NeuroImage: Clinical 45 (2025) 103716

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Functional connectivity profiles in remitted depression and their relation to ruminative thinking

Zhuo Fang [a,1], Emma Lynn [a,b,1], Verner J. Knott [a,b], Natalia Jaworska [a,b,*]

[a] University of Ottawa Institute of Mental Health Research, ON, Canada
[b] Department of Cellular & Molecular Medicine, University of Ottawa, ON, Canada

ARTICLE INFO

Keywords:
Remitted depression
Default mode network
Central executive network
Salience network
Hopeless rumination
Emotional processing

ABSTRACT

The triple network model suggests that dysfunction in three major brain networks – the default mode network (DMN), central executive network (CEN), and salience network (SN) – might contribute to cognitive impairments in various psychiatric disorders, including major depressive disorder (MDD). While hyperconnectivity in the DMN, hypoconnectivity in the CEN, and abnormal SN connectivity have been observed in acutely depressed patients, evidence for network alterations during remission is limited. Further, there are few studies examining connectivity in people in remission from MDD (rMDD) during emotional processing tasks, including during affective cognition (i.e., tasks that encompass affective processing in the context of cognitive processes, such as inhibition).

To address these literature gaps, this study compared functional connectivity (FC) between resting and task conditions, specifically during the emotional Stroop (eStroop) task, as well as between rMDD and healthy volunteers (HVs), within and between nodes of the three networks. We also explored how FC relates to rumination in the rMDD group, given that rumination tends to persist in rMDD and involves affective and cognitive networks.

We unexpectedly found greater FC during the task vs. rest condition within the DMN, and decreased FC during the task vs. rest conditions within the CEN and SN across the groups. Greater FC during the task vs. rest condition between DMN and SN nodes, as well as between CEN and SN nodes were also observed. These effects were more pronounced in the rMDD group as per our exploratory analyses. Additionally, the rMDD vs. HV group showed higher FC between DMN-CEN nodes, regardless of condition. Higher hopeless rumination scores were associated with decreased resting FC within the DMN, while higher active problem-solving scores were associated with increased task FC within the DMN in the rMDD group.

These findings suggest that tasks engaging affective cognition processes influence FC within and among the three networks, with this effect more pronounced in the rMDD group. This might indicate potential protective and compensatory mechanisms in rMDD and expands our understanding of large-scale intrinsic network connectivity alterations during remission from depression. However, given the limited sample and the exploratory nature of some of our analyses, replication is necessary.

1. Introduction

Major depressive disorder (MDD) is a severe psychiatric illness associated with significant personal and societal impairments. It affects ~3.8 % of the world's population, or ~280 million people (World Health Organization, 2023). One of the most challenging aspects of managing MDD is the relatively high risk of relapse and recurrence, with ~35 % of individuals experiencing a relapse within 15 years post-recovery (Hardeveld et al., 2010). Further, residual depressive symptoms and functional impairments during remission from depression are common and are among the most accurate predictors of MDD relapse (Israel, 2010). Cognitive dysfunction, in particular, is a frequent lingering symptom in people in remission from depression (rMDD). Meta-analyses have identified continued deficits in sustained and selective attention, memory, processing speed, semantic fluency and executive function in rMDD (Bora et al., 2013; Hasselbalch et al., 2011;

* Corresponding author at: 1145 Carling Avenue, Room 3129, Ottawa, ON K1Z-7K4, Canada.
E-mail addresses: njaworsk@uottawa.ca, natalia.jaworska@theroyal.ca (N. Jaworska).
[1] These authors contributed equally to this work; this is a joint co-authorship.

https://doi.org/10.1016/j.nicl.2024.103716
Received 1 May 2024; Received in revised form 4 September 2024; Accepted 24 November 2024
Available online 26 November 2024

Rock et al., 2014). There is also evidence for a relation between continued cognitive dysfunction and depressive relapse (Alexopoulos et al., 2000).

When studying cognitive impairment in MDD, and lingering cognitive deficits in rMDD, there has historically been a distinction between "hot" and "cold" cognition in the literature, wherein "hot" cognition involves affective stimuli incorporated into cognitive processes (e.g., inhibition). This type of cognition is referred to as affective cognition and has been studied extensively in the context of MDD, and, to a lesser extent, in rMDD. There is evidence of both a heightened negativity bias (i.e. increased reactivity towards unpleasant stimuli) and deficient positive emotional reactivity (i.e. a tendency to rate both neutral and pleasant stimuli as being less positive) in depressed vs. healthy volunteers (Bylsma et al., 2008; Gollan et al., 2016); though notable exceptions exist (Fritzsche et al., 2010). Nevertheless, biased emotional processing toward negative stimuli in MDD may be the result of a failure to disengage from negative thoughts or memories (Raes et al., 2006), deficits in cognitive control/inhibitory processes and/or an inability to regulate induced negative mood via positive recall (Gotlib & Joormann, 2010). The emotional Stroop task (eStroop) is generally thought to tap into these various domains (i.e., a task tapping into affective cognition). The eStroop is a variant of the classic Stroop task wherein participants are instructed to respond to the color of an emotional word (i.e., ignore the affective valence).

Interestingly, findings of the eStroop interference effect in healthy subjects have been inconsistent, with some studies reporting an effect, while others have not (generally focused on reaction time [RT]). A *meta*-analysis of the eStroop literature with a pooled sample size of ~800 healthy subjects found no effect of negatively or positively-valenced emotional stimuli, suggesting the absence of a pronounced affective interference effect in healthy subjects, at least as indexed by reaction time (RT; Epp et al., 2012). However, findings of the eStroop emotional bias effect in depressed people have been far more consistent. Indeed, a 2019 *meta*-analysis of the eStroop task in people with MDD found evidence of significant attentional bias towards both disorder-congruent and negatively valenced words, more generally, in MDD vs. healthy volunteers; no consistent evidence of a positive word bias was noted (Joyal et al., 2019). It is unclear if such a bias would persist in the context of rMDD; further, it is unclear whether there would be altered neural features during the eStroop in people with rMDD. Neural features sometimes emerge even in the absence of behavioural differences, providing disorder-specific insights.

One means of assessing neural features is via measures of neural network connectivity. Functional connectivity (FC) studies using network models of brain function have provided insights into the neural processes underlying MDD (Hamilton et al., 2015; Kaiser et al., 2016; Kühn & Gallinat, 2013). Abnormal functional connectivity in MDD has been found within the default mode network (DMN) (Hamilton et al., 2011; Manoliu et al., 2014; Sambataro et al., 2014), salience network (SN) (Manoliu et al., 2014) and frontoparietal central executive network (CEN) (Alexopoulos et al., 2012; Menon, 2011; Veer et al., 2010). The DMN is often referred to as the "task-negative" network, wherein the brain regions (i.e., medial prefrontal cortex [MPFC], posterior cingulate cortex [PCC], and lateral parietal cortex [LP]) are typically deactivated by goal-directed cognitive operations (Buckner et al., 2008; Gusnard et al., 2001; McKiernan et al., 2006; Raichle, 2015). Conversely, the CEN is frequently referred to as the "task-positive" network (Fox et al., 2005), as the regions comprising the network (i.e., lateral prefrontal cortex [LPFC] and posterior parietal cortex [PPC]) exhibit co-activation during cognitively challenging activities, such as working memory maintenance, rule-based problem solving and decision-making (Golland et al., 2007; Koechlin & Summerfield, 2007; Menon, 2011). The SN, also called the 'anterior insula (AI) and anterior cingulate cortex (ACC)-based network', is thought to be implicated in identifying/homing in on most relevant stimuli to guide behavior (Bolton et al., 2020; Seeley, 2019; Seeley et al., 2007); the AI and ACC nodes of the SN tend to be activated by stimuli that have subjective salience (Cormie et al., 2023; Craig, 2002; 2009). Further, the SN is thought to be implicated in regulating the activity of the CEN and DMN. As such, the SN may act as a "casual outflow hub" in switching between the CEN and DMN; interactions between the CEN and DMN, mediated by the SN, might therefore occur during cognitive processing, including during affective cognition (Fox et al., 2005; Goulden et al., 2014; Sridharan et al., 2008). While activity in and interactions between the three networks have been assessed, particularly at rest, in MDD (discussed below), there is limited work in rMDD. Assessments of these networks during affective cognition in rMDD is also lacking.

Default Mode Network (DMN): In general, studies have shown increased intrinsic DMN connectivity at rest (Ho et al., 2015; Liston et al., 2014; Zhu et al., 2012) and during emotional tasks in MDD (Ho et al., 2015; Zhang et al., 2017). A *meta*-analysis found that resting-state DMN hyperconnectivity in MDD appears to be a relatively robust feature of the disorder (Kaiser et al., 2015). However, a more recent study reported reduced rather than increased resting-state DMN FC in recurrent MDD, and the reduced DMN FC was associated with medication usage (Yan et al., 2019). Less research has been conducted on DMN features in rMDD patients. Some have found evidence of resting-state DMN hyperconnectivity in rMDD patients (Bessette et al., 2018; Wu et al., 2013), while others have not (Berwian et al., 2020). Task-based connectivity findings have also been inconsistent in rMDD, with evidence of both DMN hyperconnectivity (Wu et al., 2013) and hypoconnectivity (Bartova et al., 2015) compared to healthy volunteers. No known work exists assessing FC features during tasks of affective cognition in rMDD.

Central Executive Network (CEN): While not as extensively studied as the DMN, alterations in connectivity within the CEN have also been observed in MDD. A *meta*-analysis reported evidence of CEN hypoconnectivity in MDD (Kaiser et al., 2015). Further, CEN hypoconnectivity at rest has been linked with poor antidepressant treatment outcomes, including lingering symptoms, low remission rates, and executive dysfunction (Alexopoulos et al., 2012), highlighting the clinical relevance of alterations in functional connectivity profiles. There is comparatively less research on CEN connectivity profiles in rMDD versus active depression, but some evidence suggests that resting-state CEN hypoconnectivity persists into remission (Dong et al., 2019a; b; Liu et al., 2021b; Stange et al., 2017). Further, increased resting-state CEN connectivity after antidepressant discontinuation may predict a lower risk of subsequent relapse (Berwian et al., 2020).

Salience Network (SN): While data are sparse, decreased resting-state intrinsic SN connectivity has been observed in depressed vs. non-depressed individuals (Manoliu et al., 2014; Yang et al., 2016). Further, higher resting-state SN connectivity was associated with an antidepressant response to placebo in MDD patients, suggesting a potential association with SN connectivity profiles and response (Sikora et al., 2016). This is no known work on SN profiles in rMDD, either at rest or during tasks.

CEN-DMN: The CEN and DMN are typically negatively correlated in the healthy human brain (Menon, 2011). Attenuated negative DMN-CEN resting-state correlations have been reported in MDD patients (Kaiser et al., 2015; Manoliu et al., 2014) and in those with high familial risk for depression (Posner et al., 2016). Further, repeated transcranial magnetic stimulation (rTMS) was found to increase negative resting-state correlations (sometimes referred to as 'anticorrelations') between the DMN and CEN in acutely-ill MDD patients (Liston et al., 2014). It is feasible that the weakened negative correlation between DMN and CEN may continue during rMDD, but this is currently unknown.

CEN-SN: Nodes of the CEN (e.g., dorsal lateral prefrontal cortex [DLPFC]) and SN (e.g., AI, ACC) commonly co-activate during a wide range of cognitive tasks in the healthy human brain (Menon, 2011) as well as during resting-states (Yang et al., 2016). However, the SN and CEN connections may be altered in MDD. For example, decreased CEN-SN connectivity during resting-state have been reported in individuals with subclinical depressive symptoms (Hwang et al., 2015) and those

with MDD (Murrough et al., 2016; Yang et al., 2016); whether such decoupling might persist in rMDD is unclear.

DMN-SN: Previous studies found that individuals with MDD (Kaiser et al., 2015; Pan et al., 2020) and those with rMDD (Delaveau et al., 2017) show decreased resting-state FC between DMN and SN vs. healthy volunteers, though exceptions exist (Manoliu et al., 2014). Given the limited number of studies and the inconsistent findings, the directionality of abnormal DMN-SN connectivity in rMDD is unclear during rest or during task conditions.

Rumination & FC features: Individuals with MDD commonly face recurring, negative, and self-directed thoughts. This persistent thought pattern is referred to as rumination, which is characterized by an excessive, internally-oriented focus on negative past events, which tends to hinder external attention to problem-solving (Papageorgiou & Wells, 2003). Rumination is predictive of the onset, severity, and duration of depressive episodes (Nolen-Hoeksema, 2000; Stone et al., 2011). It has been suggested that rumination might 'exhaust' cognitive resources, potentially contributing to cognitive impairments in MDD. Indeed, there is evidence linking rumination to executive function deficits in MDD (Altamirano et al., 2010; Dickson et al., 2017) and rMDD (Demeyer et al., 2012). Moreover, imaging studies have revealed associations between rumination and brain functional connectivity profiles. For example, maladaptive passive rumination was linked with greater dominance of the DMN over other networks (Hamilton et al., 2011). Lydon-Staley et al., (2019) also reported altered DMN-CEN connectivity, which predicted maladaptive rumination following sad mood induction in rMDD. Finally, Jacobs et al., (2014) noted that DMN-CEN hyperconnectivity was linked with lower rumination scores in rMDD youth. Thus, rumination might be linked with altered FC patterns at rest and during affective cognition in rMDD.

Taken together, abnormalities in both intrinsic and inter-network connectivity of the DMN, CEN, and SN may contribute to the pathophysiology of rMDD. However, most existing research has focused on resting-state connectivity, with few studies investigating FC during tasks, particularly during affective cognition (Bartova et al., 2015; Ho et al., 2015; Menon, 2011; Wu et al., 2013; Zhang et al., 2017). Additionally, comparisons between resting-state and task-related FC are scarce, with many studies focusing only on healthy adults. For example, Bray et al., (2015) found higher intrinsic DMN connectivity in healthy individuals during rest compared to an attention-demanding task, while Elton & Gao (2014) reported increased SN-DMN connectivity during tasks relative to rest. A recent study using the generalized psychophysiological interaction (gPPI) approach (Rai et al., 2021) found no group differences in emotion regulation task-related FC between individuals with rMDD and healthy controls. However, (Rai et al., 2021) used the amygdala and subgenual anterior cingulate cortex (sgACC) as seeds, which precluded the examination of FC across other potentially relevant networks. Nevertheless, given that previous *meta*-analyses (Wang et al., 2022, 2023) have demonstrated that individuals with rMDD exhibit altered brain activation in response to tasks spanning emotional and cognitive domains (i.e., during affective cognition), coupled with our own work indicating that rMDD showed blunted neural differentiation between emotional and neutral stimuli during the eStroop compared to healthy controls (Fang et al., 2022), it is likely that FC features might also emerge in rMDD during affective cognition processing and rest.

Given the above gaps, this study addressed the following objectives in individuals with rMDD and healthy volunteers (HVs): (1) Compare behavioral outcomess between rMDD and HVs in the eStroop task (response time [RT] and accuracy). (2) Compare state/condition differences (i.e., rest vs. eStroop task) in intra- and inter-network FC, with a focus on the nodes comprising three key lareg-scale networks (SN, CEN, and DMN); (3) Examine potential group differences (i.e., rMDD vs. HVs) in intra- and inter-network FC; and (4) Explore interaction effects between condition (rest/task) and groups (rMDD/HVs) in intra- and inter-network FC. Finally, we explored the relation between rumination features and FC features within the rMDD group, expanding on previous research in this domain (Jacobs et al., 2014).

Based on prior studies, we hypothesized that rMDD would have a longer RT than HVs in general as well as a longer RT for negative words. For the FC results, we anticipated that DMN FC would be higher during rest compared to task conditions, whereas CEN and SN FC will be greater during task vs. rest conditions across both groups. Given previously-reported altered neural activation during affective cognition tasks reported in rMDD (Wang et al., 2022; 2023; Fang et al., 2022), we hypothesized that condition and group effects in FC might differ between rMDD and HVs, though, given the limited literature, directional hypotheses were not possible. Finally, we aimed to expand on previous findings of correlations between rumination and DMN dysfunction in rMDD (Jacobs et al., 2014) at rest and during the eStroop task. Ultimately, this work might increase insight into the neural features of rMDD and −in the longer term- aid with understanding risk for relapse and depression recurrence.

2. Methods

2.1. Participants

A total of N = 18 remitted depressed participants (rMDD; 14F/4M) and 21 healthy volunteers (HV; 16F/5M) were tested from the local community via posted advertisements (e.g., websites such as Kijiji and Reddit, posters at the University of Ottawa). All participants were English-speaking adults (18–65 yr) with no current or lifetime major medical illnesses or neurological conditions. Individuals with a history of substance or alcohol dependence and/or abuse, a history of head trauma with loss of consciousness for >5 min or a history of electroconvulsive therapy were excluded. Those with colour blindness were also excluded, as colour discrimination was necessary for this study (details below). Participants were also excluded if they reported high caffeine (>4 cups of coffee/day, daily) or alcohol use (>2–3 units/day, daily), to minimize the effects of these substances on FC. All participants were also asked to abstain from illicit drug and marijuana use for >2 weeks prior to testing, which was confirmed via urinalysis. Participants provided informed written consent before commencing the study, which was approved by the Royal Ottawa Mental Health Center and University of Ottawa Research Ethics Boards; compensation was $30 CDN/session.

Included rMDD individuals had >2 prior major depressive episodes as confirmed with the Mini-International Neuropsychiatric Interview (v.7.0.2) (Sheehan et al., 1998). For inclusion, the most recent depressive episode occurred within <4 yr, with remission for >3-months. rMDD participants were free of psychotropic drugs for >3-months or on the same psychopharmacology regimen for >3-months. Healthy volunteers (HV) had no lifetime psychiatric diagnoses, and a limited history of psychiatric illness among first-degree relatives (Family Interview for Genetic Studies assessed (Gejman, 1999); no psychotic disorders). There were no significant differences in age, median lifetime cannabis use, average alcohol use, lifetime illicit drug use, handedness (LQ) scores or BMI for HVs compared to rMDDs (Table 1). All p-values were generated using an exact sampling distribution for U (Sparks & Todd, 1973). Sample characteristics specific to the rMDDs are listed in Table 2.

2.2. Questionnaires & emotional stroop task

Depression and anxiety symptoms were measured with the self-report Beck Depression Inventory II (BDI-II) (Beck et al., 1961) and Beck Anxiety Inventory (BAI) (Beck et al., 1988), respectively. The Stress Reactive Rumination Scale (SRRS) (Robinson & Alloy, 2003) was used to assess how individuals currently focus on negative attributions and inferences, hopeless cognitions, and coping and problem-solving strategies after experiencing life stress. Given the exploratory nature of these analyses, SRRS subscale scores were examined in this study to more granularly assess ruminative features in rMDD (and correlated with FC; details below). Two sample t-tests (Shapiro-Wilk $p > 0.05$) and Mann-

Table 1
Demographic data for healthy volunteers (HV) and remitted depressed (rMDD) patients (rMDDs).

Sample demographics	Mean (SD)		U score	p-value	Effect size
	HV (n = 21)	*rMDD* (n = 18)			
Sex (n)	16F/5M	14F/4M	–	–	–
Age, years	29.19 (8.50)	32.11 (10.77)	220	0.39	0.14
Lifetime Cannabis Use, #incidents	71.85 (194.51)	60.33 (39.64)[a]	158	0.53	0.11
Average Alcohol Use, #drinks/week	2.51 (2.48)	2.43 (2.65)	176	0.73	0.06
Lifetime Illicit Drug Use, #incidents	5.76 (16.16)	2.56 (5.72)	198	0.81	0.05
EHI LQ	61.26 (54.59)	64.90 (52.59)	208	0.61	0.09
BMI, kg/m^2	24.36 (4.32)	24.65 (5.91)	178	0.77	0.05

Note. The effect sizes reported in this table are Cohen's r, calculated as $r = z\sqrt{N}$; EHI LQ = Edinburgh handedness inventory laterality quotient; BMI = body mass index; SD = standard deviation; F = female; M = male; [a](n = 17).

Table 2
Sample characteristics specific to the remitted depressed patients (rMDD), n = 18.

Comorbid Anxiety, n. (%)		8 (44.4)
Family History of Depression, n. (%)		10 (55.6)
Currently Medicated, no. (%)	total	8 (44.4)
	NDRI	2 (11.1)
	SNRI	2 (11.1)
	SSRI	1 (5.6)
	>1 antidepressant	3 (16.7)
# MDEs in lifetime, mean (SD)		3.65 (2.85)
Time since last MDE at screening, mean no. months (SD)		18.56 (16.4)

Note. n. = number; MDE = major depressive episode; SD = standard deviation; NDRI = norepinephrine-dopamine reuptake inhibitor; SNRI = serotonin-norepinepherine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Whitney U tests (Shapiro-Wilk $p < 0.05$) were run to examine group differences on questionnaire scores, as appropriate.

The emotional Stroop (eStroop) task (E-Prime 3.0, Psychology Software Tools, Inc.) consisted of 216 words (N = 72 positive/negative/neutral, i.e., valence condition) selected from the Affective Norms for English Words (ANEW) set (Bradley & Lang, 1999); detailed eStroop procedures have been reported elsewhere (Fang et al., 2022).

2.3. Neuroimaging data acquisition

Imaging was carried out using a Siemens 3.0T Magnetom Biograph PET-MR scanner and 12-channel head coil. Structural images were acquired using a 3D multi-echo (ME) MPRAGE sequence. Resting-state and task (i.e., eStroop task using 3-word categories: neutral, positive and negative [block design]) scans were acquired using a transverse gradient echo-planar imaging (EPI) sequence (TR = 2460 ms, TE = 25 ms, FA = 70°, 40 slices, thickness = 3 mm, FOV = 192 × 192 mm, matrix = 64 × 64 × 40, voxel = 3 × 3 × 3 mm). Fieldmaps were obtained using a double-echo spoiled gradient echo sequence (TR = 600 ms, TEs = 5.19, 7.65 ms, FA = 60°, FOV = 256 × 256; 50 slices).

2.4. Functional connectivity analyses

2.4.1. fMRI images preprocessing

Functional images were preprocessed/analyzed using SPM12 (MATLAB v.8.5 R2015a, Windows). Fieldmaps were used to correct static geometric distortions in EPI images (FieldMap toolbox). Subsequently, images were realigned to the first acquired volume using rigid body spatial transformations; this was followed by unwarping and distortion correction according to the voxel displacement map (maximum translation/rotation: 3 mm/3°). The T2 was co-registered to the MEMPRAGE image and unwarped EPI images were then co-registered to it. T1 images were segmented into six tissue types (grey & white matter, cerebrospinal fluid [CSF], skull, soft-tissue, and air); deformation field images were used to normalize EPI images into MNI space (resampled voxel: 3 × 3 × 3 mm). Spatial smoothing consisted of an 8 mm Gaussian kernel FWHM. Preprocessed functional images were then imported to the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012; http://www.nitrc.org/projects/conn) for further denoising and analyses. For all connectivity analyses, the rest condition was the entire rest scan (7.38 min), and the task condition consisted of the 18-word block presentation (7.20 min). Notably, for the task condition, only images comprising the task blocks (i.e., positive, negative, neutral image presentations) were included in the FC analyses (i.e., no rest trials were included). This approach is similar to that outlined by (Doganci et al., 2023); although, we examined FC across the entire task instead of separating different task conditions to aid with direct comparisons with the resting-state condition (i.e., match duration as much as possible).

2.4.2. Denoising

The denoising pipeline in the CONN toolbox was applied to remove nuisance signals. Specifically, signals from white matter and CSF were regressed out by estimating five potential noise components (Chai et al., 2012). The Friston 24-parameter model was utilized to regress out head motion effects from the realigned data. Scrubbing was performed using artifact detection tools with the threshold for global-signal > 5 (z-value) and for subject-motion > 0.9 mm. In addition, linear and quadratic trends were included as regressors. Temporal filtering (0.008–0.2 Hz) was then performed on the time series. Head motion and scrubbing parameters were included in the first-level as covariates of no interests. Mean Power's framewise displacement (FD) values (Power et al., 2012) were calculated and included in the group-level analyses as a covariate of no interest.

2.4.3. First-level ROI-to-ROI functional connectivity analysis

As our focus was on the functional connectivity (FC) within and between the three networks, we opted for the regions-of-interest (ROI)-to-ROI approach for FC computations. This involved selecting key nodes in each network as ROIs. Such an approach facilitates a concentrated analysis of the specified areas of interest and enhances reproducibility by maintaining consistent ROI definitions and utilizing standardized atlases.

Fifteen ROIs from the three networks that were selected from CONN's independent component analyses on Human Connectome Project (497 subjects) were used as ROIs (default within CONN; Fig. 1). The mean time series of the voxels comprising each ROI was used to estimate FC by computing the Pearson's correlation between each ROI within each network (DMN, CEN, SN), and between each pair of networks (DMN-CEN, DMN-SN, CEN-SN). The resulting correlation coefficient (*r*) was then converted into a Fisher's Z (i.e., z(r)), and extracted for group-level analyses.

2.4.4. Group-level functional connectivity analyses

A total of 18 rMDDs and 18 HVs were included in the analyses (3 controls were excluded due to missing task output data [N = 2] or low task accuracy [N = 1; 7.67 % accuracy score]). Mixed ANCOVAs were performed in R/RStudio version 4.1.3 (R Core Team, 2021) to examine condition (rest/task), group (HV/rMDD), and condition × group interaction effects in FC within and between networks. Age, current antidepressant use (yes/no), and mean Power's FD value were included as covariates of no interests. The significance threshold was set at a seed-level false discovery rate (FDR) correction of $p_{FDR} < 0.05$. If significant interaction effects were observed, post-hoc t-tests were conducted.

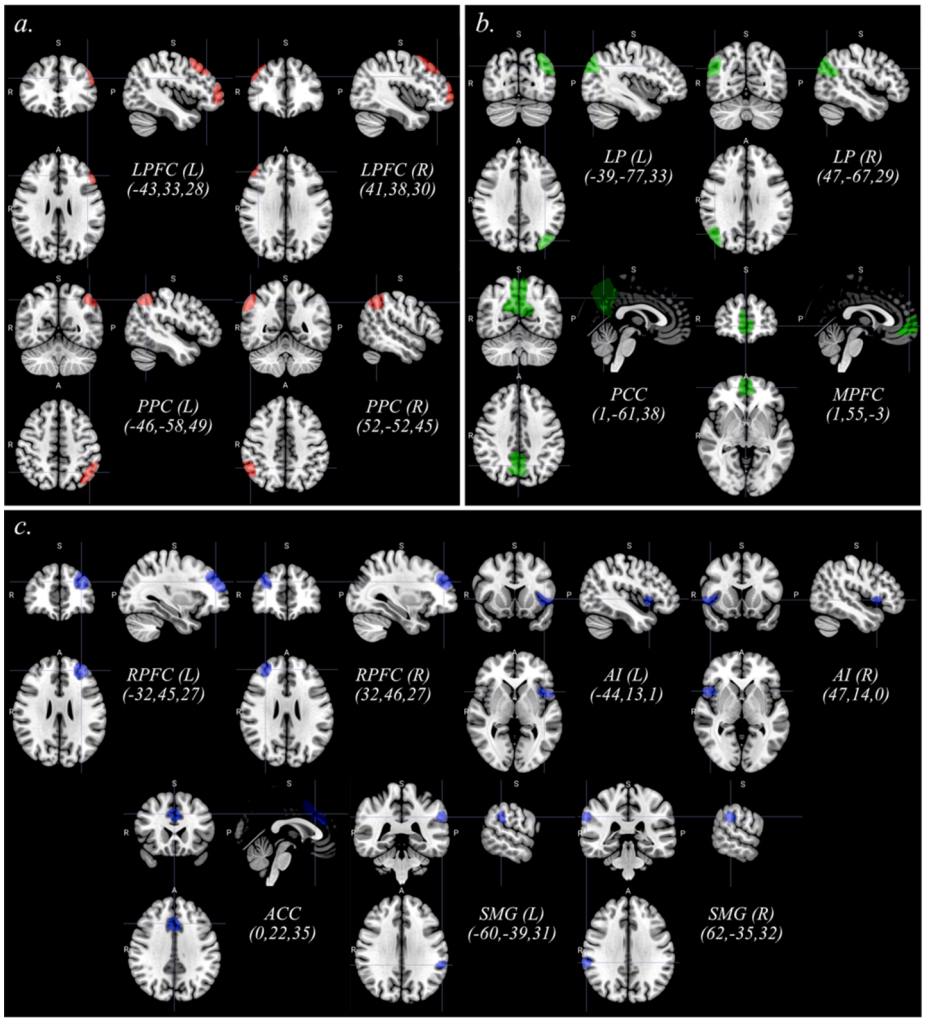

Fig. 1. Human Connectome Project independent component analyses (ICA)-derived cortical regions of interest (ROIs) in the CONN program. All ROIs are overlaid onto the Montreal Neurological Institute's 152 brain template (MNI152) template. The center of each ROI coordinate (x, y, z) is listed in brackets. **a.** Central Executive Network (CEN) ROIs: Left/right lateral prefrontal cortex (LPFC[L]/[R]), left/right posterior parietal cortex (PPC[L]/[R]); **b.** Default Mode Network (DMN) ROIs: Left/right lateral parietal cortex (LP[L]/[R]), posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC); **c.** Salience Network (SN) ROIs. Left/right rostral prefrontal cortex (RPFC[L]/[R]), left/right anterior insula (AI[L]/[R]), anterior cingulate cortex (ACC), left/right supramarginal gyrus (SMG[L]/[R]).

If only main effects were observed (i.e., no significant interactions), to test our a-priori aims and hypotheses, exploratory t-tests were conducted between two levels under the factor showing the significant effect. Bonferroni corrections were applied in the latter scenario (i.e., $p_{FDR} < 0.025$). Finally, regression analyses were conducted to explore relations between scores for all three SRRS subscales (i.e., hopeless rumination, active problem solving, and negative inferential style) and within/between network FC, in the rMDD group only. Age, antidepressant use and mean Power's FD value were again included as covariates ($p_{FDR} < 0.05$).

3. Results

3.1. Questionnaire data

There were no differences in SRRS total scores [t(37) = −1.45, p = 0.15], negative inferential scores [t(37) = −1.31, p = 0.20], and active problem-solving scores [t(37) = 0.37, p = 0.71] between rMDDs and HVs. SRRS hopeless rumination (U = 275.5, p = 0.01) and BDI (U = 264.5, p = 0.03) scores were significantly higher in rMDDs than HVs. BAI scores were not different between groups (Table 3**).**

3.2. eStroop task

Behavioral data were available for n = 18 HV and n = 18 rMDD participants. There was no main effect of valence [F(2,68) = 0.87, p = 0.43, partial h2 = 0.03], group [F(1,34) = 2.62, p = 0.11, partial h2 = 0.07], or valence × group interaction [F(2,68) = 0.34, p = 0.70] on RT. A Mann-Whitney *U* test was performed for accuracy; no significant effects were noted.

3.3. Within network FC

Default mode network (DMN): The results of the mixed ANCOVA indicated a main effect of condition (rest vs. task) on FC between the left lateral parietal cortex (L.LP) and posterior cingulate cortex (PCC), as well as between the L.LP and medial prefrontal cortex (MPFC). Post-hoc analyses revealed that resting-state FC was smaller/weaker vs. task FC (statistics in Table 4). No main group or group × conditions effect was found. However, to further explore *which* group might exhibit more pronounced condition effects, we conducted additional analyses to examine condition differences within each group separately. The results revealed that the observed condition differences in FC were significant only in the rMDD group (Table 5**;** Fig. 2).

Central Executive Network (CEN): Within the CEN, there was a

Table 3
Questionnaire score descriptive statistics and results for comparison of scores between healthy volunteers (HVs) and remitted depressed patients (rMDDs).

Questionnaires		Mean (SD)		t or U score	p-value	Effect size
		HV (n = 21)	*rMDD* (n = 18)			
SRRS	Total Score	34.02 (12.61)	40.13 (13.62)	−1.46	0.15*	0.47
	NIS	30.05 (17.32)	37.43 (17.81)	−0.31	0.20*	0.42
	HR	9.49 (10.51)	21.17 (17.54)	275.5	0.01*	0.39
	APS	60.88 (18.38)	58.57 (19.92)	0.38	0.71*	0.12
BAI Total Score		3.52 (3.49)	4.94 (4.52)	222.5	0.35*	0.15
BDI Total Score		1.43 (1.91)	4.39 (5.08)	264.5	0.03*	0.35

Note. Mann Whitney-U (non-parametric) test results are underlined.
SRRS = Stress Reactive Rumination Scale. For total score and all subscales, maximum score = 100 (respondent focuses on this to a great extent in response to a stressful event), minimum score = 0 (respondent does not focus on this at all in response to a stressful event, NIS = Negative Inferential Style Subscale, HR = Hopeless Rumination Subscale, APS = Active Problem-Solving Subscale.
BAI = Beck Anxiety Inventory, maximum score = 63 (high anxiety), minimum score = 0 (no anxiety).
BDI = Beck Depression Inventory, maximum score = 63 (high number and level of depressive symptoms), minimum score = 0 (no depressive symptoms).

Table 4
Significant condition effects in functional connectivity (FC) within and between networks.

Network	FC pairs	F (1,33)	p-FDR	Partial η^2	Post-hoc condition difference	
					z-value	p-FDR
Within network						
DMN	L.LP-PCC	5.47	0.039	0.14	−2.15	0.031
	L.LP-MPFC	9.09	0.024	0.22	−3.18	0.002
CEN	R.LPFC-L.PPC	11.63	0.010	0.26	3.18	0.001
SN	ACC-L.AI	10.33	0.042	0.24	3.33	0.003
	ACC-R.RPFC	7.87	0.042	0.19	2.57	0.010
Between network						
DMN-SN	L.LP-ACC	13.94	0.019	0.30	−3.43	0.002
	R.LP-ACC	7.12	0.042	0.18	−2.29	0.022
CEN-SN	R.LPFC-ACC	7.39	0.047	0.18	−2.59	0.010
	R.LPFC-L.RPFC	10.09	0.028	0.23	−3.07	0.004
	R.LPFC-R.AI	8.27	0.042	0.20	−2.99	0.005
	R.LPFC-L.AI	13.91	0.020	0.30	−3.45	0.002
	R.PPC-ACC	12.07	0.028	0.27	−3.61	0.002
	L.PPC-L.SMG	7.79	0.047	0.12	−2.10	0.036

Note: Negative z value indicates rest FC < task FC (white cells). Age, antidepressant use (yes/no), and mean Power's FD values were controlled. DMN: default mode network; SN: Salience network; CEN: central executive network; LP: lateral parietal cortex; PCC: posterior cingulate cortex; MPFC: medial prefrontal cortex; ACC: anterior cingulate cortex; AI: anterior insula; RPFC: rostral prefrontal cortex; LPFC: lateral prefrontal cortex; PPC: posterior parietal cortex; L: left; R: right.

significant condition (rest vs. task) effect on FC between the right lateral prefrontal cortex (R. LPFC) and left posterior parietal cortex (L.PPC). Unexpectedly, post-hoc analyses revealed that rest vs. task FC within the CEN was greater (Table 4). No main group effect or group × condition effects were found. Exploratory analyses revealed that the condition difference in FC was significant only in the rMDD group (Table 5; Fig. 3).

Salience Network (SN): Within the SN, there were main effects of condition (rest vs. task) on FC between the anterior cingulate cortex (ACC) and left anterior insula (AI), as well as between the ACC and right rostral prefrontal cortex (R. RPFC). Post-hoc analyses revealed that FC were greater in the rest vs. task condition (Table 4). No main group or group × condition effects were found. Further exploratory analyses indicated that condition effects were only significant in the HV group (Table 5; Fig. 4).

3.4. Between network FC

DMN-SN FC: Between the DMN and SN, a significant condition (rest vs. task) effect were observed in FC between bilateral LP in DMN and ACC in SN, with FC being smaller in the rest vs. task condition (Table 4); follow-up exploratory analyses revealed that only the rMDD group showed slightly significant condition differences in FC (Table 5; Fig. 5).

CEN-SN FC: Between the CEN and SN, a main effect of condition (rest vs. task) existed in FC between multiple pairs of ROIs (R.LPFC-ACC, R. LPFC-L.RPFC, R.LPFC-bilateral AI, R.PPC-ACC, and L.PPC-L.SMG; Table 4). For all pairs, FC was smaller in the rest vs. task condition (Table 4). Exploratory analyses indicated that this was largely true only in the rMDD group, except the FC between R. LPFC-ACC as well as between L.PPC and L.SMG, which was not significant in either HVs or rMDDs after Bonferroni correction (Table 5; Fig. 6).

DMN-CEN FC: Between the DMN and CEN, a main effect of group on FC existed between the PCC in DMN and R.PPC in the CEN [F (1,32) = 10.13, p_{FDR} = 0.048], with the rMDD vs. HC group having greater FC (t = 3.43, p_{FDR} = 0.001). Although no main condition effect was noted, exploratory analyses revealed that the rMDD group showed greater PCC-R.PPC FC during the task condition (t = 2.72, p_{FDR} = 0.010; Fig. 7; rest: (t = 1.98, p_{FDR} = 0.048; did not survive the Bonferroni correction).

3.5. Correlations between SRRS subscores and FC

Associations were observed between SRRS subscores and FC within the DMN. Specifically, resting-state FC within nodes of the DMN [L.LP-PCC; t(13) = −3.215, partial r = −0.652, p_{FDR} = 0.036; Fig. 8**A**] was negatively correlated with hopeless rumination scores in the rMDD group. On the other hand, task-state FC within nodes of the DMN were positively correlated with active problem solving scores in the rMDD group [PCC_MPFC; t(13) = 3.431, partial r = 0.689, p_{FDR} = 0.024, Fig. 8B; L.LP_MPFC; t(13) = 2.956, partial r = 0.634, p_{FDR} = 0.033, Fig. 8C] in the rMDD group. No association was found between SRRS subscores with other within network FC or between-networks FC features.

4. Discussion

Limited research has been conducted on FC features of major brain networks in individuals with rMDD, including comparisons of task vs. resting-state profiles. In this study, we addressed these gaps by examining FC within and between the most consistent nodes comprising three prominent large-scale brain networks (i.e., DMN, CEN, SN) during an affective cognition taks (eStroop) and resting-state in people with rMDD and healthy volunteers (HVs). In brief, we unexpectedly found greater task vs. resting-state FC within the DMN, and decreased task vs. resting-state FC in the CEN and SN. However, *a priori* exploratory analyses showed condition effects (i.e., rest or task) on FC *within* the DMN and CEN were more pronounced for the rMDD group, while the condition effects on FC *within* the SN were significant only for HVs. Condition effects were also noted on FC between DMN-SN nodes, as well as between CEN-SN nodes, and were mainly significant in the rMDD group. Notably, FC between DMN-CEN nodes were higher in the rMDD vs. HV group, regardless of condition. Finally, exploratory assessments yielded a negative association between hopeless rumination scores in the rMDD group and resting-state FC within the DMN (i.e., higher scores were associated with decreased within-network DMN connectivity), while positive correlations between active problem-solving scores and task FC within the DMN existed (i.e., higher scores were associated with

Table 5
Condition effects in functional connectivity (FC) within and between networks per group.

Network	FC pairs	HVs			rMDD		
		F (1,16)	z-value	p-FDR	F (1,16)	z-value	p-FDR
DMN	L.LP-MPFC	3.06	−1.89	0.198	6.47	−2.37	**0.024***
	L.LP-PCC	0.46	−0.64	0.508	6.17	−2.10	**0.024***
CEN	R.LPFC-L.PPC	1.28	1.04	0.296	14.90	3.73	**0.001***
SN	ACC-L.AI	6.87	2.88	**0.019***	3.80	1.83	0.207
	ACC-R.RPFC	8.03	2.90	**0.019***	2.00	1.13	0.264
DMN-SN	L.LP-ACC	4.17	−1.99	0.116	11.29	−3.23	**0.008****
	R.LP-ACC	0.68	−0.76	0.423	8.96	−2.77	**0.009****
CEN-SN	R.LPFC-ACC	1.01	−0.698	0.330	6.46	−2.94	**0.026**
	R.LPFC-L.RPFC	2.80	−1.51	0.211	8.2	−3.07	**0.017***
	R.LPFC-R.AI	1.02	−1.04	0.330	10.97	−3.65	**0.008****
	R.LPFC-L.AI	2.92	−1.65	0.211	15.85	−4.04	**0.006****
	R.PPC-ACC	2.39	−1.66	0.211	11.12	−3.81	**0.008****
	L.PPC-L.SMG	6.07	−1.97	0.150	1.87	−1.34	0.191

Note: Negative z value reflects resting FC < task FC (white cells). Seed-level FDR correction was first applied. Bonferroni correction was then conducted to correct the multiple comparisons (i.e., two t-tests were done for the condition factor); thus, the significant threshold was at $p_{FDR} < 0.025$ for the post-hoc analyses. *$p_{FDR} < 0.025$; **$p_{FDR} < 0.01$. Age, antidepressant use (yes/no), and mean Power's FD values were controlled for as covariates. DMN: default mode network; SN: Salience network; CEN: central executive network; LP: lateral parietal cortex; PCC: posterior cingulate cortex; MPFC: medial prefrontal cortex; ACC: anterior cingulate cortex; AI: anterior insula; RPFC: rostral prefrontal cortex; LPFC: lateral prefrontal cortex; PPC: posterior parietal cortex; L: left; R: right.

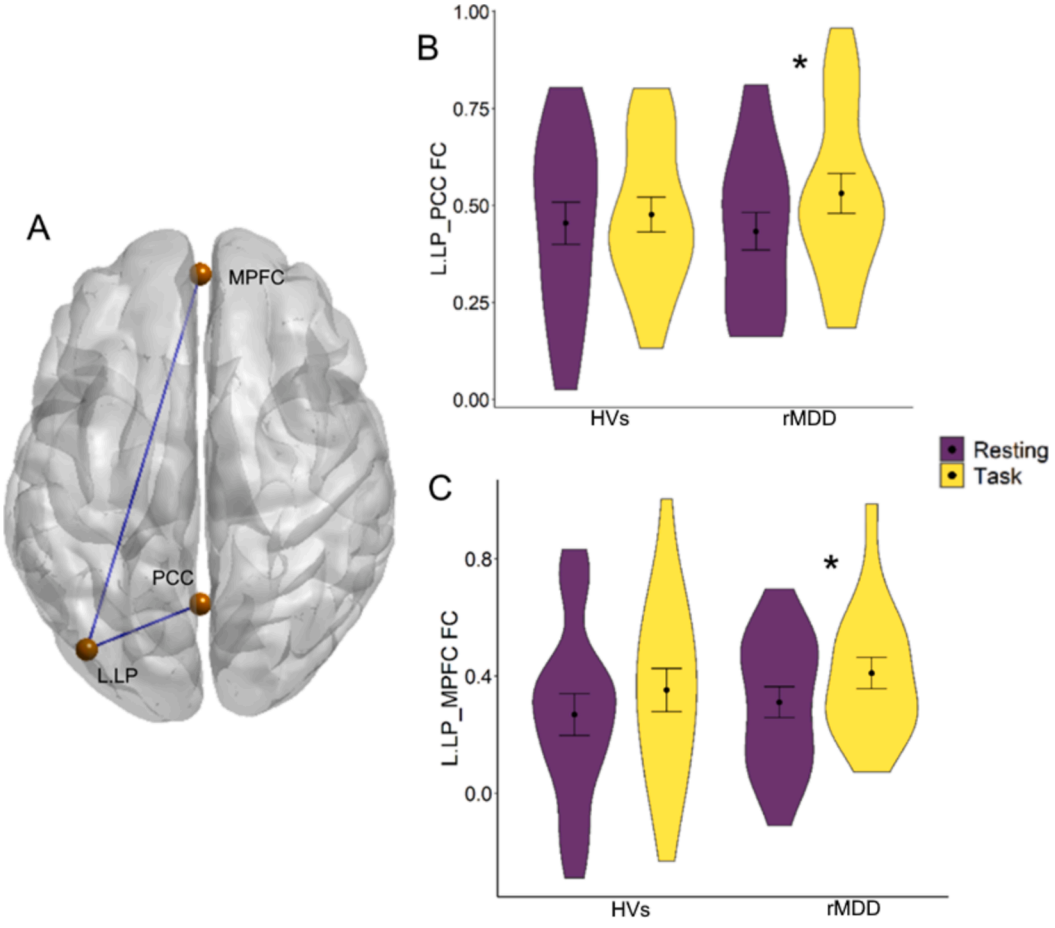

Fig. 2. Decreased functional connectivity (FC) within the default mode network (DMN) during rest vs. task condition. (A) Main condition effects in DMN FC; **(B)** Condition effect in L.LP-PCC FC; **(C)** Condition effect in L.LP-MPFC FC. Age, antidepressant use (yes/no), and mean Power's FD value were included as covariates. Significant threshold was set at $p_{FDR} < 0.05$ for ANCOVA analyses (**A**) and $p_{FDR} < 0.025$ for exploratory t-tests (**B-C**). LP: lateral parietal cortex; PCC: posterior cingulate cortex; MPFC: medial prefrontal cortex; L: left; R: right; HVs: healthy volunteers, rMDD: remitted depressed group.

increased within-network DMN connectivity). These results are discussed below.

4.1. Behavioral results of eStroop

There was no evidence of behavioral differences (RT, accuracy) between emotional conditions during the eStroop task. This finding contrasts with previous studies that reported a negative bias in rMDD (Epp

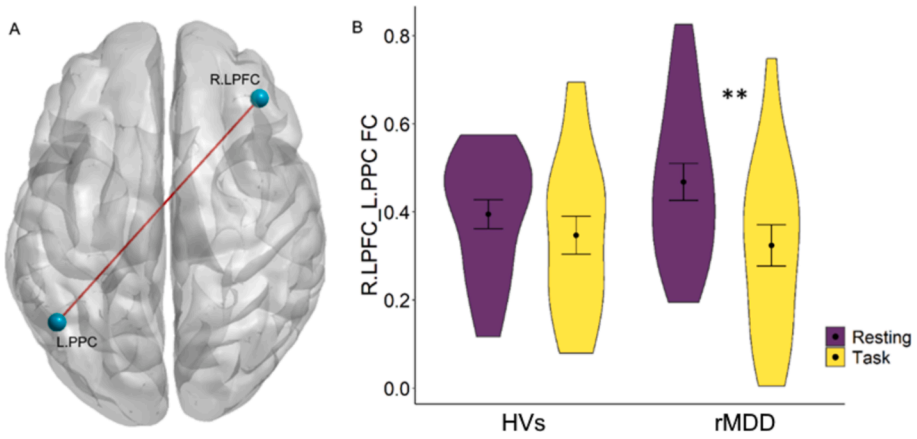

Fig. 3. Greater functional connectivity (FC) within the central executive network (CEN) during rest vs. task condition. (A) Main condition effects in CEN FC; **(B)** Condition effect in R.LPFC-L.PPC FC. Age, antidepressant use (yes/no), and mean Power's FD value were included as covariates. Significant threshold was set at $p_{FDR} < 0.05$ for ANCOVA analyses (**A**) and $p_{FDR} < 0.025$ for exploratory t-tests (**B**). LPFC: lateral prefrontal cortex; PPC: posterior parietal cortex; L: left; R: right; HVs: healthy volunteers, rMDD: remitted depressed group.

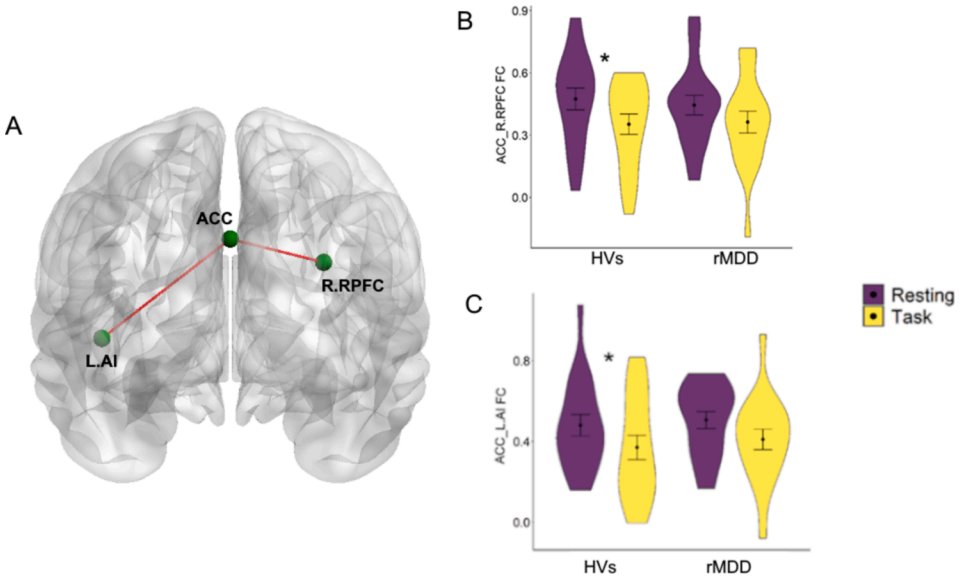

Fig. 4. Greater functional connectivity (FC) within the salience network (SN) during rest vs. task condition. (A) Main condition effects of SN FC; **(B)** Condition effect of ACC-R.RPFC FC; **(C)** Condition effect of ACC-L.AI FC. Age, antidepressant use (yes/no), and mean Power's FD value were included as covariates. Significant threshold was set at $p_{FDR} < 0.05$ for ANCOVA analyses (**A**) and $p_{FDR} < 0.025$ for exploratory t-tests (**B-C**). ACC: anterior cingulate cortex; RPFC: rostral prefrontal cortex; AI: anterior insula; L: left; R: right; HVs: healthy volunteers, rMDD: remitted depressed group.

et al., 2012; Joyal et al., 2019) but aligns with data from HVs, which tends to show a limited or no such bias on the eStroop task (Epp et al., 2012). There was also no evidence of impaired processing speed (i.e., longer RTs) in rMDD vs. HV groups. However, the rMDD cohort exhibited slightly longer (albeit insignificant) RTs; a larger sample size might have yielded a significant effect. The absence of significant negative bias in the rMDD cohort might be partially explained by the choice of words. The emotional words were selected from the ANEW dataset to maximize or minimize valence and then optimize arousal. While it has been suggested that using disorder-congruent and/or self-relevant words may be important in eliciting attentional biases in MDD (Segal et al., 1995) though, two *meta*-analyses found no difference in effect size between depression-specific and generally negative words (Epp et al., 2012; Joyal et al., 2019) in MDD patients during the eStroop suggesting that word choice is not necessarily influential; granted, this is less clear in rMDD.

4.2. Intra-network FC

Across the whole sample, greater FC within nodes comprising the DMN was noted during the eStroop vs. resting-state condition; this is inconsistent with previous studies that generally report greater FC within DMN regions during rest vs. attention (Bray et al., 2015), memory (Fransson & Marrelec, 2008), and auditory (Arbabshirani et al., 2013; Fransson, 2006) tasks. However, (Harrison et al., 2008) found stronger correlations among specific DMN regions during a moral dilemma task vs. resting-state, suggesting that increased DMN FC during rest vs. task might be task dependent (Arbabshirani et al., 2013). Previous research has shown that self-reference/stimulus relevance and emotion play a significant role in sustaining and evoking activity within DMN regions (Gusnard et al., 2001), specifically within the PCC (Northoff, 2016; Qin & Northoff, 2011). Further, a review by Yeshurun et al. (Yeshurun et al., 2021) posited that the DMN should not be considered solely active during internally-oriented or stimulus-independent processes; instead, DMN activity might serves as a bridge between the external and

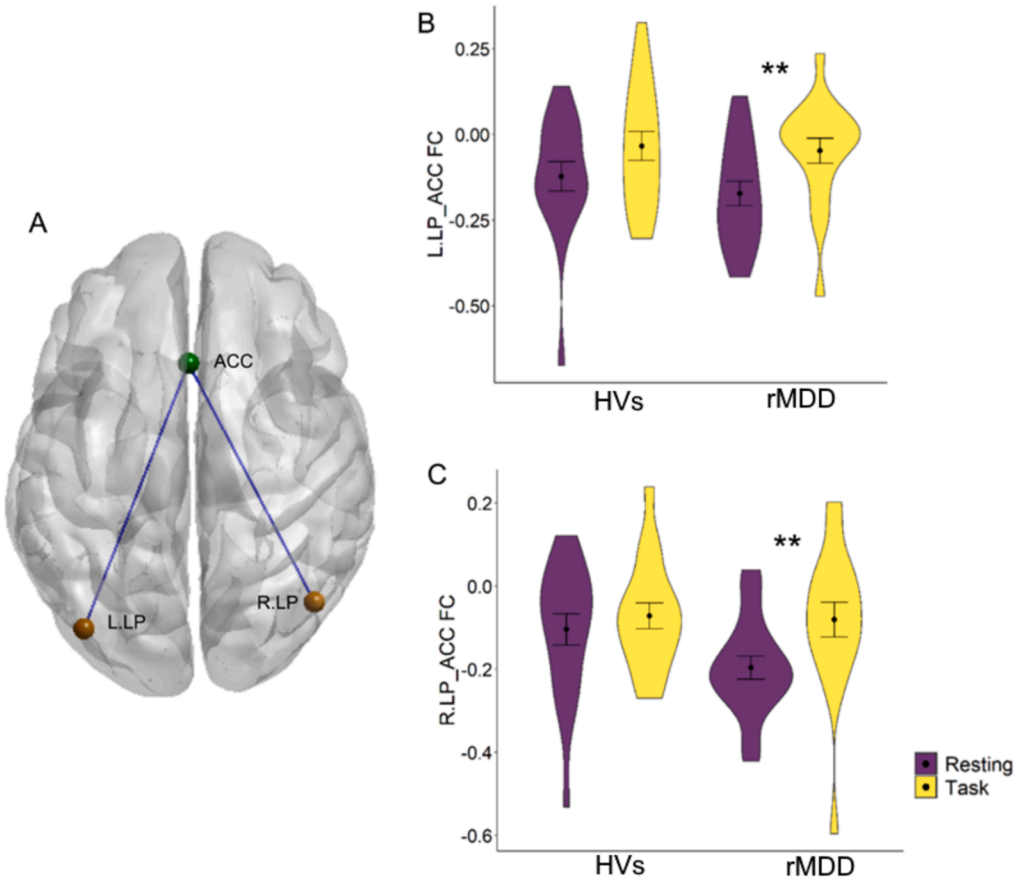

Fig. 5. Decreased functional connectivity (FC) between the default mode network (DMN) and salience network (SN) during rest vs. task conditions. **(A)** Main condition effects of DMN-SN FC; **(B)** Condition effect in L.LP-ACC FC; **(C)** Condition effect in R.LP-ACC FC. Age, antidepressant use (yes/no), and mean Power's FD value were included as covariates. Significant threshold was set at $p_{FDR} < 0.05$ for ANCOVA analyses (**A**) and $p_{FDR} < 0.025$ for exploratory t-tests (**B-C**). LP: lateral parietal cortex; ACC: anterior cingulate cortex; L: left; R: right; HVs: healthy volunteers, rMDD: remitted depressed group.

internal/interior worlds, particularly when external stimuli are related to social cognition (Yeshurun et al., 2021). Such insights might aid with the interpretation of our observed increased DMN node connectivity during the eStroop task vs. rest. Specifically, possible self-referential thought(s) evoked by the task (i.e., salient words) might have elicited greater DMN region engagement during the task vs. rest. Exploratory analysis showed that this condition effect was only significant in the rMDD group, suggesting that individuals in remission from depression may exhibit greater self-involvement/self-reference during this affective cognition task compared to healthy volunteers (HVs).

Previous studies have found that rMDD individuals showed decreased CEN resting-state FC vs. controls, and this CEN hypo-connectivity could account for residual clinical symptoms, particularly in the cognitive domain (Alexopoulos et al., 2012; Dong et al., 2019a; Liu et al., 2021a). In contrast, we did not observe group differences in resting-state FC in the CEN. The discrepancy may be attributed to the mixed-medication status of our rMDD sample; a study by Liu et al. (Liu et al., 2021b) reported that people with rMDD exhibited decreased CEN FC (vs. controls), but this group difference disappeared after 6 months of paroxetine treatment. As such, it is feasible that the inclusion of both medicated and medication-free individuals in our study, while increasing clinical validity, might have attenuated putative group differences in CEN resting-state FC. We did observe greater rest vs. task FC between the R. LPFC and L.PPC (i.e., CEN nodes) across the entire sample, though this was only significant in the rMDD group. Given that limited work has assessed FC between rest vs. task in the CEN, it is challenging to compare our work with those of others. However, one previous study reported decreased efficiency/connectivity of the CEN following negative mood induction (Provenzano et al., 2019). In addition, another electroencephalographic study found that during the eStroop task, individuals with depression had more long-range connections than healthy controls and abnormal functional connectivity in the dorsolateral PFC, which is a component of the CEN (Guo et al., 2018). Such data suggest that affective cognition tasks might influence CEN FC. We also found that FC within the SN was greater during rest vs. task conditions across the entire sample. The SN is known to facilitate a 'network switch' from CEN engagement to DMN disengagement, and vice versa. Further, the CEN and SN have been shown to coactivate during a wide range of cognitive tasks (Menon, 2011); thus, the SN activity pattern appears to mimic what we observed in the CEN. Notably, our exploratory analyses showed that the increased rest vs. task intrinsic SN connectivity was only significant in HVs. Provenzano et al., (2019) reported that negative mood induction increased SN efficiency; thus, it is possible that the affective nature of the task may have been more salient in the rMDD group thus accounting for the lack of difference in intrinsic SN FC compared to the rest condition.

4.3. *Inter-network FC*

Regarding inter-network FC, both the DMN and CEN exhibited greater FC with SN nodes during the eStroop vs. rest conditions across the entire sample; most of these condition effects were significant only in the rMDD group. As outlined, previous work has demonstrated the SN facilitates switching between the DMN and CEN (Doll et al., 2013; Goulden et al., 2014; Sridharan et al., 2008), and tends to co-activate with the CEN across various cognitive tasks (Menon, 2011). As such,

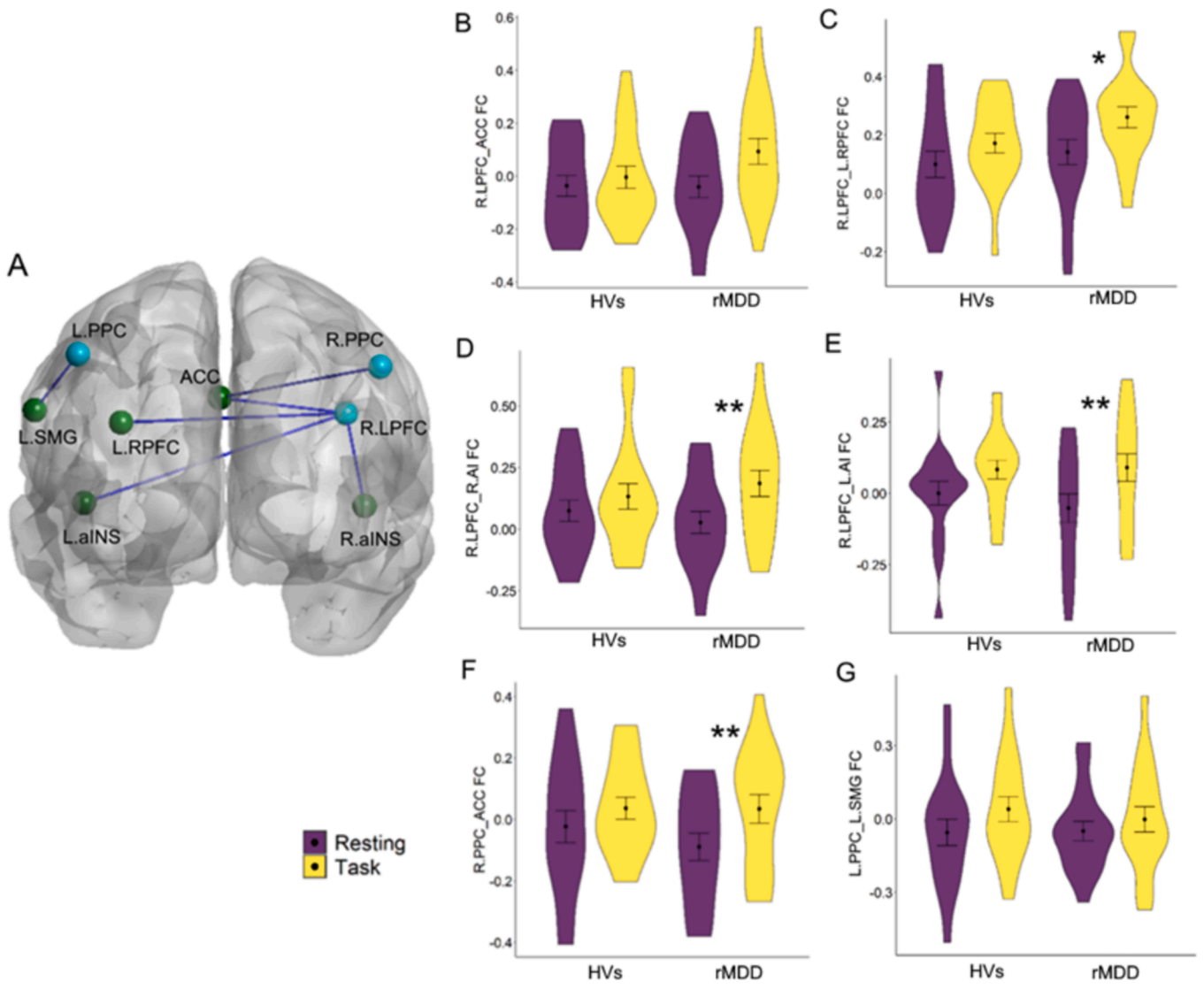

Fig. 6. Decreased functional connectivity (FC) between the central executive network (CEN) and salience network (SN) during rest vs. task conditions. **(A)** Main condition effects of CEN-SN FC; **(B)** Condition effect in R.LPFC-ACC FC; **(C)** Condition effect in R.LPFC-L.RPFC FC; **(D)** Condition effect in R.LPFC-L.AI FC; **(E)** Condition effect in R.LPFC-R.AI FC; **(F)** Condition effect in R.PPC-ACC FC; **(G)** Condition effect in L.PPC-L.SMG FC. Age, antidepressant use (yes/no), and mean Power's FD value were included as covariates. Significant threshold was set at $p_{FDR} < 0.05$ for ANCOVA analyses (**A**) and $p_{FDR} < 0.025$ for exploratory t-tests (**B-G**). LPFC: lateral prefrontal cortex; ACC: anterior cingulate cortex; RPFC: rostral prefrontal cortex; AI: anterior insula; PPC: posterior parietal cortex; SMG: supramarginal gyrus; L: left; R: right; HVs: healthy volunteers, rMDD: remitted depressed group.

our results suggest that rMDD participants might demonstrate overall more pronounced 'switching' between the CEN/DMN via the engagement of the SN to meet task demands and maintain performance.

Notably, the rMDD group also exhibited greater FC between the PCC in the DMN and R.PPC in the CEN compared to HVs across both conditions. Further exploratory analyses revealed that this group difference persisted in the task condition, but did not survive Bonferroni correction in the rest condition. Given the limited evidence on task-state FC in rMDD, comparing our findings directly with other studies is challenging. However, Jacobs et al., (2014) demonstrated hyperconnectivity at rest between the PCC and parietal region of the CEN in youth with rMDD. Jacobs et al., (2014) also noted that this hyperconnectivity was linked to lower self-reported rumination scores. On the other hand, Posner et al., (2016) reported reduced negative connectivity between the DMN and CEN in individuals at high vs. low risk for depression at rest based on family history. Taken together, the observed hyperconnectivity between the PCC and R. PPC in individuals with rMDD suggests an alteration in the interaction between the DMN and CEN, though the implications of this warrant further study.

4.4. Associations between FC and rumination scores in rMDD

Finally, a negative association existed between hopeless rumination scores and DMN FC (i.e., PCC-L.LP) at rest in rMDD participants, indicating that greater rumination was associated with decreased connectivity within the posterior node of the DMN. Previous studies have reported positive associations between rumination and FC in the anterior part of the DMN (e.g., OFC, DLPFC, ACC; Berman et al., 2011; Cooney et al., 2010; Hamilton et al., 2011; Ho et al., 2015; Zhu et al., 2012). However, others have reported negative correlations between FC in the posterior aspect of the DMN (e.g., PCC, parietal cortex) and rumination in individuals with MDD and in rMDD (Jacobs et al., 2016; Rosenbaum et al., 2017). These data, coupled with our own findings, suggest that the anterior and posterior aspects of the DMN might play different roles in rumination in individuals in MDD and rMDD (Zhu et al., 2012). Additionally, we found positive correlations between active problem-solving and FC within nodes of the DMN (i.e., PCC-MPFC; L.LP-MPFC). This finding is consistent with prior findings of robust within-DMN FC during a goal-directed mental simulation task

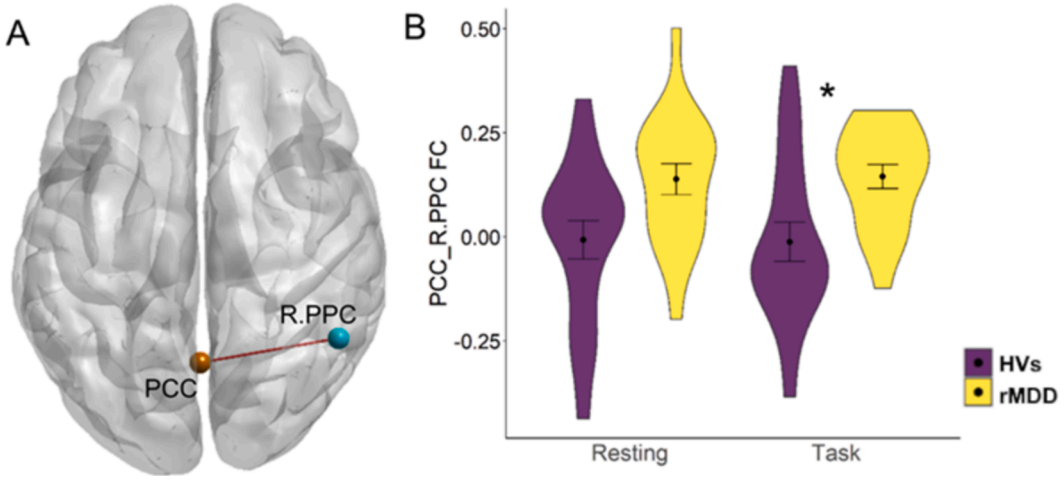

Fig. 7. Greater functional connectivity (FC) between the central executive network (CEN) and salience network (SN) in the remitted depressed (rMDD) vs. healthy volunteer (HV) groups. (A) Main group effect in CEN-SN FC; **(B)** Group effect in PCC_R.PPC FC for both rest and task conditions. Age, antidepressant use (yes/no), and mean Power's FD value were included as covariates. Significant threshold was set at $p_{FDR} < 0.05$ for ANCOVA analyses (**A**) and $p_{FDR} < 0.025$ for exploratory t-tests (**B-C**). PCC: posterior cingulate cortex; PPC: posterior parietal cortex; L: left; R: right.

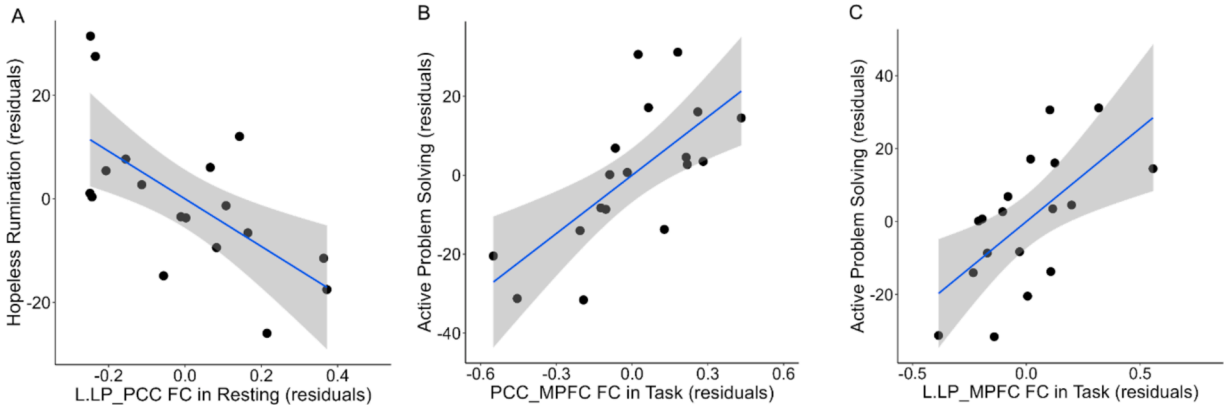

Fig. 8. Association between SRRS subscores and FC within nodes of the DMN in remitted depressed individuals (A) Negative correlation between hopeless rumination scores and resting FC between L.LP and PCC; **(B)** Positive correlation between active problem solving scores and task FC between PCC and MPFC; (C) Positive correlation between active problem solving scores and task FC between L.LP and MPFC; Age, antidepressant use (yes/no), and mean Power's FD value were included as covariates ($p_{FDR} < 0.05$).

(Gerlach et al., 2011) and increased connectivity between the fusiform gyrus and core DMN aspects in individuals who were good at social problem-solving (Poerio et al., 2017). Additionally, intrinsic DMN connectivity has been associated with intrinsic thought (Fox et al., 2005), which may support adaptive problem-solving (Menon, 2023). Further, our exploratory analyses indicated that increased DMN FC during task (vs. rest) was only significant in the rMDD group, perhaps reflecting that those in remission from MDD might be more prone to self-referential thoughts. Together, these data suggest that, in the rMDD cohort, increased connectivity within the DMN during a mildly challenging affective cognition task might be adaptive; granted, this warrants further investigation and replication.

4.5. Limitations

The current study has several limitations. First, our sample size was small (although well-characterized), which limits statistical power. Second, our rMDD sample was comprised of people with a mixed medication status (44.4 % medicated), which might have influenced the FC findings. To address this, we controlled for medication status in our statistics. However, exclusion of medication status as a covariate did not substantially influence the outcomes (data not shown). Nevertheless, this research should be replicated with a larger sample to ensure adequate statistical power for more granular assessments, such as comparisons of medicated and unmedicated cohorts. Third, it is important to note that the exploratory analyses conducted in the current study were based on our *a priori* hypothesis that rMDD and HVs might exhibit condition effects in FC, given altered brain activation patterns observed in previous studies in rMDD cohorts (Wang et al., 2022, 2023; Fang et al., 2022). In other words, it was feasible that more pronounced differences would be noted during the task in the rMDD cohort. While most condition effects appeared to be more pronounced in the rMDD group, the lack of a significant group × condition interaction in intra-network FC suggests that these findings should be interpreted with caution. Future studies with larger sample sizes are needed to confirm whether rMDD exhibits distinct condition (i.e., task vs. rest) effects within the three networks examined herein. Fourth, although the sex distributions were balanced between the rMDD and HV groups, and the inclusion of sex as a covariate did not change our results (data not shown), the lack of sex and/or gender-based analyses is a limitation considering known gender and sex differences in MDD prevalence, symptomology, disease course and connectivity features. Fifth, although the ROI-to-ROI approach has the advantage of reducing statistical comparisons/spurious results and enhances comparisons with others'

work, this dimensional reduction might overlook information about distributed network activity in rMDD. Additionally, to compare triple network FC patterns between rest and task conditions, a standard FC analysis approach was used. While not the aim of the current work, to better investigate tasked-based FC, psychophysiological interaction (PPI) analysis should be considered in the future to compare valence effects in the eStroop task (neutral, positive, negative words). Last, while we did not aim to predict relapse risk or specifically compare individuals with a single episode to those with multiple episodes, exploring these aspects would be an excellent direction for future research.

5. Conclusions

To our knowledge, this study is the first to compare putative condition (rest vs. task) and group (HVs vs. rMDD) differences in triple network FC features in the context of rMDD. Overall, we observed condition-related differences in FC between nodes of the triple network, suggesting that affective cognition tasks may alter functional coupling between these networks. While further confirmatory studies are needed, our observations hint at more pronounced condition differences (i.e., rest vs. eStroop/task) in the FC of the triple network within the rMDD group. Notably, the rMDD group exhibited increased FC between DMN and CEN aspects. Further, our finding of a negative association between rumination scores and resting-state DMN FC implies that decreased FC might be associated with decreased resilience. Conversely, the positive association between active problem-solving scores and DMN FC during the task suggests that enhanced internal mental processes during a relatively low demand but affective/perhaps self-referential task might be adaptive in rMDD. The current study provides insights into the triple network FC profiles of individuals in remission from MDD and the neural correlates of rumination.

CRediT authorship contribution statement

Zhuo Fang: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Emma Lynn:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Verner J. Knott:** Conceptualization. **Natalia Jaworska:** Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the 'Emerging Researchers in Mental Health Research (eRIM(h)) Award' supported by the Insitute of Mental Health Research (awarded to Natalia Jaworska). All authors report no biomedical financial interests or potential conflicts of interest.

Author contributions

N.J. and V.K. designed the current study. E.L. was responsible for the data collection. Z.F., E.L., and N.J. conducted the data analyses and prepared the manuscript. All authors discussed the results, edited and revised the manuscript.

Data availability

Data will be made available on request.

References

Alexopoulos, G.S., Meyers, B.S., Young, R.C., Kalayam, B., Kakuma, T., Gabrielle, M., Sirey, J.A., Hull, J., 2000. Executive dysfunction and long-term outcomes of geriatric depression. *Arch. Gen. Psychiatry* 57 (3), 285–290.

Alexopoulos, G.S., Hoptman, M.J., Kanellopoulos, D., Murphy, C.F., Lim, K.O., Gunning, F.M., 2012. Functional connectivity in the cognitive control network and the default mode network in late-life depression. *J. Affect. Disord.* 139 (1), 56–65.

Altamirano, L.J., Miyake, A., Whitmer, A.J., 2010. When mental inflexibility facilitates executive control: beneficial side effects of ruminative tendencies on goal maintenance. *Psychol. Sci.* 21 (10), 1377–1382.

Arbabshirani, M.R., Havlicek, M., Kiehl, K.A., Pearlson, G.D., Calhoun, V.D., 2013. Functional network connectivity during rest and task conditions: a comparative study. *Hum. Brain Mapp.* 34 (11), 2959–2971. https://doi.org/10.1002/hbm.22118.

Bartova, L., Meyer, B.M., Diers, K., Rabl, U., Scharinger, C., Popovic, A., Pail, G., Kalcher, K., Boubela, R.N., Huemer, J., et al., 2015. Reduced default mode network suppression during a working memory task in remitted major depression. *J. Psychiatr. Res.* 64, 9–18.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. *Arch. Gen. Psychiatry* 4 (6), 561–571.

Beck, A.T., Epstein, N., Brown, G., Steer, R.A., 1988. An inventory for measuring clinical anxiety: psychometric properties. *J. Consult. Clin. Psychol.* 56 (6), 893–897. https://doi.org/10.1037/0022-006X.56.6.893.

Berman, M.G., Peltier, S., Nee, D.E., Kross, E., Deldin, P.J., Jonides, J., 2011. Depression, rumination and the default network. *Soc. Cogn. Affect. Neurosci.* 6 (5), 548–555. https://doi.org/10.1093/scan/nsq080.

Berwian, I.M., Wenzel, J.G., Kuehn, L., Schnuerer, I., Kasper, L., Veer, I.M., Seifritz, E., Stephan, K.E., Walter, H., Huys, Q.J.M., 2020. The relationship between resting-state functional connectivity, antidepressant discontinuation and depression relapse. *Sci. Rep.* 10 (1), 22346.

Bessette, K.L., Jenkins, L.M., Skerrett, K.A., Gowins, J.R., DelDonno, S.R., Zubieta, J.-K., McInnis, M.G., Jacobs, R.H., Ajilore, O., Langenecker, S.A., 2018. Reliability, convergent validity and time invariance of default mode network deviations in early adult major depressive disorder. *Front. Psych.* 9, 244.

Bolton, T.A.W., Wotruba, D., Buechler, R., Theodoridou, A., Michels, L., Kollias, S., Rössler, W., Heekeren, K., Van De Ville, D., 2020. Triple network model dynamically revisited: lower salience network state switching in pre-psychosis. *Front. Physiol.* 11, 66.

Bora, E., Harrison, B.J., Yücel, M., Pantelis, C., 2013. Cognitive impairment in euthymic major depressive disorder: a meta-analysis. *Psychol. Med.* 43 (10), 2017–2026.

Bradley, M.M., Lang, P.J. (1999). *Affective norms for English words (ANEW): Instruction manual and affective ratings*.

Bray, S., Arnold, A.E.G.F., Levy, R.M., Iaria, G., 2015. Spatial and temporal functional connectivity changes between resting and attentive states. *Hum. Brain Mapp.* 36 (2), 549–565. https://doi.org/10.1002/hbm.22646.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124 (1), 1–38.

Bylsma, L.M., Morris, B.H., Rottenberg, J., 2008. A meta-analysis of emotional reactivity in major depressive disorder. *Clin. Psychol. Rev.* 28 (4), 676–691. https://doi.org/10.1016/j.cpr.2007.10.001.

Chai, X.J., Castañón, A.N., Öngür, D., Whitfield-Gabrieli, S., 2012. Anticorrelations in resting state networks without global signal regression. *Neuroimage* 59 (2), 1420–1428.

Cooney, R.E., Joormann, J., Eugène, F., Dennis, E.L., Gotlib, I.H., 2010. Neural correlates of rumination in depression. *Cogn. Affect. Behav. Neurosci.* 10 (4), 470–478. https://doi.org/10.3758/CABN.10.4.470.

Cormie, M.A., Kaya, B., Hadjis, G.E., Mouseli, P., Moayedi, M., 2023. Insula-cingulate structural and functional connectivity: an ultra-high field MRI study. *Cereb. Cortex* 33 (17), 9787–9801.

Craig, A.D., 2002. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat. Rev. Neurosci.* 3 (8), 655–666.

Craig, A.D., 2009. How do you feel—now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* 10 (1), 59–70.

Delaveau, P., Arruda Sanchez, T., Steffen, R., Deschet, K., Jabourian, M., Perlbarg, V., Gasparetto, E.L., Dubal, S., e Silva, J., Fossati, P., 2017. Default mode and task-positive networks connectivity during the N-Back task in remitted depressed patients with or without emotional residual symptoms. *Hum. Brain Mapp.* 38 (7), 3491–3501.

Demeyer, I., De Lissnyder, E., Koster, E.H.W., De Raedt, R., 2012. Rumination mediates the relationship between impaired cognitive control for emotional information and depressive symptoms: a prospective study in remitted depressed adults. *Behav. Res. Ther.* 50 (5), 292–297.

Dickson, K.S., Ciesla, J.A., Zelic, K., 2017. The role of executive functioning in adolescent rumination and depression. *Cogn. Ther. Res.* 41, 62–72.

Doganci, N., Iannotti, G.R., Ptak, R., 2023. Task-based functional connectivity identifies two segregated networks underlying intentional action. *Neuroimage* 268. https://doi.org/10.1016/j.neuroimage.2023.119866.

Doll, A., Sorg, C., Manoliu, A., Wöller, A., Meng, C., Förstl, H., Zimmer, C., Wohlschläger, A.M., Riedl, V., 2013. Shifted intrinsic connectivity of central executive and salience network in borderline personality disorder. *Front. Hum. Neurosci.* https://doi.org/10.3389/fnhum.2013.00727.

Dong, D., Li, C., Ming, Q., Zhong, X., Zhang, X., Sun, X., Jiang, Y., Gao, Y., Wang, X., Yao, S., 2019a. Topologically state-independent and dependent functional connectivity patterns in current and remitted depression. *J. Affect. Disord.* 250 (February), 178–185. https://doi.org/10.1016/j.jad.2019.03.030.

Dong, D., Ming, Q., Zhong, X., Pu, W., Zhang, X., Jiang, Y., Gao, Y., Sun, X., Wang, X., Yao, S., 2019b. State-independent alterations of intrinsic brain network in current

and remitted depression. *Prog. Neuro-Psychopharmaco. Biol. Psychiatry* 89 (July 2018), 475–480. https://doi.org/10.1016/j.pnpbp.2018.08.031.
Elton, A., Gao, W., 2014. Divergent task-dependent functional connectivity of executive control and salience networks. *Cortex* 51, 56–66.
Epp, A.M., Dobson, K.S., Dozois, D.J.A., Frewen, P.A. (2012). A systematic meta-analysis of the Stroop task in depression. In *Clinical Psychology Review* (Vol. 32, Issue 4, pp. 316–328). Elsevier Inc. doi; 10.1016/j.cpr.2012.02.005.
Fang, Z., Lynn, E., Huc, M., Fogel, S., Knott, V.J., Jaworska, N., 2022. Simultaneous EEG + fMRI study of brain activity during an emotional Stroop task in individuals in remission from depression. *Cortex* 155, 237–250. https://doi.org/10.1016/j.cortex.2022.07.010.
Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc. Natl. Acad. Sci.* 102 (27), 9673–9678.
Fransson, P., 2006. How default is the default mode of brain function?: further evidence from intrinsic BOLD signal fluctuations. *Neuropsychologia* 44 (14), 2836–2845.
Fransson, P., Marrelec, G., 2008. The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: evidence from a partial correlation network analysis. *Neuroimage* 42 (3), 1178–1184.
Fritzsche, A., Dahme, B., Gotlib, I.H., Joormann, J., Magnussen, H., Watz, H., Nutzinger, D.O., Von Leupoldt, A., 2010. Specificity of cognitive biases in patients with current depression and remitted depression and in patients with asthma. *Psychol. Med.* 40 (5), 815–826. https://doi.org/10.1017/S0033291709990948.
Gejman, P.V. (1999). Family Interview for Genetic Studies. *Genome-Wide Association Study of Schizophrenia*.
Gerlach, K.D., Spreng, R.N., Gilmore, A.W., Schacter, D.L., 2011. Solving future problems: default network and executive activity associated with goal-directed mental simulations. *Neuroimage* 55 (4), 1816–1824.
Gollan, J.K., Hoxha, D., Hunnicutt-Ferguson, K., Norris, C.J., Rosebrock, L., Sankin, L., Cacioppo, J., 2016. Twice the negativity bias and half the positivity offset: evaluative responses to emotional information in depression. *J. Behav. Ther. Exp. Psychiatry* 52, 166–170. https://doi.org/10.1016/j.jbtep.2015.09.005.
Golland, Y., Bentin, S., Gelbard, H., Benjamini, Y., Heller, R., Nir, Y., Hasson, U., Malach, R., 2007. Extrinsic and intrinsic systems in the posterior cortex of the human brain revealed during natural sensory stimulation. *Cereb. Cortex* 17 (4), 766–777.
Gotlib, I.H., Joormann, J., 2010. Cognition and depression: current status and future directions. *Annu. Rev. Clin. Psychol.* 6, 285–312. https://doi.org/10.1146/annurev.clinpsy.121208.131305.
Goulden, N., Khusnulina, A., Davis, N.J., Bracewell, R.M., Bokde, A.L., McNulty, J.P., Mullins, P.G., 2014. The salience network is responsible for switching between the default mode network and the central executive network: replication from DCM. *Neuroimage* 99, 180–190. https://doi.org/10.1016/j.neuroimage.2014.05.052.
Guo, Z., Wu, X., Liu, J., Yao, L., Hu, B., 2018. Altered electroencephalography functional connectivity in depression during the emotional face-word Stroop task. *J. Neural Eng.* 15 (5), aacdbb. https://doi.org/10.1088/1741-2552/aacdbb.
Gusnard, D.A., Akbudak, E., Shulman, G.L., Raichle, M.E., 2001. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc. Natl. Acad. Sci.* 98 (7), 4259–4264.
Hamilton, J.P., Furman, D.J., Chang, C., Thomason, M.E., Dennis, E., Gotlib, I.H., 2011. Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination. *Biol. Psychiatry* 70 (4), 327–333. https://doi.org/10.1016/j.biopsych.2011.02.003.
Hamilton, J.P., Farmer, M., Fogelman, P., Gotlib, I.H., 2015. Depressive rumination, the default-mode network, and the dark matter of clinical neuroscience. *Biol. Psychiatry* 78 (4), 224–230. https://doi.org/10.1016/j.biopsych.2015.02.020.
Hardeveld, F., Spijker, J., De Graaf, R., Nolen, W.A., Beekman, A.T.F., 2010. Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatr. Scand.* 122 (3), 184–191.
Harrison, B.J., Pujol, J., López-Solà, M., Hernández-Ribas, R., Deus, J., Ortiz, H., Soriano-Mas, C., Yücel, M., Pantelis, C., Cardoner, N., 2008. Consistency and functional specialization in the default mode brain network. *Proc. Natl. Acad. Sci. USA* 105 (28), 9781–9786. https://doi.org/10.1073/pnas.0711791105.
Hasselbalch, B.J., Knorr, U., Kessing, L.V., 2011. Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. *J. Affect. Disord.* 134 (1–3), 20–31.
Ho, T.C., Connolly, C.G., Blom, E.H., LeWinn, K.Z., Strigo, I.A., Paulus, M.P., Frank, G., Max, J.E., Wu, J., Chan, M., et al., 2015. Emotion-dependent functional connectivity of the default mode network in adolescent depression. *Biol. Psychiatry* 78 (9), 635–646.
Hwang, J.W., Egorova, N., Yang, X.Q., Zhang, W.Y., Chen, J., Yang, X.Y., Hu, L.J., Sun, S., Tu, Y., Kong, J., 2015. Subthreshold depression is associated with impaired resting-state functional connectivity of the cognitive control network. *Transl. Psychiatry* 5 (11), e683–e.
Israel, J.A., 2010. The impact of residual symptoms in major depression. *Pharmaceuticals* 3 (8), 2426–2440.
Jacobs, R.H., Jenkins, L.M., Gabriel, L.B., Barba, A., Ryan, K.A., Weisenbach, S.L., Verges, A., Baker, A.M., Peters, A.T., Crane, N.A., Gotlib, I.H., Zubieta, J.K., Phan, K.L., Langenecker, S.A., Welsh, R.C., 2014. Increased coupling of intrinsic networks in remitted depressed youth predicts rumination and cognitive control. *PLoS One* 9 (8). https://doi.org/10.1371/journal.pone.0104366.
Jacobs, R.H., Watkins, E.R., Peters, A.T., Feldhaus, C.G., Barba, A., Carbray, J., Langenecker, S.A., 2016. Targeting ruminative thinking in adolescents at risk for depressive relapse: Rumination-focused cognitive behavior therapy in a pilot randomized controlled trial with resting state fMRI. *PLoS One* 11 (11), 1–17. https://doi.org/10.1371/journal.pone.0163952.
Joyal, M., Wensing, T., Levasseur-Moreau, J., Leblond, J., Sack, A. T., & Fecteau, S. (2019). Characterizing emotional Stroop interference in posttraumatic stress disorder, major depression and anxiety disorders: A systematic review and meta-analysis. In *PLoS One* (Vol. 14, Issue 4). Public Library of Science. doi; 10.1371/journal.pone.0214998.
Kaiser, R.H., Andrews-Hanna, J.R., Wager, T.D., Pizzagalli, D.A., 2015. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. *JAMA Psychiat.* 72 (6), 603–611.
Kaiser, R.H., Whitfield-Gabrieli, S., Dillon, D.G., Goer, F., Beltzer, M., Minkel, J., Smoski, M., Dichter, G., Pizzagalli, D.A., 2016. Dynamic resting-state functional connectivity in major depression. *Neuropsychopharmacology* 41 (7), 1822–1830. https://doi.org/10.1038/npp.2015.352.
Koechlin, E., Summerfield, C., 2007. An information theoretical approach to prefrontal executive function. *Trends Cogn. Sci.* 11 (6), 229–235.
Kühn, S., Gallinat, J., 2013. Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis. *Schizophr. Bull.* 39 (2), 358–365.
Liston, C., Chen, A.C., Zebley, B.D., Drysdale, A.T., Gordon, R., Leuchter, B., Voss, H.U., Casey, B.J., Etkin, A., Dubin, M.J., 2014. Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biol. Psychiatry* 76 (7), 517–526.
Liu, J., Fan, Y., Zeng, L.-L., Liu, B., Ju, Y., Wang, M., Dong, Q., Lu, X., Sun, J., Zhang, L., Guo, H., Zhao, F., Li, W., Zhang, L., Li, Z., Liao, M., Zhang, Y., Hu, D., Li, L., 2021b. The neuroprogressive nature of major depressive disorder: evidence from an intrinsic connectome analysis. *Transl. Psychiatry* 11 (1). https://doi.org/10.1038/s41398-021-01227-8.
Liu, G., Jiao, K., Zhong, Y., Hao, Z., Wang, C., Xu, H., Teng, C., Song, X., Xiao, C., Fox, P. T., Zhang, N., Wang, C., 2021a. The alteration of cognitive function networks in remitted patients with major depressive disorder: an independent component analysis. *Behav. Brain Res.* 400 (July 2020), 113018. https://doi.org/10.1016/j.bbr.2020.113018.
Lydon-Staley, D.M., Kuehner, C., Zamoscik, V., Huffziger, S., Kirsch, P., Bassett, D.S., 2019. Repetitive negative thinking in daily life and functional connectivity among default mode, fronto-parietal, and salience networks. *Transl. Psychiatry* 9 (1), 234.
Manoliu, A., Meng, C., Brandl, F., Doll, A., Tahmasian, M., Scherr, M., Schwerthöffer, D., Zimmer, C., Förstl, H., Bäuml, J., et al., 2014. Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. *Front. Hum. Neurosci.* 7, 930.
McKiernan, K.A., D'Angelo, B.R., Kaufman, J.N., Binder, J.R., 2006. Interrupting the "stream of consciousness": an fMRI investigation. *Neuroimage* 29 (4), 1185–1191.
Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn. Sci.* 15 (10), 483–506. https://doi.org/10.1016/j.tics.2011.08.003.
Menon, V. (2023). 20 years of the default mode network: A review and synthesis. In *Neuron* (Vol. 111, Issue 16, pp. 2469–2487). Cell Press. doi; 10.1016/j.neuron.2023.04.023.
Murrough, J.W., Abdallah, C.G., Anticevic, A., Collins, K.A., Geha, P., Averill, L.A., Schwartz, J., DeWilde, K.E., Averill, C., Jia-Wei Yang, G., et al., 2016. Reduced global functional connectivity of the medial prefrontal cortex in major depressive disorder. *Hum. Brain Mapp.* 37 (9), 3214–3223.
Nolen-Hoeksema, S., 2000. The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *J. Abnorm. Psychol.* 109 (3), 504.
Northoff, G., 2016. Is the self a higher-order or fundamental function of the brain? The "basis model of self-specificity" and its encoding by the brain's spontaneous activity. *Cogn. Neurosci.* 7 (1–4), 203–222.
Pan, F., Xu, Y., Zhou, W., Chen, J., Wei, N., Lu, S., Shang, D., Wang, J., Huang, M., 2020. Disrupted intrinsic functional connectivity of the cognitive control network underlies disease severity and executive dysfunction in first-episode, treatment-naive adolescent depression. *J. Affect. Disord.* 264, 455–463.
Papageorgiou, C., Wells, A. (2003). Nature, functions, and beliefs about depressive rumination. *Depressive Rumination: Nature, Theory and Treatment*, 1–20.
Poerio, G.L., Sormaz, M., Wang, H.-T., Margulies, D., Jefferies, E., Smallwood, J., 2017. The role of the default mode network in component processes underlying the wandering mind. *Soc. Cogn. Affect. Neurosci.* 12 (7), 1047–1062.
Posner, J., Cha, J., Wang, Z., Talati, A., Warner, V., Gerber, A., Peterson, B.S., Weissman, M., 2016. Increased default mode network connectivity in individuals at high familial risk for depression. *Neuropsychopharmacology* 41 (7), 1759–1767. https://doi.org/10.1038/npp.2015.342.
Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* 59 (3), 2142–2154.
Provenzano, J., Verduyn, P., Daniels, N., Fossati, P., Kuppens, P., 2019. Mood congruency effects are mediated by shifts in salience and central executive network efficiency. *Soc. Cogn. Affect. Neurosci.* 14 (9), 987–995. https://doi.org/10.1093/scan/nsz065.
Qin, P., Northoff, G., 2011. How is our self related to midline regions and the default-mode network? *Neuroimage* 57 (3), 1221–1233.
Raes, F., Hermans, D., Williams, J.M.G., 2006. Negative bias in the perception of others' facial emotional expressions in major depression: The role of depressive rumination. *J. Nerv. Ment. Dis.* 194 (10), 796–799. https://doi.org/10.1097/01.nmd.0000240187.80270.bb.
Rai, S., Griffiths, K., Breukelaar, I.A., Barreiros, A.R., Chen, W., Boyce, P., Hazell, P., Foster, S., Malhi, G.S., Bryant, R.A., Harris, A.W.F., Korgaonkar, M.S., 2021. Investigating neural circuits of emotion regulation to distinguish euthymic patients with bipolar disorder and major depressive disorder. *Bipolar Disord.* 23 (3), 284–294. https://doi.org/10.1111/bdi.13042.
Raichle, M.E., 2015. The brain's default mode network. *Annu. Rev. Neurosci.* 38, 433–447.

Robinson, M.S., Alloy, L.B., 2003. Negative cognitive styles and stress-reactive rumination interact to predict depression: a prospective study. *Cogn. Ther. Res.* 27, 275–291.
Rock, P.L., Roiser, J.P., Riedel, W.J., Blackwell, A., 2014. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol. Med.* 44 (10), 2029–2040.
Rosenbaum, D., Haipt, A., Fuhr, K., Haeussinger, F.B., Metzger, F.G., Nuerk, H.C., Fallgatter, A.J., Batra, A., Ehlis, A.C., 2017. Aberrant functional connectivity in depression as an index of state and trait rumination. *Sci. Rep.* 7 (1), 1–12. https://doi.org/10.1038/s41598-017-02277-z.
Sambataro, F., Wolf, N.D., Pennuto, M., Vasic, N., Wolf, R.C., 2014. Revisiting default mode network function in major depression: evidence for disrupted subsystem connectivity. *Psychol. Med.* 44 (10), 2041–2051. https://doi.org/10.1017/S0033291713002596.
Seeley, W.W., 2019. The salience network: a neural system for perceiving and responding to homeostatic demands. *J. Neurosci.* 39 (50), 9878–9882.
Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. *J. Neurosci.* 27 (9), 2349–2356.
Segal, Z.V., Truchon, C., Gemar, M., Guirguis, M., Horowitz, L.M., 1995. A priming methodology for studying self-representation in major depressive disorder. *J. Abnorm. Psychol.* 104 (1).
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., et al., 1998. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J. Clin. Psychiatry* 59 (20), 22–33.
Sikora, M., Heffernan, J., Avery, E.T., Mickey, B.J., Zubieta, J.-K., Peciña, M., 2016. Salience network functional connectivity predicts placebo effects in major depression. *Biol. Psychiatry: Cognit. Neurosci. Neuroimaging* 1 (1), 68–76.
Sparks, D.N., Todd, A.D., 1973. Algorithm AS 60: latent roots and vectors of a symmetric matrix. *J. Roy. Stat. Soc.: Ser. C (Appl. Stat.)* 22 (2), 260–265.
Sridharan, D., Levitin, D.J., Menon, V., 2008. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc. Natl. Acad. Sci.* 105 (34), 12569–12574.
Stange, J.P., Bessette, K.L., Jenkins, L.M., Peters, A.T., Feldhaus, C., Crane, N.A., Ajilore, O., Jacobs, R.H., Watkins, E.R., Langenecker, S.A., 2017. Attenuated intrinsic connectivity within cognitive control network among individuals with remitted depression: temporal stability and association with negative cognitive styles. *Hum. Brain Mapp.* 38 (6), 2939–2954.
Stone, L.B., Hankin, B.L., Gibb, B.E., Abela, J.R.Z., 2011. Co-rumination predicts the onset of depressive disorders during adolescence. *J. Abnorm. Psychol.* 120 (3), 752.
Veer, I.M., Beckmann, C.F., Van Tol, M.-J., Ferrarini, L., Milles, J., Veltman, D.J., Aleman, A., Van Buchem, M.A., van der Wee, N.J., Rombouts, S.A.R.B., 2010. Whole brain resting-state analysis reveals decreased functional connectivity in major depression. *Front. Syst. Neurosci.* 4, 41.
Wang, Z., Zou, Z., Xiao, J., Wang, P., Luo, Y., Min, W., He, Y., Yuan, C., Su, Y., Yang, C., Chang, F., Zhu, H. (2022). Task-related neural activation abnormalities in patients with remitted major depressive disorder: A coordinate-based meta-analysis. In *Neuroscience and Biobehavioral Reviews* (Vol. 143). Elsevier Ltd. doi; 10.1016/j.neubiorev.2022.104929.
Wang, Z., He, D., Yang, L., Wang, P., Zou, Z., Xiao, J., Min, W., He, Y., Zhu, H., 2023. Common and distinct patterns of task-related neural activation abnormalities in patients with remitted and current major depressive disorder: a systematic review and coordinate-based meta-analysis. *Neurosci. Biobehav. Rev.* 152. https://doi.org/10.1016/j.neubiorev.2023.105284.
Whitfield-Gabrieli, S., Nieto-Castanon, A., 2012. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect.* 2 (3), 125–141.
World Health Organization. (2023). *Depressive disorder (depression)*.
Wu, D., Yuan, Y., Bai, F., You, J., Li, L., Zhang, Z., 2013. Abnormal functional connectivity of the default mode network in remitted late-onset depression. *J. Affect. Disord.* 147 (1–3), 277–287.
Yan, C.G., Chen, X., Li, L., Castellanos, F.X., Bai, T.J., Bo, Q.J., Cao, J., Chen, G.M., Chen, N.X., Chen, W., Cheng, C., Cheng, Y.Q., Cui, X.L., Duan, J., Fang, Y.R., Gong, Q.Y., Bin, W., Guo, Hou, Z.H., Hu, L., Zang, Y.F., 2019. Reduced default mode network functional connectivity in patients with recurrent major depressive disorder. Proc. Natl. Acad. Sci. USA 116 (18), 9078–9083. https://doi.org/10.1073/pnas.1900390116.
Yang, Y., Zhong, N., Imamura, K., Lu, S., Li, M., Zhou, H., Li, H., Yang, X., Wan, Z., Wang, G., Hu, B., Li, K., 2016. Task and resting-state fMRI reveal altered salience responses to positive stimuli in patients with major depressive disorder. *PLoS One* 11 (5), 1–19. https://doi.org/10.1371/journal.pone.0155092.
Yeshurun, Y., Nguyen, M., Hasson, U., 2021. The default mode network: where the idiosyncratic self meets the shared social world. *Nat. Rev. Neurosci.* 22 (3), 181–192. https://doi.org/10.1038/s41583-020-00420-w.
Zhang, B., Li, S., Zhuo, C., Li, M., Safron, A., Genz, A., Qin, W., Yu, C., Walter, M., 2017. Altered task-specific deactivation in the default mode network depends on valence in patients with major depressive disorder. *J. Affect. Disord.* 207, 377–383.
Zhu, X., Wang, X., Xiao, J., Liao, J., Zhong, M., Wang, W., Yao, S., 2012. Evidence of a dissociation pattern in resting-state default mode network connectivity in first-episode, treatment-naive major depression patients. *Biol. Psychiatry* 71 (7), 611–617.