connectivity, alterations in connectivity between the a/pDMN and other resting-state networks, including frontoparietal networks and the Salience Network, have also been reported in MDD (Kaiser et al., 2015).

Rumination has consistently been associated with increased resting-state a/pDMN-connectivity in MDD (Cooney et al., 2010; Berman et al., 2011; Hamilton et al., 2011, 2015; Lemogne et al., 2012, Zhu et al., 2012, Luo et al., 2015). Moreover, DMN-abnormalities have also been identified in subjects at risk for depression (Marchetti et al., 2012) and patients in remission (Nixon et al., 2014; Zamoscik et al., 2014; Bartova et al., 2015). In remitted adolescent-onset MDD, reduced ability to de-activate DMN-areas during a working-memory task was associated with rumination (Bartova et al., 2015). Regarding CR, three studies with different paradigms reported that sad mood-induction increased connectivity in DMN-areas in remitted-MDD (Far et al., 2011; Foland-Ross et al., 2014; Zamoscik et al., 2014). For example, Zamoscik et al. (2014) found increased connectivity between the PCC and the parahippocampal-gyri during sad-autobiographical recall.

Given evidence of DMN-abnormalities in subjects at risk for and remitted from MDD, and the association of the DMN with cognitive risk-factors for recurrence, CR and rumination, DMN-characteristics likely represent a neural MDD vulnerability marker (Marchetti et al., 2012). However, the number of studies on this subject is still sparse. To confirm this, more research, including stress/mood inductions which are thought to increase CR and rumination (Lau et al., 2004) on DMN-connectivity as a vulnerability-marker in remitted-patients is needed. In addition, studies applying mood-inductions in remitted-MDD included patients on antidepressants, which might have confounded DMN-connectivity results (Li et al., 2013a; Posner et al., 2013). Last, resting-state connectivity after mood-induction has not yet been examined.

We therefore compared the effect of mood-induction by sad vs neutral autobiographical-recall on DMN resting-state functional-connectivity in patients with rrMDD, not taking antidepressants, and matched controls with no personal/familial history of MDD. We hypothesized an overall increase in within a/pDMN-connectivity in rrMDD patients vs controls, which would be further increased after the mood-induction. We expected the mood-induction to increase CR and rumination and thus hypothesized that these dimensional measures would be associated with differences in DMN-connectivity.

Materials and Methods

Participants

Sixty-two rrMDD patients with ≥2 depressive episodes as defined by the Structured Clinical Interview for DSM-disorders (SCID), in stable remission for ≥2 months according to DSM IV-criteria, and 41 healthy controls were scanned. Hamilton Depressive Rating Scale (HDRS) scores were ≤7 and patients were not taking antidepressant medication for ≥8 weeks. The mean time between the inclusion in the study with SCID assessment and fMRI scanning was 39.8 (SD: 24.1) days. Controls did not have any history of personal or familial psychiatric disease, as determined by the SCID. All participants were aged 35–65 years. We excluded subjects with alcohol/drug dependency; psychotic or bipolar disorder; predominant anxiety disorder; severe personality disorder; electroconvulsive therapy within 2 months before scanning; history of severe head trauma; neurological disease; severe general physical illness and no Dutch/English proficiency. rrMDD patients and controls were matched for age, sex, educational level and working class. Subjects were recruited through identical advertisements in freely available online and house-to-house papers, posters in public spaces and from previous studies in our and affiliated research centres (Mocking et al., 2016). The study was approved by the accredited Medical Ethical Committee (METC) of the Academic Medical Centre (AMC). Written informed consent was obtained from all participants.

Questionnaires

Hamilton depression rating scale-17 (HDRS-17). The HDRS-17 is an observer rated MDD-symptom scale to assess the severity of depression. The internal consistency was high, with a previously reported Cronbach’s α of 0.80 (Rush et al., 1986)
We assessed rumination in the past week with the 26-item self-report Ruminative Responses Scale (Nolen-Hoeksema, 1991) which consists of items that describe responses to a depressed mood that are focused on the self, symptoms, or consequences of depressed mood. The internal consistency of the RRS is excellent, with a Cronbach’s α was 0.93 in the current study.

Ruminative responses scale (RRS-NL). We assessed rumination in the past week with the 26-item self-report Ruminative Responses Scale (Nolen-Hoeksema, 1991) which consists of items that describe responses to a depressed mood that are focused on the self, symptoms, or consequences of depressed mood. The internal consistency of the RRS is excellent, with a Cronbach’s α was 0.93 in the current study.

Mood-induction paradigm

In the MRI-scanner participants completed both a neutral and sad mood-induction modified from Segal et al. (2006). In preparation of the MRI-procedure, participants described a memory which they regarded as neutral (doing dishes) and one which they regarded as one of the saddest in their life (losing a job, death of a spouse). Participants were encouraged to describe as many details of the most vivid memory as possible. In addition, participants chose one neutral/sad fragment of music from 10 different fragments. See Supplementary material for more information about the music fragments and distribution of music preferences for rrMDD and controls (S1/S2). We scripted these memories in key-sentences for display on the screen in the MRI-scanner. During memory display, we played the chosen neutral or sad music. After the neutral mood-induction (before the first resting-state scan), participants were asked to rate their current mood on a scale of 0–10 (0 being extremely sad; 10 extremely happy). Participants rated their mood again after the resting-state scan. After the sad resting-state scan, the most extreme sadness was rated. In addition, subjects rated their mood before and after the sad mood-induction. The gap between the neutral and sad mood-induction in which participants completed other fMRI tasks was ±125 min, including a 30 min break. We designed the sad mood-induction to be at the end of all neutral and sad mood-induction modified from Segal et al. (2006). In preparation of the MRI-procedure, participants described a memory which they regarded as neutral (doing dishes) and one which they regarded as one of the saddest in their life (losing a job, death of a spouse). Participants were encouraged to describe as many details of the most vivid memory as possible. In addition, participants chose one neutral/sad fragment of music from 10 different fragments. See Supplementary material for more information about the music fragments and distribution of music preferences for rrMDD and controls (S1/S2). We scripted these memories in key-sentences for display on the screen in the MRI-scanner. During memory display, we played the chosen neutral or sad music. After the neutral mood-induction (before the first resting-state scan), participants were asked to rate their current mood on a scale of 0–10 (0 being extremely sad; 10 extremely happy). Participants rated their mood again after the resting-state scan. After the sad resting-state scan, the most extreme sadness was rated. In addition, subjects rated their mood before and after the sad mood-induction. The gap between the neutral and sad mood-induction in which participants completed other fMRI tasks was ±125 min, including a 30 min break. We designed the sad mood-induction to be at the end of all fMRI scanning, as it would have been too straining for participants to continue fMRI scanning and tasks after the sad mood-induction (S3).

Image acquisition and analyses

A 3 Tesla Philips Achieva XT scanner (Philips Medical Systems, Best, the Netherlands), equipped with a 32-channel SENSE head coil, was used to obtain the images. A high-resolution T1-weighted 3D structural image was acquired using fast-field echo (FFE) for anatomical reference (220 slices; TR: 8.3 ms; TE: 3.8 ms; FOV: 240 × 188; 240 × 240 matrix; voxel size: 1 × 1 × 1 mm³). Functional images were acquired with T2*-weighted gradient echo planar imaging (EPI) sequences. Participants were instructed to close their eyes and to not fall asleep. The scans comprised 210 volumes of 37 axial-slices (TR: 2000 ms; TE: 27.6 ms; FOV: 240 × 240; 80 × 80 matrix; voxel size = 3 × 3 × 3 mm³). Slices were oriented parallel to the AC-PC transverse plane and acquired in ascending order with a gap of 0.3 mm.
case of neuroimaging research, there is evidence that using a pooled error can be more powerful than using a partitioned error (Henson, 2005), although this issue remains under debate. In order to approach this issue empirically and document the effect of partitioned variance, we additionally performed analyses using GLM flex (http://mrtools.mgh.harvard.edu), which uses a partitioned error (see S-Results in the Supplementary material).

In a full factorial model in SPM12, the effect of mood (neutral/sad mood-induction) was a within-subject factor, and group (rrMDD/control) a between-subjects factor. We examined the group*mood-induction interactions and corrected for multiple comparisons with Bonferroni correction for examining five networks \( P < 0.01 \) (0.05 divided by 5), FWE cluster corrected with an initial height threshold of \( P < 0.005 \) uncorrected. We chose an a-priori cluster defining threshold of \( P < 0.005 \) because we were interested in diffuse whole brain effects as we (i) measured connectivity differences after the mood induction, and (ii) measured patients remitted from MDD as opposed to during the acute phase of MDD. Finally, we extracted functional-connectivity values of significant clusters (first eigenvariate) and quantified correlations between functional-connectivity differences between neutral and sad mood with RRS and LEIDS-R scores. For analyses with RRS-scores, we excluded one univariate outlier based on z-scores >3. For correlations between RRS and connectivity change, we used Spearman rank correlation because RRS-scores were not normally distributed in controls (log transformation did not lead to a normal distribution).

We additionally examined for multivariate outliers based on Mahalanobis distance (De Maesschalck et al., 2000). Additionally, to examine whether correlations differed between rrMDD and controls, we tested group*RMS and group*LEIDS-R interactions in linear regression analyses with connectivity-changes as dependent variable.

**Results**

**Sample characteristics**

Seventy-two rrMDD patients and 46 controls were initially eligible of which 62 and 41 were scanned, respectively. Of these participants, we excluded five rrMDD with excessive head motion (within-scan movement >3 mm and within-scan rotation >1.5°), two rrMDD due to technical difficulties, and three rrMDD and two controls with abnormal brain anatomy (judged by a neuro-radiologist). Fifty-two rrMDD and 39 controls were included in the ICA analysis (S7). No significant differences were observed between rrMDD and controls for sex, age, education, IQ, living situation, employment status and handedness. The rrMDD showed significant higher levels of residual depressive symptoms (HDRS) \( P < 0.001 \), CR (LEIDS-R) \( P < 0.001 \) and ruminatin (RRS), \( P < 0.001 \) (Table 1). Comparisons between rrMDD and controls did not change when restricted to the sample selected for the ICA analyses.

**Mood-ratings**

Both groups reported comparable neutral to positive mood after neutral mood-induction (\( P = 0.95 \)). Mood-scores (±SD) decreased slightly during neutral resting state (rrMDD: \(-0.5 ± 0.94\), controls: \(0.22 ± 0.66\); \( P = 0.002 \)), without a group*mood interaction (\( P = 0.146 \)). The sad mood-induction significantly decreased mood-scores in both groups (\( P < 0.001 \)), without a group*mood-induction interaction (\( P = 0.58 \)). The saddest mood reported during the second resting-state was significantly lower in rrMDD than in controls (\( P = 0.016 \); Table 2).

**Resting-state connectivity**

The aDMN component showed no significant group*mood-induction interaction. There was a main effect of mood-induction with increased connectivity in the contrast sad vs neutral mood-induction in the left insula (both rrMDD and controls; peak coordinates: \( x = -28, y = -8, z = 18 \), \( k = 881, Z = 3.86, p_{\text{FWE}} < 0.005 \)).

The pDMN component showed a significant group*mood-induction interaction: compared to rrMDD, controls showed increased connectivity after sad vs neutral mood-induction of the pDMN with the right medial temporal lobe including the right hippocampus (\( x = 38, y = -44, z = 0, k = 40, y = -22, z = -18, k = 875, Z = 4.38, p_{\text{FWE}} = 0.006 \); Figure 1A and B). Further exploration using an xzy toolbox (http://www.gin.cnrs.fr/AAL/ lang=en; Tzourio-Mazoyer et al., 2002), revealed that 80.1% of the cluster consisted of voxels located in the hippocampus, 7.54% of the right parahippocampal gyrus, 5.71% of the right precuneus, 1.60% of the temporal inferior gyrus right, 1.60% of the right calcarine cortex and 1.03% of the right temporal medial gyrus. No significant main effect of mood-induction was observed. Post-hoc analyses stratified for group showed that in controls, sad mood-induction increased connectivity of the pDMN with the medial temporal lobe, including the right hippocampus and right medial temporal gyrus, (\( x = 32, y = -52, z = 6, k = 805, Z = 4.73, p_{\text{FWE}} = 0.010 \)) and left middle frontal gyrus (\( x = -36, y = 10, z = 44, k = 511, Z = 3.75, p_{\text{FWE}} = 0.044 \)). In rrMDD, there were no significant increases or decreases in connectivity after sad mood-induction (\( P > 0.05 \)). In order to assess whether effects were DMN-specific we additionally examined the right and left CEN and the SN. There were no significant group*mood-induction interactions for the left and right CEN and SN (all \( P > 0.05 \)).

Additional analyses by means of two sample T-tests for resting-state connectivity after neutral mood-induction showed that there were no significant differences between rrMDD and controls during neutral mood state for the a/pDMN and the left/right CEN and SN (all \( P > 0.05 \)).

**Correlation analyses**

We finally assessed whether the effects of sad mood-induction on pDMN-hippocampus-connectivity were associated with CR- or ruminatin-scores. There were significant negative correlations between this connectivity for neutral vs sad mood-induction with LEIDS-R scores \( \text{CR} \) \( r = -0.21, P = 0.046 \), and RRS-scores (ruminatin) \( r = -0.26 P = 0.017 \) (Figure 2A and B). Because residual symptoms were not associated with pDMN-hippocampus connectivity change (\( P = 0.36 \)), we did not additionally correct for residual symptomatology in our analyses. The correlations between RRS and connectivity-change remained significant after excluding one multivariate outlier \( r = -0.22, P = 0.045 \). Group*RMS and group*LEIDS-R interactions were not significant in linear regression analyses with hippocampal connectivity-change as dependent variable (\( P = 0.31 \) and \( P = 0.43 \), respectively), indicating that the correlation-coefficients did not differ between groups. The change in pDMN-hippocampus connectivity was not associated with mood-change after sad mood-induction (\( P = 0.49 \)) or lowest mood during second resting-state (\( P = 0.14 \)). In the rrMDD group, we found no association between the number of previous episodes and change in pDMN-hippocampus connectivity (\( P = 0.126 \)). Together, these results suggest that individuals with higher CR...
and rumination showed attenuated pDMN-hippocampus connectivity after sad mood induction, regardless of whether they were in the control or rrMDD group.

**Discussion**

This study examined DMN resting-state connectivity after recalling sad autobiographical memories in medication-free rrMDD patients vs controls, and the association with CR and rumination. Contrary to the a-priori hypothesized increased overall DMN-connectivity in rrMDD, after sad vs neutral autobiographical-recall, controls showed increased pDMN connectivity to a cluster consisting mostly of the hippocampus, and additionally of temporal/occipital regions, which was not present in rrMDD. Moreover, less pDMN-hippocampus connectivity was associated with two MDD-recurrence risk-factors: higher CR and rumination. This suggests that aberrant connectivity between the pDMN and the hippocampus and temporal/occipital areas in remitted-MDD after sad autobiographical recall represents a neural MDD-vulnerability factor. There were no interaction-effects of group*mood-induction on the salience network, suggesting that effects were specific for the DMN. Moreover, there were no baseline connectivity differences (after neutral mood-induction) between rrMDD and controls.

We hypothesize that the aberrant pDMN-hippocampus connectivity in rrMDD, thus the failure to show increased connectivity between the pDMN and hippocampus after sad autobiographical recall, might be related to the phenomenon of over-general autobiographical memory (OAM), persisting in rrMDD (Spinholven et al., 2006). OAM refers to the observation that individuals retrieve autobiographical memories in a less detailed, more generic form, referring to series of events and general self-knowledge, which occurs more in MDD-vulnerable subjects (Sumner, 2012). OAM has been associated with a poor MDD-prognosis and is maintained by rumination (Sumner, 2012). Indeed, during resting-state, connectivity of the hippocampus and other temporal areas with (posterior)-DMN areas is increased during autobiographical thoughts (Andrews-Hanna et al., 2010). Task-based studies show that the hippocampus is recruited more during retrieval of specific compared to generic memories (Maguire and Mummery, 1999) and that hippocampus activity is associated with the vividness of memories (Addis et al., 2004; Ford and Kensinger, 2016). In depression, hippocampus connectivity was reduced during autobiographical recall, even when specificity of memories was matched (Hach et al., 2014). In addition, it has been suggested that individuals who spontaneously invoke more specific memories have a stronger connectivity of the hippocampus to the DMN during resting-state (Yang et al., 2012). Thus, our result of aberrant connectivity between the pDMN and hippocampus might indicate that...
Fig. 1. Group x mood interaction regarding the connectivity of the posterior DMN map with the right hippocampus. (A) Cluster of 875 voxels (x = 38, y = -44, z = 0) covering the right hippocampus was more connected with the posterior DMN after sad autobiographical recall in controls, but not in remitted-patients (p (FWE corrected) = 0.006). Color scales represent t-values. (B) Mean connectivity change and standard error in the right hippocampus, plotted for every group and mood state. Patients showed no significant change in connectivity in response to sad mood-induction, while controls show an increase of connectivity.
Further supportive of this hypothesis, detailed memories are thought to be stored in and retrieved by the hippocampus, whereas memories that are generic are incorporated in neocortical networks of overlapping memories (Preston and Eichenbaum, 2013). The storage and retrieval of memories is influenced by pre-existing schemas; self-learned knowledge about the world, the self and others. For instance, van Kesteren et al. (2010) found that the existence of prior schemas was associated with reduced connectivity between cortical areas and the hippocampus during memory encoding (van Kesteren et al., 2010). This pattern persisted during 15 min resting-state, suggesting that when memories fit into schemas, they are also less processed by the hippocampus during rest. In rrMDD, dysfunctional schemas have been found to persist and, corroborative with the theory of CR, can be (further) activated by sad mood (Lau et al., 2004). For rrMDD patients, negative autobiographical memories will better fit with prior (depressive) schemas and might thus be retrieved by other neural structures than the hippocampus. In a post-hoc analysis we examined the correlation between change in connectivity between de pDMN and controls were more engaged in details of their specific memory after autobiographical recall than remitted-MDD, leading to an increase in hippocampal involvement within the DMN, which was absent in remitted-MDD.

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mood-induction, highlights the importance of stressful triggers, such as sad autobiographical memories, to unmask MDD-vulnerability (Lau et al., 2004). However, differences between groups even after sad mood-induction were more subtle than we initially expected.

Zamoscik et al. (2014) used a comparable mood-induction with sad autobiographical-induction and identified increased connectivity between the pCC (pDMN) and bilateral parahippocampal gyrus (PHG) in rMDD compared to controls (Zamoscik et al., 2014). These results appear contradictory to our observed decreased connectivity between the pDMN and hippocampus. Differences between Zamoscik et al. and our study might be explained by the fact that Zamoscik et al. did not contrast sad- to neutral mood-induction and included patients on antidepressants. An alternative explanation of differences between our study and Zamoscik et al. is that we examined resting-state connectivity after autobiographical recall, instead of during. During the task, subjects might be more intensely engaged in their memory, resulting in increased pDMN-PHG connectivity, implicated in memory processing. We suggest that after sad mood-induction, when subjects are no longer required to focus on details of their negative memory, OAM might become more pronounced, characterized by a failure to increase pDMN-hippocampus-connectivity rMDD. Indeed, some behavioral studies suggest that, in rMDD, OAM has to first be activated by a state of rumination (such as a mood-induction; Raes et al., 2012). Both studies highlight the role of dysfunctional memory processes in association with neural substrates, as a vulnerability in remitted MDD.

A strength of this study is that we examined a large rMDD sample in stable remission and not taking medication. This allowed us to examine effects of vulnerability instead of depressive-state, and without confounding effects of antidepressants. A second strength is that we used a repeated-measures design to contrast sad- with neutral autobiographical-recall, increasing the likelihood that our effects are due to sad mood-induction. A first limitation is that we used a relatively lenient initial threshold for cluster-wise correction of \( P < 0.005 \) uncorrected, because we were interested in diffuse effects after mood-induction in a group of patients remitted from depression. Because a recent study reported that using lenient initial cluster based thresholds can result in too many false positive findings (Ekuild et al., 2016), we also examined results when using an initial threshold of \( P < 0.001 \) (FWE cluster corrected \( P < 0.05 \)). When using this more stringent threshold, only a cluster containing occipital and temporal areas (right calcarine cortex 98.26%, right fusiform gyrus, 0.69, precuneus 0.35%) remained significant (FWE \( P = 0.023 \)). With this more stringent threshold of \( P < 0.001 \), we also observe a cluster which includes right hippocampus 44.14%, right parahippocampal gyrus 30.63%, right temporal inferior gyrus 21.62% and right fusiform gyrus 1.80\% (\( x = -40, y = -22, z = -18, k = -111 \)), which is however no longer significant (FWE \( P = 0.30 \)). Supplementary Figure S10 shows how the spatial extent of the cluster changes for \( P < 0.005 \) and \( P < 0.001 \). Thus, our result of increased pDMN-hippocampus connectivity is likely a subtle effect which does not survive a more stringent threshold. To investigate the reproducibility of our findings, results of this study should be replicated by future studies, and should be included by meta-analyses. Second, the nature of resting-state precludes certainty about subjects’ thoughts during the scan. Thus, we cannot be certain that rMDD-subjects were engaged in over-general autobiographical memories. Nevertheless, considering the function of the hippocampus and the associations of attenuated hippocampal-pDMN connectivity with rumination, and CR, it is likely that our findings are representative of...
dysfunctional (memory) processing. Future studies using a comparable paradigm should also include measures of (trait) OAM. Finally, although examining patients free of antidepressants precludes confounding medication-effects, this might have led to inclusion of a sample of subjects not representative of the general rMDD-population.

## Conclusion
After sad autobiographical recall, connectivity between the pDMN and a cluster consisting mostly of the hippocampus was increased in healthy controls, whereas unmedicated remitted-MDD patients failed to show this greater pDMN-hippocampal connectivity. The observed reduced connectivity was associated with known risk-factors for recurrence; CR and rumination. Aberrant pDMN-hippocampus connectivity after sad autobiographical recall in remitted MDD might represent an MDD vulnerability marker. This study adds evidence that the DMN is an important neural-network that is persistently dysfunctional during remission in patients at high risk for recurrence, but only in the presence of stressful triggers.

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## Supplementary data
Supplementary data are available at SCAN online.

Conflict of interest. None declared.

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