

**Resting state and task triple network connectivity profiles in remitted depressed patients compared with healthy volunteers**

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## ABSTRACT

In addition to mood symptoms, major depressive disorder (MDD) is characterized by cognitive impairments that can have detrimental impacts on quality of life and daily function, and have been found to persist into remission. In particular, altered affective cognition (e.g. biased attention to negative stimuli) has been reported in MDD, and may continue into remission. Unfortunately, current pharmacotherapies do not adequately address cognitive dysfunction in acute or remitted MDD. Understanding the neurobiological underpinnings of affective cognitive dysfunction in remitted MDD may help inform the development of new interventions to address this lingering problem and the associated poorer functional outcomes.

The triple network model posits that altered functioning of three key networks implicated in normal cognitive function – the default mode network (DMN), central executive network (CEN) and salience network (SN) – underlies cognitive dysfunction in a variety of psychiatric illnesses, including MDD. Though notable exceptions exist, work in acutely depressed MDD patients has found evidence of DMN hyperconnectivity, CEN hypoconnectivity and aberrant SN connectivity both at rest and during the completion of various cognitive tasks. The evidence for triple network connectivity alterations persisting into remission is less robust, and warrants further investigation. Furthermore, there is a paucity of studies examining remitted MDD connectivity during affective tasks.

As such, the primary objectives of this thesis were to: 1) compare resting-state and task triple network connectivity profiles in remitted MDD patients (rMDDs) and healthy volunteers (HVs) at rest, during an affective (emotional Stroop [eStroop]) task, and during rest vs. the task and, 2) assess the relationship between DMN and CEN

connectivity and measures of daily functioning, quality of life and/or negative, self-relational rumination in the rMDD cohort.

Behaviourally, there were findings of an affective attentional bias and impaired processing speed in the rMDD vs. HVs, as revealed by a computerized cognitive test battery. However, we found no evidence of DMN hyperconnectivity or CEN hyperconnectivity in the rMDD study sample. We did find evidence of altered intrinsic CEN and CEN-SN connectivity between the rest and task conditions that seemed driven by the rMDD sample, as well as positive CEN-DMN correlations across the entire sample both at rest and during the eStroop task. Surprisingly, we also found higher intrinsic DMN connectivity during the eStroop task vs. at rest across the whole sample. Finally, we found a positive relationship between task-based CEN connectivity and hopeless rumination, and a significant negative relationship between resting state and task-based DMN connectivity and psychosocial dysfunction in the rMDD sample.

These findings contribute to our understanding of large-scale intrinsic network connectivity alterations during remitted depression, and their relationship to functional outcomes.

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**ABBREVIATIONS**

ACC	Anterior Cingulate Cortex
aCompCor	Anatomical Component-Based Noise Correction Procedure
AI	Anterior Insula
AI(L)	Left Anterior Insula
AI(R)	Right Anterior Insula
ANCOVA	Analysis of Covariance
ANEW	Affective Norms for English Words
ANOVA	Analysis of Variance
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BIC	Brain Imaging Centre
BMI	Body Mass Index
BOLD	Blood-Oxygen-Level-Dependent
CANTAB	Cambridge Neuropsychological Test Automated Battery
CEN	Central Executive Network
CSF	Cerebrospinal Fluid
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DMS	Delayed Matching to Sample Task
DSM	Diagnostic and Statistical Manual
DTI	Diffusion Tensor Imaging
EEG	Electroencephalography
EHI	Edinburgh Handedness Inventory
EPI	Echo Planar Imaging
ERT	Emotion Recognition Task
eStroop	Emotional Stroop Task
FC	Functional Connectivity
FD	Framewise Displacement
FDR	False Discovery Rate
FIGS	Family Interview for Genetic Studies
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
GRE	Gradient Echo
HV	Healthy Volunteers
IDS-SR	Inventory for Depressive Symptomatology, Self-Report version
IPS	Intraparietal Sulcus
LP	Lateral Parietal Cortex
LP(L)	Left Lateral Parietal Cortex
LP(R)	Right Lateral Parietal Cortex

LPFC(L)	Left Lateral Prefrontal Cortex
LPFC(R)	Right Lateral Prefrontal Cortex
LQ	Laterality Quotient
M.I.N.I.	Mini-International Neuropsychiatric Interview
MADRS	Montgomery Asberg Depression Rating Scale
MDCRT	Median Correct Reaction Time
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MDRT	Median Reaction Time
MEMPRAGE	Multi-Echo Magnetization Prepared Rapid Acquisition Gradient Echo
MPFC	Medial Prefrontal Cortex
MTL	Medial Temporal Lobe
NAART	North American Adult Reading Test-Revised
OTS	One Touch Stockings of Cambridge Task
PCC	Posterior Cingulate Cortex
PPC	Posterior Parietal Cortex
PPC(L)	Left posterior parietal cortex
PPC(R)	Right posterior parietal cortex
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire
QC	Quality Control
rMDD	Remitted Major Depressive Disorder
ROI	Region of Interest
RPFC(L)	Left Rostral Prefrontal Cortex
RPFC(R)	Right Rostral Prefrontal Cortex
RT	Reaction Time
RTI	Reaction Time Task
RVP	Rapid Visual Information Processing Task
SAS	Social Adjustment Scale
SCID	Structured Clinical Interview
SMG(L)	Left Supramarginal Gyrus
SMG(R)	Right Supramarginal Gyrus
SN	Saliency Network
SPM12	Statistical Parametric Mapping
SRRS	Stress Reactive Rumination Scale
SWM	Spatial Working Memory Task
TE	Echo Time
TMS	Transcranial Magnetic Stimulation
TR	Repetition Time
WSAS	Work and Social Adjustment Scale

## **Chapter 1: INTRODUCTION**

### **1.1 Major Depressive Disorder**

Major depressive disorder (MDD) is a severe psychiatric illness that is associated with significant personal and societal impairment. The estimated yearly prevalence of depressive disorders (MDD and persistent depressive disorder) in Canada is ~4.3% (1.44 million people affected/year), thereby having a profound impact on the daily lives of Canadians and their families.<sup>1</sup>

### **1.2 Disease Burden**

According to the latest (2017) estimates for the Canadian population, ~150,300 years of life are lost on a yearly basis due to ill health, disability and early death associated with MDD.<sup>1</sup> Globally, depressive disorders are the single largest contributor to non-fatal health-loss, leading to a total of 50 million years lived with disability in 2015 alone.<sup>2</sup> Furthermore, MDD has been consistently associated with poorer daily function and role performance. For example, marital dysfunction and dissatisfaction are strongly related to depressive symptoms, as are maladaptive parenting behaviours and poor financial success (lower personal and household income).<sup>3</sup> There is even evidence that MDD may be a causal risk factor for certain physical diseases, and may elevate mortality risk for these diseases.<sup>3</sup> Beyond the personal and familial burdens of depression, MDD also has far-reaching implications on the economy. The impacts of mental illness on productivity in the workplace include absenteeism, presenteeism (i.e., reduced efficiency) and unemployment. The most recent (2011) Canadian estimates suggest that more than \$6.4 billion are lost each year because of mental illness-related productivity losses alone. The total annual cost of mental illness was estimated to be \$48.7 billion in Canada, representing ~2.8% of Canada's gross domestic product.<sup>4</sup>

### ***1.2.1 Relapse, Recurrence and Remission***

Unfortunately, MDD is also characterized by a high risk of relapse (return of symptoms) and recurrence (multiple depressive episodes). Estimates from specialized mental health care settings suggest that the risk of recurrence one year post-recovery is around 25%, increasing to 85% after 15 years. In the general population, the risk of recurrence 15 years post recovery is approximately 35%.<sup>5</sup> Persistence of some residual depressive symptoms and/or functional impairments into remission is common. The presence of residual symptoms during remission is the single most accurate predictor of risk of relapse for MDD.<sup>6</sup> Remitted MDD (rMDD) patients with residual symptoms are not only at a higher risk of relapse, they are also more likely to experience a chronic illness course and are at an increased risk for psychosocial and socio-economic impairments.<sup>6</sup> One common residual symptom following remission from MDD is cognitive dysfunction: a 3-year prospective study found 94% prevalence of cognitive problems during the acute phase, and 44% during remission.<sup>7</sup>

## **1.3 Cognitive Dysfunction in MDD and Remitted MDD**

Cognitive dysfunction has been identified across many domains in acute MDD, including executive attention, memory, attention, verbal fluency, and cognitive flexibility.<sup>8,9</sup> Meta-analyses of cognitive dysfunction in remitted MDD have identified significant continued deficits in sustained and selective attention, memory, processing speed, semantic fluency and executive function.<sup>8,10,11</sup>

### ***1.3.1 Cognitive Impairment and Functioning***

The exact nature of the relationship between cognition and functional outcomes in depression is still being explored. There is, however, preliminary evidence of both a

predictive and correlational relationship between cognitive dysfunction and daily functioning in acute MDD. For example, one study of recurrent, acutely ill MDD patients found cognitive deficits in the domains of attention, ideational fluency, learning, and nonverbal functions to be predictive of functional disability (acquired difficulty in performing everyday tasks) six months later. Improved cognitive function was also found to be concurrently associated with functional recovery at the 6-month follow-up.<sup>12</sup> Cognitive impairments have also been found to predict global disability, poorer quality of life,<sup>13</sup> and impaired workplace performance<sup>13,14</sup> in MDD. There is also some evidence of a relationship between continued cognitive dysfunction in remission and depressive relapse, though findings have been mixed; some studies have noted evidence of a predictive relationship,<sup>15</sup> while others have not.<sup>16,17</sup>

Despite the high prevalence of cognitive impairment during acute and remitted MDD, and the associated poor functional outcomes, antidepressant pharmacotherapies have demonstrated only modest beneficial effects on cognition.<sup>18</sup> Interestingly, there is some evidence that cognitive impairments during MDD may actually predict poorer treatment response for some antidepressant drugs.<sup>19</sup> Furthermore, a recent systematic review of the effects of biological and psychological interventions on cognition in acute and remitted MDD revealed a relative paucity of trials examining remitted MDD in particular.<sup>20</sup> This lack of research not only limits inferences of causality, it also leaves a gap in evidence-based care for individuals who are remitted from the mood symptoms of MDD but are/may still be suffering from cognitive impairments and their associated poorer functional outcomes. Understanding the neurobiological basis of cognitive

impairment in rMDD may help fill this gap by informing the development of new interventions and focusing the scope of trials for existing interventions in remitted MDD.

### ***1.3.2 Emotional Processing Deficits in MDD***

When studying cognitive impairment in MDD, there is often a distinction between “hot” and “cold” cognition, wherein “hot” cognition involves affective stimuli. This type of cognition is also referred to as affective cognition, and has been studied extensively in the context of MDD. 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.<sup>21,22</sup> This biased emotional processing may be the result of a failure to disengage from negative thoughts or memories,<sup>23</sup> deficits in cognitive control/inhibitory processes and/or an inability to regulate induced negative mood via positive recall.<sup>24</sup>

### **1.4 The Emotional Stroop Task**

One cognitive task - with an emotional component - where MDD deficits are apparent is the emotional Stroop task (eStroop). The classic Stroop task involves presenting words indicating colour (eg. red, yellow) in incongruous ink (eg. the word red in yellow ink). Participants must name the ink colour while ignoring the word. Incongruous words consistently yield longer latencies than congruent words, a finding known as the “Stroop effect”.<sup>25</sup> The Stroop task is therefore thought to tap into selective attention and cognitive flexibility. Emotional versions of the task involve presenting words of negative (e.g. terror), positive (e.g. rainbow) or neutral (e.g. table) valence in different ink colours. Respondents again indicate ink colour, but, this time, word valence

may interfere with the task, as reflected by slower reaction times (RT) to emotional (negative and/or positive) versus neutral words. Findings of the eStroop interference effect in healthy subjects have been inconsistent, with some studies finding an effect,<sup>26-29</sup> and others finding no effect.<sup>30,31</sup> Some of this inconsistency may be attributable to variable methodology (i.e. word choice – arousal has been found to modulate the eStroop effect in healthy volunteers,<sup>26</sup> potential for negative or positive mood induction across a block vs. during a randomized design,<sup>32</sup> etc). It is, however, important to note that a systematic meta-analysis of eStroop literature with a pooled sample size of ~800 healthy subjects found no effect of negatively or positively-valenced emotional stimuli,<sup>33</sup> suggesting the likely absence of an affective interference effect in healthy subjects, at least as indexed by RT (it is feasible that neural differences exist).

#### ***1.4.1 Emotional Stroop Task Performance in MDD***

Findings of the eStroop emotional bias effect in depressed samples have been far more consistent than they have been in healthy subjects. In fact, a recent (2019) meta-analysis of the eStroop task in MDD found evidence of significant attentional bias towards both disorder-congruent and generally negative words in MDD vs. healthy volunteers, and no evidence of a positive word bias.<sup>32</sup> A previous (2012) meta-analysis of the eStroop task in clinically depressed, dysphoric, and sad mood induction samples similarly found evidence of a significant bias towards negative words in the MDD sample only, and no evidence of an affective bias towards positive words.<sup>33</sup> As such, negative bias in the eStroop task is sometimes characterized as a distinguishing feature between depressed vs. healthy samples. There have, however, been studies that have found no group differences in affective bias between MDD and healthy cohorts.<sup>29</sup>

Research on the eStroop effect in remitted depression (rMDD) is much more limited, but there is some preliminary evidence of negative attentional bias in remitted populations, consistent with the acutely depressed individuals.<sup>29,34,35</sup> There have also been findings of longer RTs to all stimuli (negative, neutral and positive) in remitted and acutely depressed individuals vs. healthy volunteers during the eStroop task,<sup>34,35</sup> suggesting impaired processing speed in remitted and acute MDD.

### **1.5 Neurological Underpinnings of Depression**

Neuroimaging has provided important insights into the neural processes underlying MDD, including those that may underlie the interplay of affective and cognition dysfunction in the disorder. In particular, network models of brain function have been increasingly used to explain the neural etiology of psychiatric disorders. Generally speaking, brain networks are composed of a collection of brain regions with temporally correlated activity<sup>36</sup> (a feature typically established via functional connectivity, usually via functional magnetic resonance imaging [fMRI]) and the connections (edges) that link them (established with structural connectivity, via diffusion tensor imaging [DTI] *in vivo* or post-mortem dissections *in vitro*).<sup>37</sup> Large-scale intrinsic connectivity networks are relatively robust, with spontaneous activity within network nodes strongly coupled with one another, regardless of mental state (i.e. during sleep, loss of consciousness, at rest and during tasks); though the strength of the connections may be modulated depending on context.<sup>37</sup> The intrinsic connectivity of networks have also been shown to be less sensitive to artifact pollution (e.g. physiological noise), thus offering a relatively reliable method of characterizing large-scale brain organization across a variety of mental states.

Three large-scale intrinsic connectivity networks have been identified as being particularly important in maintaining normal cognitive function: the default mode network (DMN), central executive network (CEN) and salience network (SN). A seminal 2005 paper by Fox and colleagues found that activity in regions now known to comprise the DMN (i.e., medial prefrontal cortex [MPFC], posterior cingulate cortex [PCC], and lateral parietal cortex [LP]) was routinely lower during a demanding cognitive task, while activity in regions comprising a ‘task-positive’ network (i.e., intraparietal sulcus [IPS], frontal eye field region of the precentral sulcus and the middle temporal region) was routinely higher during the task. Moreover, the activity profiles of these networks were negatively correlated with one another. These findings led Fox et al. to establish the theory that there might be ‘task-positive’ and ‘task-negative’ networks that are diametrically opposed in the healthy human brain.<sup>38</sup> The most commonly studied ‘task-positive’ network in the context of MDD is the frontoparietal CEN, which has been implicated in cognitive control, while the regions studied in the Fox et al. paper underlie the dorsal attention network, which tends to be engaged during visual attention tasks.<sup>39</sup> Comparisons of functional connectivity have shown higher intrinsic DMN connectivity at rest compared to during an attentionally-demanding task in healthy individuals.<sup>40</sup> The opposite pattern (higher connectivity during the attentional task vs. at rest) has been found for the “task-positive” dorsal attention network.<sup>40</sup> These findings suggest that intrinsic network connectivity patterns mirror the “task-negative” (DMN) and “task-positive” (CEN) activity patterns established in the original Fox et al. study.

Later on, a study by Sridharan and colleagues implicated the SN in the activation of the CEN and deactivation of the DMN, thereby acting as a ‘causal outflow hub’

implicated in coordinating the switching between these ‘task-positive’ and ‘task negative’ intrinsic connectivity networks.<sup>41</sup>

The negative correlation between the DMN and CEN has been replicated,<sup>42</sup> but the existence of a diametrically opposite relation between the two networks has been contested in light of evidence that regressing out the mean global signal introduces spurious negative correlations between time series.<sup>43</sup> It has been suggested that the negative task-positive/task-negative internetwork correlations may not truly exist, but were rather artificially introduced by way of this preprocessing method.<sup>44</sup> However, more recent findings of a robust negative correlation between the CEN and DMN using novel alternative denoising tools like CompCor<sup>45</sup> suggest that the task-positive/task-negative findings may indeed be biological in origin.<sup>46</sup> Nevertheless, the use of global signal regression as a denoising technique has continued despite the controversy,<sup>42</sup> perhaps muddying the literature and obscuring the precise relation between these large-scale networks.

### ***1.5.1 Default Mode Network***

The DMN is arguably the best-established and most studied resting-state network. The anchoring nodes of this network are the PCC and MPFC.<sup>37,38</sup> The other nodes of the network are more variably identified in the literature; however, the most common among these are the LP<sup>38</sup> and MTL,<sup>37,47,48</sup> though the caudate, cerebellum, hippocampus, middle temporal gyrus and inferior parietal lobule have all been used as seed regions for the DMN in the MDD literature.<sup>49</sup> This wide variability in seed choice may contribute, in part, to the mixed DMN (or, “so called” DMN) findings in MDD. The PCC is thought to underlie a variety of self-referential processes, including evaluating how one relates to

one's experience, social cognitive processing and craving.<sup>50</sup> The MPFC has been implicated in value processing and emotional experience.<sup>51</sup> Together, the primary nodes of the DMN are thought to comprise a system of self-referential mental processes.

There have been findings of increased intrinsic DMN connectivity at rest<sup>52-54</sup> and during emotional tasks<sup>53,55</sup> in acutely depressed individuals when compared with healthy volunteers. A 2015 meta-analysis noted resting-state DMN hyperconnectivity in MDD, which appeared to be unaffected by variability in seed anatomy, age or depression severity, suggesting that it is a relatively robust feature of the disorder.<sup>49</sup> There is also some evidence of DMN hyperconnectivity in individuals with high familial risk for depression,<sup>56</sup> suggesting it may be a trait (vs. state) marker of depression. Comparatively less research has been devoted to exploring DMN connectivity profiles in remitted MDD patients, and the evidence for DMN dysregulation during remission is therefore less robust. There have been mixed findings in remitted MDD, with some studies finding evidence of resting-state DMN hyperconnectivity alterations compared to healthy volunteers,<sup>47,57</sup> and others finding no such group differences.<sup>58</sup> The task-based connectivity findings have been similarly mixed, with evidence of both DMN hypoconnectivity<sup>47</sup> and hyperconnectivity.<sup>59</sup> These inconsistencies may be attributable to sample characteristics (e.g., one study found significant task-based DMN connectivity alterations in adolescent-onset but not adult-onset rMDD)<sup>59</sup> and/or methodological variability (i.e. scan length, analysis techniques, choice of DMN seed regions etc), particularly task choice.

#### *1.1.1.1 Default Mode Network Interference Hypothesis of Cognitive Dysfunction*

Individuals with MDD often experience repetitive, negative, self-focused thoughts. These intrusive thought patterns are referred to as rumination, and are characterized by a focus on past events, as well as low confidence in and/or effort to problem-solve.<sup>60</sup> Rumination has been found to predict the onset,<sup>61–63</sup> severity<sup>62,63</sup> and duration<sup>62</sup> of depressive episodes. It has been proposed that rumination may deplete cognitive resources, thereby contributing to the cognitive impairments observed in MDD. Indeed, there is evidence of a link between rumination and executive function (specifically set-shifting) impairments in MDD<sup>64,65</sup> and in rMDD.<sup>66</sup>

It has been proposed that increased DMN activity (and connectivity) may interfere during cognitive tasks thereby contributing to cognitive dysfunction in MDD.<sup>67</sup> The ‘default-mode network interference’ hypothesis suggests that this interference is linked to negative introspective thoughts (i.e. rumination) characteristic of the self-referential DMN, and that task performance might decline as a function of reduced attentional resources. There have been experimental findings that support this hypothesis. For example, reduced rumination following rumination-focused cognitive behavioural therapy in remitted depression has been associated with reduced intrinsic DMN connectivity.<sup>68</sup>

### ***1.5.2 Central Executive Network***

The CEN, also known as the frontoparietal network due to its spatial distribution, has been implicated in a variety of cognitive functions. In particular, it has been associated with working memory maintenance, rule-based problem solving and decision-making for goal-directed behaviors.<sup>37</sup> The anchoring nodes of this network are the dorsolateral prefrontal cortex (DLPFC) and lateral posterior parietal cortex (PPC), with

the caudate and cerebellum occasionally identified as nodes in the MDD literature.<sup>49</sup> As is the case with the DMN, variable seed choice may contribute, in part, to the diversity of CEN findings in MDD. The left DLPFC has been implicated in emotional judgement<sup>69</sup> and information manipulation in working memory<sup>70</sup>, whereas the right DLPFC is thought to be involved in attention to emotional judgement<sup>69</sup> and spatial reasoning.<sup>70</sup> The PPC has been implicated in emotional regulation, specifically positive reappraisal.<sup>71</sup>

Depression-related CEN connectivity alterations have not been studied as extensively as those of the DMN; nevertheless, there have been some findings of resting-state CEN hypoconnectivity in MDD.<sup>54,72</sup> In fact, a 2015 meta-analysis found evidence of resting-state hypoconnectivity within the CEN in MDD which was unmoderated by age, medication status or depression severity, suggesting that CEN hypoconnectivity might be a relatively robust feature of MDD, regardless of sample characteristics.<sup>49</sup> Furthermore, depressive CEN hypoconnectivity at rest has been associated with poor antidepressant treatment outcomes (symptom persistence, low remission, apathy, and executive dysfunction), suggesting these connectivity alterations are behaviourally relevant.<sup>72</sup> There have been comparatively fewer studies examining CEN profiles in remitted MDD, but there is preliminary evidence of resting-state CEN hypoconnectivity persisting into remission,<sup>73</sup> and of increased intrinsic resting-state CEN connectivity after antidepressant discontinuation predicting a lack of subsequent relapse in remitted patients.<sup>58</sup> There is a marked gap in the literature examining task-based CEN connectivity in MDD and rMDD, with most prior literature having focused on activity (not connectivity) in the CEN during tasks.

### ***1.5.3 Salience Network***

The SN is anchored in the dorsal anterior cingulate cortex (ACC) and anterior insula (AI). It has been implicated in the bottom-up detection of salient events and subsequent switching between internally focused and externally focused attention, and their associated patterns of brain activity, facilitating a reaction to salient stimuli.<sup>41</sup> Effective connectivity estimates by way of Granger causality analysis have established a causal role of the AI in switching between the “task-negative” DMN and “task-positive” CEN activity patterns.<sup>74</sup>

Given that its functional role is dependent on interactions with other networks, not a lot of studies have examined intrinsic SN functional connectivity alterations in remitted or acutely ill depressed patients. However, there is some evidence of decreased resting-state intrinsic SN connectivity in depressed individuals compared to healthy volunteers.<sup>75,76</sup> Furthermore, there is evidence that aberrant SN connectivity in depression is modulated by depressive symptomology, with one study finding higher intrinsic SN connectivity in apathetic vs. non-apatetic late-life depression.<sup>77</sup> There is also a potential link with treatment response: higher resting-state SN connectivity has been associated with both successful antidepressant response and with placebo-induced depressive symptom reduction in MDD patients.<sup>78</sup> These findings suggest further investigation of SN connectivity alterations in both MDD and rMDD is warranted.

#### ***1.5.4 Inter-network Connectivity***

The CEN and DMN are typically negatively correlated in the healthy human brain.<sup>37</sup> There have been findings of attenuated (weaker negative correlation) resting-state DMN-CEN connectivity in acutely-ill MDD patients<sup>49,76</sup> and in individuals with high familial risk for depression.<sup>56</sup> Furthermore, altered connectivity between the DMN and

CEN has been found to predict maladaptive rumination following sad mood induction<sup>79</sup> and has been linked to ruminative tendencies<sup>57</sup> in rMDD, suggesting that this aberrant internetwork connectivity may play an important role in rumination. Interestingly, antidepressant treatment with excitatory transcranial magnetic stimulation (TMS) over the left DLPFC has been found to increase negative correlations between the DMN and CEN in acutely ill MDD patients,<sup>54</sup> thus ‘normalizing’ the abnormal patterns of weak inter-network negative correlations found to underlie the depressive state.

Nodes of the CEN (DLPFC) and SN (AI, ACC) commonly co-activate during a wide range of cognitive tasks in the healthy human brain.<sup>37</sup> There have been findings of decreased connectivity between the CEN and SN at rest in individuals with sub-clinical depressive symptoms<sup>80</sup> and those with diagnosed MDD.<sup>81</sup>

There is evidence of increased coupling of the SN and DMN during tasks vs. at rest in healthy adults, suggesting context-dependent cooperation/coactivation patterns between the networks in the healthy brain.<sup>82</sup> Interestingly, the connectivity between the SN and DMN has also been found to increase as a function of increased working memory load in healthy adults, suggesting that task demands play a key role in the interplay between these two networks.<sup>83</sup> There have been findings of decreased resting-state DMN-SN connectivity during depression<sup>49,84</sup> and remitted MDD (relative to non-depressed volunteers),<sup>85</sup> suggesting a potential breakdown of normal internetwork communication in acutely and formerly depressed states. However, there have also been findings of increased functional connectivity between the SN and DMN in acutely depressed individuals relative to healthy controls.<sup>76</sup> Given the relative paucity of studies, the directionality of abnormal DMN-SN connectivity in MDD and rMDD remains unclear.

### ***1.5.5 The Triple Network Model***

Together, the DMN, CEN and SN comprise what is known as the ‘triple network model’, which has been proposed as a common framework for understanding the neurological underpinnings of cognitive dysfunction in multiple psychiatric disorders, including MDD.<sup>37</sup> This model posits that abnormalities in these three networks (i.e. abnormal intrinsic and inter-network connectivity) are responsible for the cognitive dysfunction experienced during MDD. These abnormalities can manifest in two main ways: alterations to the nodes themselves (eg. grey matter, white matter, and/or cytoarchitecture alterations in specific brain regions) or dysfunctional communication between the nodes (eg. small-world architecture abnormalities and/or connectivity alterations).<sup>37</sup> It is also acknowledged that altered structure can underlie altered connectivity between regions (and vice versa). This thesis will focus on exploring putatively dysfunctional communication between DMN, CEN and SN nodes in rMDD.

### **1.6 Objectives**

The main objective of this thesis is to compare resting-state and task triple network connectivity profiles in rMDD patients and healthy volunteers (HVs), with a focus on DMN and CEN connectivity, with exploratory SN analyses. Connectivity will be assessed: 1) at rest; 2) during the eStroop task, and 3) during rest vs. the eStroop task. Behavioural outcomes of the eStroop task will also be assessed (RT, accuracy).

A secondary objective is to assess the relationship between DMN and CEN connectivity and daily functioning, quality of life and/or negative, self-relational rumination in remitted depression. Given that cognitive impairment in depression has been linked to functional disability<sup>12</sup>, psychosocial dysfunction<sup>86</sup> and poorer quality of

life<sup>13</sup>, correlations between neural profiles associated with cognitive dysfunction (i.e., DMN/CEN connectivity alterations) and daily function or quality of life may emerge in the remitted depression sample. We also aimed to replicate previous findings of correlations between negative self-relational rumination and DMN dysfunction in rMDD.<sup>68</sup>

## 1.7 Hypotheses

We did not expect to find differences in eStroop accuracy between the HVs and rMDDs based on previous findings (i.e. an expected ceiling effect).<sup>87</sup> We expected longer RTs to negatively-valenced words compared to neutral words in rMDDs, indicating an attentional bias towards negative stimuli. We also expected to see longer RTs in rMDDs vs. HVs across all affective conditions, indicating impaired processing speed within an emotional context.

Based on previous, albeit limited, research, we expected to find increased DMN connectivity at rest and during an emotional Stroop (eStroop) task in rMDD participants vs. HVs. We expected decreased CEN connectivity in rMDDs vs. HVs at rest, and increased CEN connectivity during the task vs. at rest in HVs and rMDDs. Task-based CEN connectivity, SN and inter-network connectivity profiles were explored, as data on connectivity profiles in these large-scale networks is lacking in rMDD cohorts. Indeed, this is even true in acutely depressed individuals, as most task-based work has focused on *activity* within network nodes rather than connectivity.

We expected worse daily functioning and quality of life to correlate with higher DMN connectivity and lower CEN connectivity at rest and during the task in the rMDD sample. Higher levels of negative, self-relational rumination were expected to correlate

with higher DMN connectivity and lower CEN connectivity at rest and during the task in the rMDD sample.

## **Chapter 2: METHODS**

The data presented and analyzed as part of this thesis was embedded in a larger study. Importantly, simultaneous electroencephalography (EEG) and fMRI were acquired for the resting state and task conditions. This necessitated specific hardware, procedural, and scanning parameter choices in order to maintain safety standards and maximize data quality for both modalities. Some references to these EEG-fMRI procedures will be made throughout the thesis because of the effects these procedures had on fMRI data acquisition and analysis.

### **2.1 Participants**

18 remitted depressed participants (rMDD; 14F/4M) and 21 healthy volunteers (HV; 16F/5M) were recruited 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 years old) with no current or lifetime major medical illnesses or neurological conditions that could have a substantial impact on neuroimaging results (e.g. stroke, frequent migraines, seizures). Prospective participants 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. Individuals with colour blindness were also excluded, as colour discrimination was necessary for this study, specifically for eStroop task completion (details below). Further, all participants were required to have a body mass index (BMI) <38 kg/m<sup>2</sup> due to the physical constraints of the MRI scanner bore. Participants were also excluded if they reported high caffeine (>4 cups of coffee/day, daily) or alcohol use (>2-3 units/day,

daily). All were also asked to abstain from illicit drug and marijuana use for 2 weeks prior to testing, which was confirmed via urinalysis during the baseline session.

Included rMDD participants were required to have at least two lifetime major depressive episodes (MDEs). Prior MDD diagnoses (based on Diagnostic and Statistical Manual [DSM]-5 criteria) and MDEs were confirmed by one of three trained clinical interviewers via the Mini-International Neuropsychiatric Interview (M.I.N.I. version 7.0.2).<sup>88</sup> The most recent depressive episode was required to have occurred within the past 4 years, with remission achieved for at least 3 months. Remitted participants also had demonstrated recovery from their last depressive episode, as indexed by a Montgomery Asberg Depression Rating Scale (MADRS) score  $\leq 9$  at the time of assessment. Those who scored higher on the MADRS, but otherwise fulfilled all other criteria, were included on a case-by-case basis at the discretion of the study investigators. Additionally, all rMDD participants were free of psychotropic drugs for at least 3 months or were taking the same antidepressant prescriptions consistently with no changes in dosage for  $\geq 3$  months. Remitted participants also were required to have self-reported cognitive impairment, as indicated by a score  $\geq 1$  on the Inventory for Depressive Symptomatology, Self-Report version (IDS-SR)<sup>89</sup> item #15 (see Procedures, Phone Screen [*Section 2.2.2*, page 18]).

HVs had no lifetime DSM-5 psychiatric diagnoses (M.I.N.I.-assessed) and had either no or a limited family (first-degree relatives) history of psychiatric illness, as assessed via Family Interview for Genetic Studies (FIGS).<sup>90</sup> A family history of an Axis 1 disorder was considered exclusionary, though a family history of successfully treated mood or anxiety disorders (requiring no hospitalization) was generally considered

acceptable (decided on a case-by-case basis). HVs also had no self-reported cognitive impairment, as indicated by a score of 0 on the IDS-SR item #15 (details below). rMDDs and HVs were matched for gender, age, handedness and education.

## **2.2 Procedures**

### **2.2.1 Overview**

All participants first underwent a telephone screen to establish basic study eligibility. Eligible participants attended an in-person baseline session, during which they underwent a thorough clinical interview, completed a computerized cognitive battery (Cambridge Neuropsychological Test Automated Battery [CANTAB]),<sup>91</sup> completed questionnaires, and practiced the neuroimaging task used in this study. Further, all underwent a session in the mock scanner situated at the Royal's Brain Imaging Centre (BIC). Participants were then brought in for a second session to complete the neuroimaging portion of the study at the BIC (details below).

### **2.2.2 Telephone Screen**

All prospective participants were telephone-screened, during which basic demographic information was acquired, as well as a general medical and psychiatric history. During the screening call, individuals were asked to rate their concentration and decision-making abilities on item #15 of the IDS-SR:

*For the past 7 days, how would you rate your concentration and decision making?*

[0] There is no change in my usual capacity to concentrate or make decisions.

[1] I occasionally feel indecisive or find that my attention wanders.

[2] Most of the time, I struggle to focus my attention or to make decisions.

[3] I cannot concentrate well enough to read or cannot make even minor decisions.

Additionally, the Beck Depression Inventory (BDI)<sup>92</sup> was administered to confirm non-significant depression symptoms ( $\leq 21$  – a liberal score so as not to exclude individuals with sub-clinical depression symptoms; absence of depression was subsequently confirmed in-person). Several Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID)-adapted questions were also asked to confirm the absence of DSM-5 psychiatric illnesses (verified during in-person). Questions from the FIGS were also asked. Finally, the BIC screening form was administered to ensure no imaging-related safety concerns. The telephone screen took ~20-45 min to complete (**Appendix I**).

### ***2.2.3 In-Person Baseline Session***

All eligible participants were invited to attend an in-person baseline session (~3hr). At this time, participants were interviewed by a trained clinical interviewer during which a brief life history was collected to confirm the presence and timing of prior depressive episodes in the rMDD group, and the absence of psychiatric illness in the HV group. Psychiatric history was ascertained with the M.I.N.I and possible depressive symptoms were established with the MADRS. The Timeline Followback method<sup>93</sup> was used to acquire quantitative estimates of lifetime cannabis and illicit drug usage. The North American Adult Reading Test-Revised (NAART)<sup>94</sup> was administered as a crude metric of intelligence.

The following questionnaires were also administered during the baseline session: Edinburgh Handedness Inventory (EHI),<sup>95</sup> Beck Anxiety Inventory (BAI),<sup>96</sup> BDI, Quality

of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF),<sup>97</sup> Social Adjustment Scale (SAS),<sup>98</sup> Work and Social Adjustment Scale (WSAS)<sup>99</sup> and the Stress Reactive Rumination Scale (SRRS).<sup>100</sup> The EHI was administered to confirm left/right handedness. The BAI and BDI were administered to measure putative anxiety and depression symptoms. The Q-LES-Q-SF, SAS and WSAS were administered because there is evidence that cognitive impairment in depression is associated with poorer quality of life and psychosocial functioning.<sup>12,14,101–103</sup> Finally, the SRRS was administered because DMN dysfunction has been tied to negative, self-relational rumination<sup>68</sup> (**Appendix II**).

#### *2.2.3.1 Computerized Cognitive Testing (CANTAB)*

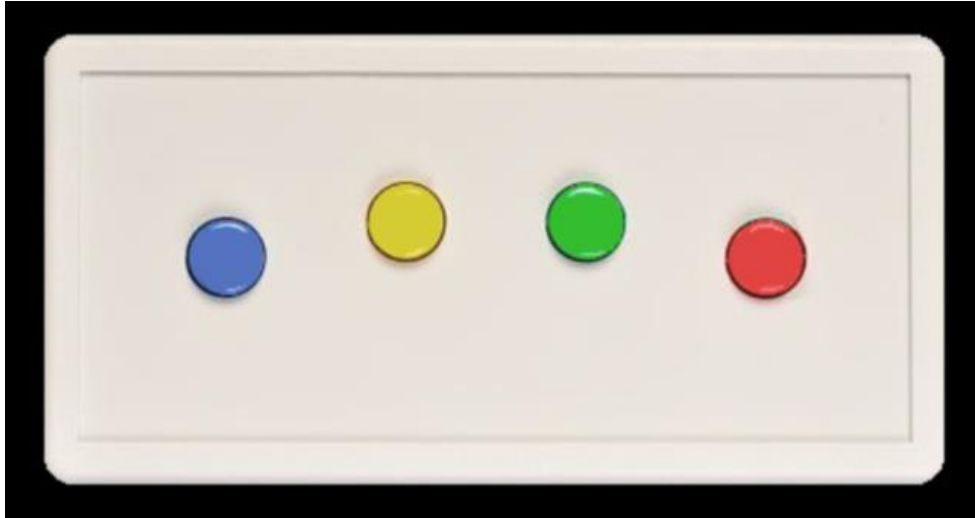
During the baseline session, participants also completed the CANTAB automated test battery (Cambridge Cognition Ltd © 2020) for depression and affective disorders. The battery was administered on an iPad and used as an objective measure of putative cognitive impairment in the rMDD group relative to the HV group (in addition to self-reported impairment as indexed by question #15 on the IDS-SR). Participants were seated in a quiet interview room during CANTAB administration (~45 min). All tasks include verbal instructions in English, and a few demonstration and practice trials prior to the actual task. The following tasks were administered: a) Reaction Time (RTI; 3 min) task, which measures motor and mental response speeds, b) Rapid Visual Information Processing (RVP; 7 min) task, which measures sustained and selective attention and processing speed, c) Delayed Matching to Sample (DMS; 7 min) task, which measures visual matching ability and short-term visual recognition memory, d) Spatial Working Memory (SWM; 4 min) task, which assesses working memory and executive function, e) One Touch Stockings of Cambridge (OTS; 10 min) task, which measures executive

function, specifically spatial planning and working memory, and the f) Emotion Recognition Task (ERT; 6-10 min), which measures the ability to identify basic emotional facial expressions (sadness, happiness, fear, anger, disgust or surprise). See **Appendix III** for detailed task descriptions.

## **2.3 Neuroimaging**

### **2.3.1 Mock Scanner Procedures**

During the baseline session, participants were taken to the mock scanner at the BIC. First, participants were asked to complete a practice version of the eStroop task (described in *Section 2.3.3*, page 23), which was administered during the subsequent testing day. Participants were provided with a brief description of the task and instructed to respond using a four-colour MRI-compatible response box (**Figure 2.1**) The practice task was first administered while the participant was seated at a desktop computer, and then while inside the mock scanner. The practice version of the task consisted of 12 trials and was administered via E-Prime 3.0 (Psychology Software Tools, Sharpsburg, PA). Before entering the mock scanner, participants were given earplugs to simulate real scanner conditions, a mock call bell (held in left hand), and response box (held in right hand). Once the participant was supine, the mock head coil was placed over their head, and they were moved into the mock scanner. An audio file of MRI scanner sounds was then played through a speaker system for ~1 min to familiarize participants with the scanner experience, followed by the practice version of the task. The behavioural output file from the practice task was checked for mistakes; the task was re-administered if the participant got <80% trials correct. None of the participants experienced severe claustrophobia that would preclude further participation in neuroimaging.



**Figure 2.1.** MR-compatible response pad. Held in right hand; index finger over blue button, middle finger over yellow button, ring/fourth finger over green button and pinky over red button.

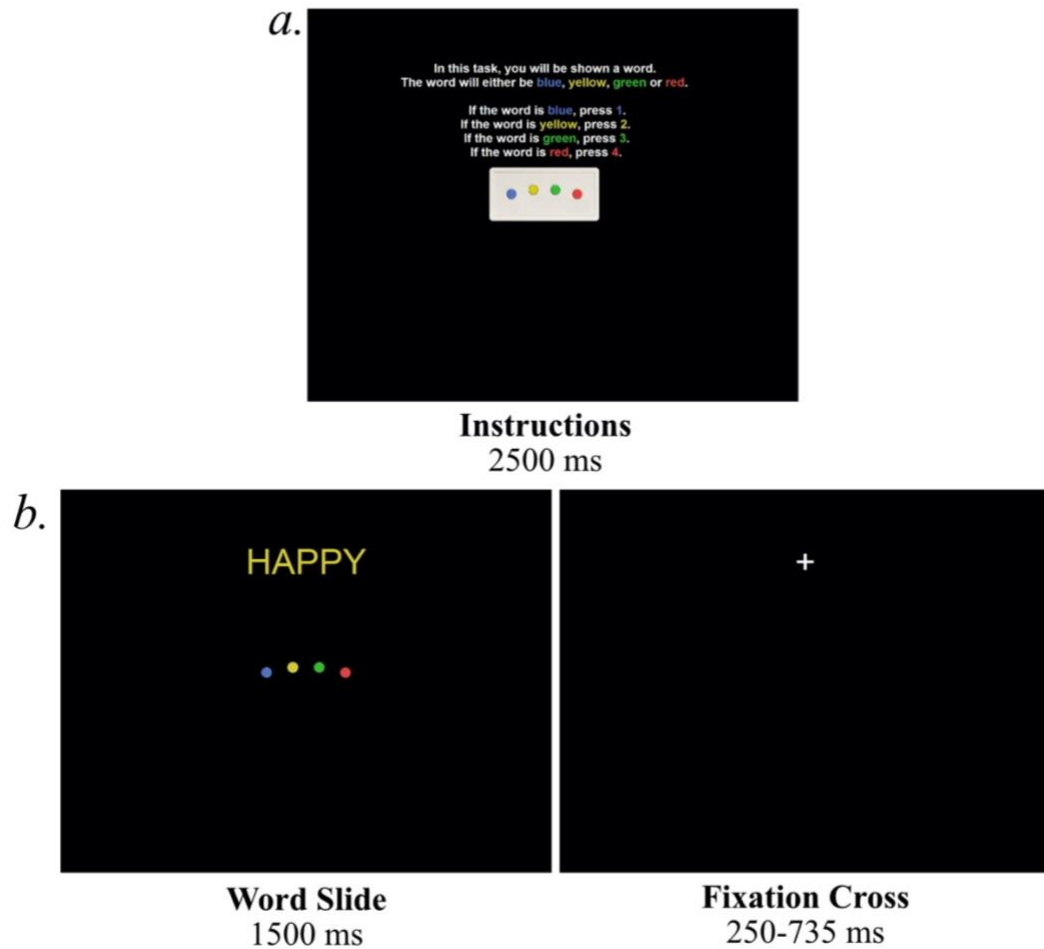
### **2.3.2 Overview of Neuroimaging Procedures**

During the second in-person session, participants underwent MRI scanning. After being cleared by the MR technologist, participants first underwent a high-resolution structural scan (among other scans, not discussed as part of this study) before being pulled out of the scanner for an EEG hook-up (~20 min). Simultaneous EEG-fMRI was acquired during the subsequent resting-state and eStroop task scans. This necessitated a second, low-resolution structural scan to be acquired when the participant re-entered the scanner. During the resting-state scan, individuals were instructed to look at the displayed fixation cross, relax and think of nothing in particular. The rest scan duration was ~7.38 min.

### **2.3.3 Emotional Stroop Task**

The eStroop task consisted of 216 words (72 positively-valenced, 72 negatively-valenced, 72 neutral; see **Appendix IV** for full list of words) selected from the Affective

Norms for English Words set (ANEW).<sup>104</sup> All words were 3-10 letters long, with length matched per category. The positively and negatively-valenced words were matched for arousal (based on ANEW norms). Words were presented in blue, yellow, red, or green font. Participants were instructed to indicate word colour via a button press, using their right hand, on the MR-compatible response pad. Task instructions were displayed for 25 s at the beginning (**Figure 2.2**). Adapted from Szekely et al.,<sup>87</sup> the eStroop task was administered as a block design (6 blocks each of negatively-valenced, positively-valenced and neutral words) with 12 words/block. Each trial consisted of a word (capital letters, 10-pt Arial font) presented in the centre of the screen (black background) for 1500 ms. Each word was followed by a white fixation cross on a black background (250–735 ms, mean = 492.63 ms). Four fixation blocks (25 s) were randomly dispersed between the 18 word blocks (task duration: ~10.0 min). The task was displayed to participants in the scanner via a rear-facing mirror affixed to the head coil, which reflected the images displayed on an MRI-compatible 40” LCD monitor (NordicNeuroLab©).



**Figure 2.2.** eStroop task schematic. *a. Instruction slide.* Displayed for 2500 ms at beginning of task once triggered by scan start; *b. Example of a single trial.* Consists of a word in coloured ink presented on a black background (1500 ms) followed by a fixation cross (mean ISI: 492.63 ms, with a jittered duration: 250–735 ms).

### 2.3.4 Neuroimaging Parameters

All scans were acquired at the BIC with a Siemens 3T Biograph mMR MR-PET scanner, using a 12-channel head coil (Siemens mMR head/neck coil).

The initial high-resolution structural scan was acquired via a T1-weighted multi-echo magnetization prepared rapid acquisition gradient echo (MEMPRAGE) sequence with a repetition time (TR) of 2530 ms, 4 echo times (TE); TE1 = 1.69 ms, TE2 = 3.55 ms, TE3 = 5.41 ms and TE4 = 7.27 ms, and a flip angle of 7°. Voxel sizes were 1x1x1

mm (1 mm slice thickness). In total, 192 slices were acquired using a 256 mm<sup>2</sup> field of view (FOV). Scan duration was ~6 min.

The low-resolution structural scan was a T2\*-weighted MEMPRAGE sequence with TR = 3930 ms, TE = 94 ms, and a flip angle of 120°. Voxel sizes were 0.3x0.3x3 mm (3 mm slice thickness). In total, 40 slices were acquired in the axial direction using a FOV read of 220 mm and FOV phase of 81.3%. Scan duration was ~1.1 min.

The resting-state and task scans were acquired via the same T2\*-weighted echo planar imaging (EPI) sequence, with TR = 2460 ms, TE = 25 ms, and a flip angle of 70°. Slice thickness was 3 mm, with voxel sizes of 3x3x3 mm. In total, 40 slices were acquired with a FOV of 192 mm. Resting-state scan duration was ~7.4 min, and task scan duration was ~10.0 min.

Finally, a field map was acquired via a gradient echo (GRE) sequence with a TR = 600 ms, 2 echo times; TE1 = 5.19 ms, TE2 = 7.65 ms, and a flip angle of 60°. Slice thickness was 4 mm. In total, 50 slices were acquired with a FOV of 256 mm. Scan duration was ~1.2 min.

### **2.3.5 *fMRI Preprocessing***

fMRI data were preprocessed in Statistical Parametric Mapping (SPM12), which runs on Matlab.<sup>105</sup> Functional images were corrected for movement using a least squares cost function and six-parameter rigid body spatial transformation. Field map data was used to correct for static geometric distortions during this motion correction step. The data was then slice-time corrected using sinc-interpolation. Because the high-resolution structural and functional image acquisition was interceded by an EEG hook-up (i.e., functional images were obtained in an inevitably different position and with an EEG cap),

a double co-registration procedure was employed. First, the low-resolution structural scan was co-registered to the high-resolution scan, followed by the co-registration of the functional data to the low-resolution scan. Both co-registrations were achieved via the normalized mutual information cost function. The structural data was segmented into 6 tissue classes and normalized to the ICBM-152 space template. Functional data was subsequently indirectly normalized using the same deformation fields as for the structural data. Finally, the functional images were smoothed with an 8 mm Gaussian kernel. Visual inspection of data was carried out following each preprocessing step to ensure data quality standards.

### **2.3.6 Connectivity Analysis**

The pre-processed data were subsequently imported into the fMRI connectivity analysis program CONN,<sup>106</sup> which also runs on Matlab. Several quality control (QC) steps were carried out in CONN prior to denoising. Histograms of subject-level values for maximum motion (mm), mean motion (mm), maximum global signal change (whole-brain blood-oxygen-level-dependent [BOLD] signals), and mean global signal change were generated to identify outliers, which were defined as values outside of the 3<sup>rd</sup>/1<sup>st</sup> quartile  $\pm$  1.5 inter-quartile range. Furthermore, resting-state and task group differences in global signal change and mean motion were assessed using independent samples t-tests via the calculator tool in CONN. No significant group differences were observed for either of these measures pre-denoising (two-tailed  $p < 0.05$ ). For all connectivity analyses, the rest condition was defined as the entire rest scan (7.38 min), and the task condition was defined as the 18 word blocks (7.20 min), excluding the task instructions and fixation blocks.

### 2.3.6.1 Denoising

Given the high susceptibility of connectivity data to motion artifacts and other confounding features, further denoising was carried out before final analysis. CONN employs a two-step denoising pipeline consisting of linear regression of potential confounding effects in the BOLD signal followed by temporal band-pass filtering.

The anatomical component-based noise correction procedure (aCompCor)<sup>45</sup> employed in CONN's denoising pipeline estimates and adjusts for noise components on a voxel-wise, subject and session-specific basis via ordinary least squares regression. The confounds corrected for included noise components from cerebral white matter and cerebrospinal fluid (CSF), estimated subject-motion parameters, artifact detection tool (ART)-identified outlier scans, and constant and first-order linear session effects.

Five potential noise components were estimated for each of the two anatomical regressors using normalized, subject-specific white matter and CSF masks generated in the segmentation stage of the pre-processing pipeline. A one-voxel binary erosion was applied to voxels with values above 50% in these masks prior to component estimation. The first noise component was computed as the average BOLD signal, and the next four as the first components of a principal component analysis of covariance within the subspace orthogonal to the average BOLD signal. Twelve noise components (three translation, three rotation, and their first-order derivatives) were defined from the subject-motion parameters estimated during preprocessing to correct for the effects of motion on the BOLD signal. Fourteen noise components were generated as potential confounding effects to remove the influence of outlier scans on the BOLD signal. These components were generated in CONN via the ART toolbox. Scans exceeding a framewise

displacement (FD) composite movement threshold of 1.5 mm or a z-normalized differenced mean image intensity threshold of 3 standard deviations from the mean were labelled as outliers and subsequently scrubbed from the data. Finally, constant and linear BOLD signal trends within each scan (rest and task) were convolved with a canonical hemodynamic response function in order to reduce the influence of slow trends and initial magnetization transients.

In total, forty noise components were regressed from the BOLD signal. The data was then temporally filtered via a discrete cosine transform windowing operation. A band-pass filter of 0.008-0.2 Hz was applied.

#### *2.3.6.2 Denoising Quality Control Checks*

Several QC plots were generated post-denoising. These reports were visually assessed to check the efficacy of the denoising procedures. The first plot displayed the distribution of functional connectivity (FC) values between randomly selected pairs of points in the brain before and after denoising. Prior to denoising, FC distributions show large inter-scan (rest, task) and inter-subject variability, with varying levels of positive skew, consistent with the influence of global or large-scale physiological and subject-motion effects. After effective denoising, the FC distributions should be more centered with slightly larger tails on the positive side.

The second plot displayed correlations between FC values (from a randomly selected 1000-node network) and several QC measures (mean global signal change, maximum global signal change and mean motion).<sup>107</sup> The presence of residual correlation between FC and QC measures could mean there is reasonable risk of the main effect of interest being confounded by residual motion or outlier effects. A  $\geq 95\%$  match between

the null distribution and post-denoising distributions suggest a lack of “noticeable QC-FC associations”,<sup>106</sup> though certain caveats must be considered: QC-FC correlations are sensitive to outliers, and are unreliable when there is a lack of variability in the QC measure.<sup>107</sup> As such, the use of several quality checks is preferable for the assessment of non-normal QC measures.

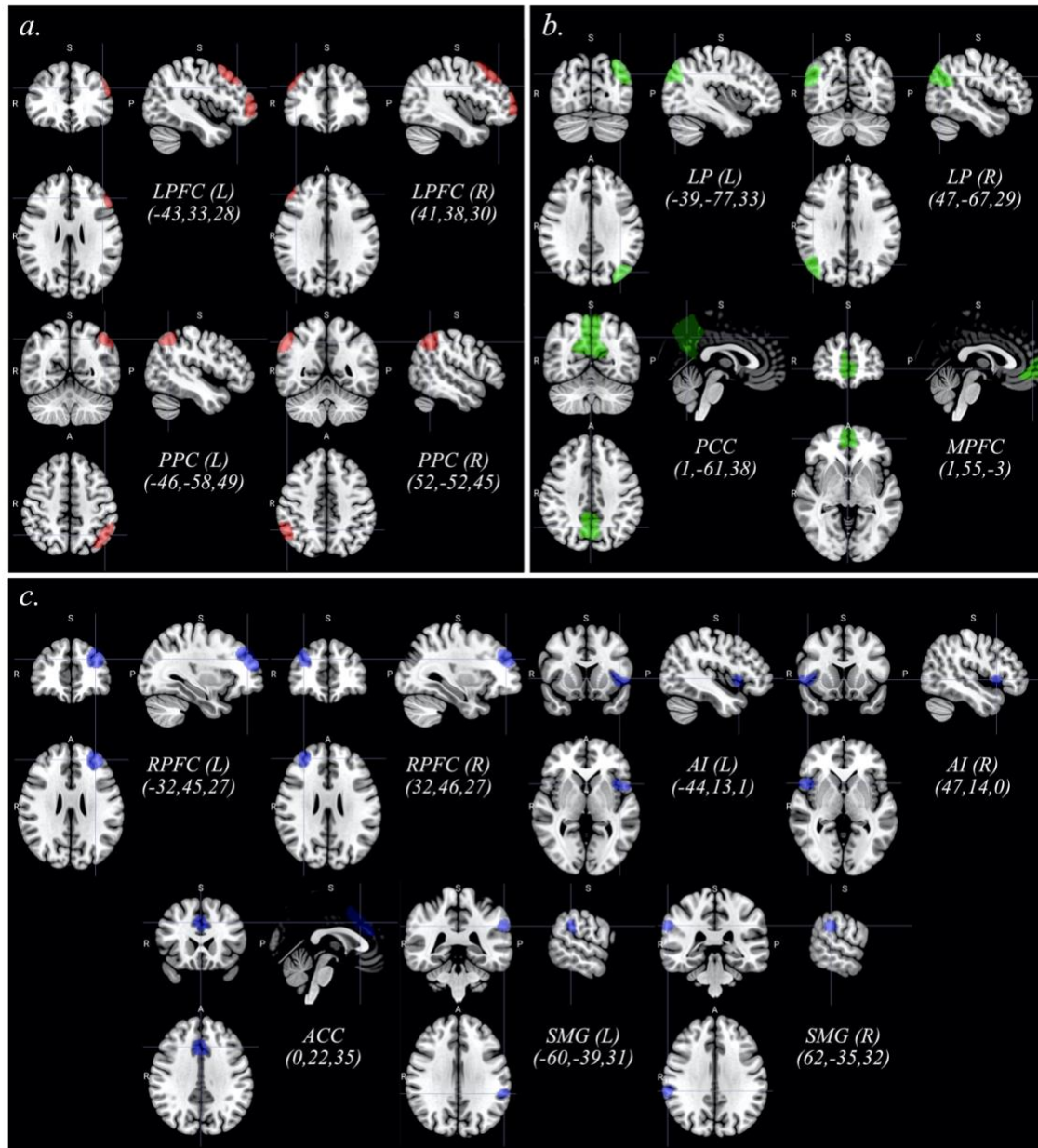
The third type of QC plot generated was subject-level carpet plots of global signal pre- and post-denoising. The carpet plot is a two-dimensional representation of global signal in the brain, wherein each column represents an individual volume, and each row is an individual voxel in that volume. Prior to denoising, there may be rough transitions between voxels due to movement, scanner drift, and physiological noise. Successful denoising results in a visibly smoother carpet plot.

The final QC plots generated were subject-wise scatterplots of correlation coefficients ( $r$ ) vs. distance (mm) before and after denoising. In datasets examined prior to denoising, correlation coefficients at all distances are elevated, but correlations at short distances are the most elevated. After successful denoising (that removes all types of motion-related noise effectively), the correlation coefficients should be normalized (closer to 0, with slight tendencies towards positive correlations for closer voxels).<sup>108</sup>

### 2.3.6.3 *First-level Analyses*

Subject-level connectivity matrices were computed to characterize the connectivity between pairs of regions of interest (ROIs) among a pre-defined set of regions. Each element in the ROI-to-ROI connectivity matrices was defined as a Fisher-transformed bivariate correlation coefficient between a pair of ROIs. The ROIs used in these analyses were human connectome project ICA-derived cortical ROIs. These are the

default network nodes in CONN and are as follows: *a. CEN ROIs*. Left lateral prefrontal cortex (LPFC[L]), right lateral prefrontal cortex (LPFC[R]), left posterior parietal cortex (PPC[L]), right posterior parietal cortex (PPC[R]); *b. DMN ROIs*. Left lateral parietal cortex (LP[L]), right lateral parietal cortex (LP[R]), posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC); *c. SN ROIs*. Left rostral prefrontal cortex (RPFC[L]), right rostral prefrontal cortex (RPFC[R]), left anterior insula (AI[L]), right anterior insula (AI[R]), anterior cingulate cortex (ACC), left supramarginal gyrus (SMG[L]), right supramarginal gyrus (SMG[R]; **Figure 2.3**).



**Figure 2.3.** Human connectome project independent component analyses (ICA)-derived cortical regions of interest (ROIs). All ROIs are overlaid onto the MNI-152 template. Center of ROI coordinate (x, y, z) is listed in brackets beside each ROI. *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]).

### 2.3.6.4 Second-level Analyses

#### 2.3.6.4.1 Sample Triple Network Connectivity Characteristics

Connectivity contrasts were carried out for each network (DMN, CEN, SN), and each pair of networks (DMN-CEN, DMN-SN, CEN-SN) to establish the connectivity characteristics for the whole sample and then the HV and rMDD groups. Separate one-sample t-tests (or, regressions, when adding a covariate, details below) were carried out to determine resting-state within and between-network connectivity characteristics for the whole sample and both groups. Separate one-sample t-tests (or, regressions, when adding a covariate, details below) were also carried out to determine the task within and between-network connectivity characteristics for all subjects and each group. Finally, separate paired t-tests (or, analysis of covariance [ANCOVA], details below) were carried out to assess rest vs. task within and between-network connectivity characteristics for all subjects and each group (**Table 2.1**).

**Table 2.1.** *Sample triple network connectivity characteristics connectivity contrasts*

Analysis Type	Contrast	
	Between-Subjects	Between-Conditions
One-sample t-test	All Subjects [1]	Rest [1]
		Task [1]
	rMDD [1]	Rest [1]
		Task [1]
	HV [1]	Rest [1]
		Task [1]
Regression	All Subjects, Age [1 0]	Rest [1]
		Task [1]
	rMDD, Age [1 0]	Rest [1]
		Task [1]
	HV, Age [1 0]	Rest [1]
		Task [1]
Paired t-test	All Subjects [1]	Rest > Task [1 -1]
ANCOVA	All Subjects, Age [1 0]	Rest > Task [1 -1]

*Note.* Age is used as an example covariate in this table. Contrasts were also run with antidepressant use as a covariate.

rMDD = remitted depressed patients, HV = healthy volunteers

#### 2.3.6.4.2 Part 1: Within-Network Connectivity Analyses

For each network (DMN, CEN, SN), five analyses were conducted. The first two analyses were paired t-tests assessing rest vs. task *within* the HV and rMDD groups (or, ANCOVA when a covariate was included, details below). Second, two-sample t-tests were conducted to assess putative *between* group differences (rMDD vs. HV) during rest and the task (or, one-way ANCOVA when adding a covariate, details below). Finally, a 2x2 analysis of variance (ANOVA) assessing rest vs. task for rMDD vs. HV (or 2-way ANCOVA when adding a covariate, details below) was conducted (**Table 2.2**).

**Table 2.2.** *Within and between-network connectivity contrasts*

Analysis Type	Contrast	
	Between-Subjects	Between-Conditions
Paired t-test	rMDD [1]	Rest > Task [1 -1]
	HV [1]	Rest > Task [1 -1]
ANCOVA	rMDD, Age [1 0]	Rest > Task [1 -1]
	HV, Age [1 0]	Rest > Task [1 -1]
Two-sample t-test	rMDD > HV [1 -1]	Rest [1]
	rMDD > HV [1 -1]	Task [1]
1-way ANCOVA	rMDD > HV, Age [1 -1 0]	Rest [1]
	rMDD > HV, Age [1 -1 0]	Task [1]
2x2 ANOVA	rMDD > HV [1 -1]	Rest > Task [1 -1]
2-way ANCOVA	rMDD > HV, Age [1 -1 0]	Rest > Task [1 -1]

*Note.* Age is used as an example covariate in this table. Contrasts were also run with antidepressant use as a covariate.

rMDD = remitted depressed patients, HV = healthy volunteers

All contrasts were first false discovery rate (FDR) corrected at the analysis level, and then followed up by node-specific seed-level FDR correction if the analysis-level p-

value was significant ( $p < 0.05$ ). The seed-level correction applies FDR separately per each seed ROI; because the correction is dependent on the seed region itself, and the seed regions vary in size, the seed-level p-FDR values were not all bi-directionally consistent. Only bi-directionally significant seed-level correction p-FDR results were reported ( $p < 0.05$ ). In the case of unequal p-FDR values depending on the seed region selected, the most conservative of the two was reported.

Group-wise regression analyses were carried out for three potential covariates: mean-centered age (referred to simply as age), sex (male, female) and handedness (left, right, ambidexterous). Sex and handedness were not found to significantly predict correlation within any of the three networks ( $p < 0.05$ ) for any of the contrasts of interest (data not shown). Age was found to predict correlation within the DMN in the HV group only for the rest vs. task contrast (p-FDR analysis-level=0.03). Furthermore, though the mean age was not significantly different between HVs and rMDDs ( $t(37) = -0.95$ ,  $p = 0.35$ ), age was not normally distributed within the HV group (Shapiro-Wilk;  $p < 0.001$ ). As such, age was included as a covariate of no interest in the connectivity analyses (results without this covariate are also presented).

Regression analyses were also carried out for antidepressant use in the rMDD group (medicated, unmedicated). Antidepressant usage was found to significantly predict correlation in the DMN (rest vs. task, p-FDR analysis-level=0.04). As such, this was included as a covariate of no interest.

#### 2.3.6.4.3 Part 2: Between-Network Connectivity Analyses

The same five analyses listed above were also carried out between networks (DMN-CEN, SN-DMN and SN-CEN).

## **2.4 Statistical Analyses**

All statistical analyses were conducted via IBM SPSS Statistics Version 27 (Release 27.0.1.0) unless otherwise specified. Outliers were assessed by boxplot, normality was assessed via the Shapiro-Wilk's test ( $p > 0.05$ ), and homogeneity of variances was assessed by Levene's test for equality of variances ( $p > 0.05$ ).

### **2.4.1 Group Demographics**

Separate Mann-Whitney U tests were carried out for each continuous demographic of interest to test for differences between the HV and rMDD groups. All of the demographics were non-normally distributed, as indicated by significant ( $p < 0.05$ ) results for the Shapiro-Wilk test for normality. Tests were carried out for age (years), lifetime cannabis use (# of incidents), average alcohol use (# of drinks consumed/week), lifetime illicit drug use (# of incidents), handedness laterality quotient (LQ) and BMI ( $\text{kg}/\text{m}^2$ ).

### **2.4.2 Questionnaire Data**

Separate independent samples t-tests were carried out for the SRRS, Q-LES-Q-SF, SAS-M questionnaire total scores, NAART full-scale IQ scores, and the negative inferential style and active problem solving subscales of the SRRS to test for potential differences between groups. Separate Mann-Whitney U tests were run to determine if there were differences in questionnaire scores (Shapiro-Wilk  $p < 0.05$ ) that did not meet parametric test assumptions, namely SRRS hopeless rumination subscale scores, WSAS total scores, BAI, MADRS and BDI total scores.

### **2.4.3 eStroop Task**

Separate two-way mixed ANOVAs were carried out for eStroop task RT and accuracy. The within-subject condition was word valence (negative, neutral, positive), and the between-subject condition was group (rMDD, HV).

#### **2.4.4 CANTAB Cognitive Tasks**

Separate independent samples t-tests or Mann-Whitney U tests (in the case of non-normally distributed data) were carried out for each key output measure for the six tasks administered as part of the CANTAB depression battery (see **Appendix III** for task and output measure descriptions).

#### **2.4.5 CEN and DMN Connectivity, Rumination and Self-Reported Quality of Life**

Linear regressions were carried out between within-network (DMN and CEN) rest, task, and rest vs. task ROI-to-ROI connectivity correlation coefficients and SRRS, Q-LES-Q-SF, WSAS and SAS questionnaire scores for the rMDD group only. The significant ( $p < 0.01$ , to adjust for multiple comparisons) linear regressions were followed-up with multiple regressions including age and antidepressant use as independent variables to test for their effects as covariates of no-interest. All regressions were first conducted via IBM SPSS Statistics Version 27 (Release 27.0.1.0) to test the basic assumptions of linear regressions, and generate model outcome values, and then were repeated within CONN to generate seed-level p-FDR values ( $p < 0.05$ ).

#### **2.4.6 CEN Connectivity and eStroop Task Performance**

Exploratory linear regressions were carried out between within-network CEN task and rest vs. task ROI-to-ROI correlation coefficients and the negative, neutral and positive eStroop reaction times within the rMDD group only using the same procedures as listed above in section 2.4.5.

### Chapter 3: RESULTS

Assumptions of no outliers, normality and homogeneity of variance were met for all parametric statistics tests unless otherwise specified.

#### 3.1 Sample Demographics

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 3.1**). All p-values were generated using an exact sampling distribution for U.<sup>109</sup> Median or mean rank values for the non-parametric sample statistics are listed in **Table 3.2**. Sample characteristics specific to the rMDDs are listed in **Table 3.3**.

**Table 3.1.** *Sample demographics for healthy volunteers (HV) and remitted depressed 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) <sup>a</sup>	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 Total, LQ	61.26 (54.59)	64.90 (52.59)	208	0.61	0.09
BMI, kg/m <sup>2</sup>	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  $r = \frac{z}{\sqrt{N}}$

EHI LQ = Edinburgh Handedness Inventory laterality quotient, BMI = body mass index

n = number, SD = standard deviation, F = female, M = male, -- = not applicable

<sup>a</sup>(n=17)

**Table 3.2.** *Sample demographics: Non-parametric descriptive statistics and data characteristics for healthy volunteers (HVs) and remitted depressed patients (rMDDs).*

Sample Demographics	Distributions similar shape?	Median or Mean Rank	
		HV (n=21)	rMDD (n=18)
Age, years	N	<u>18.52</u>	<u>21.72</u>
Lifetime Cannabis Use, #incidents	Y	5.00	1.50
Average Alcohol Use, #drinks/week	Y	2.50	1.00
Lifetime Illicit Drug Use, #incidents	Y	0.00	0.00
EHI Total, LQ	Y	83.33	85.00
BMI, kg/m <sup>2</sup>	N	<u>20.52</u>	<u>19.39</u>

Note. Mean rank values are underlined

EHI LQ = Edinburgh Handedness Inventory laterality quotient, BMI = body mass index

Y = yes, N = no

**Table 3.3.** *Sample characteristics specific to the remitted depressed patients (rMDD).*

<b>rMDD Sample Characteristics</b> (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 (25.0)
	SNRI	2 (25.0)
	SSRI	1 (12.5)
	>1 antidepressant	3 (37.5)
# 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-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor

### 3.2 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], active problem-solving scores [t(37)=0.37, p=0.71] or NAART full-scale IQ scores [t(37)=0.58, p=0.57] between rMDDs and HVs. Q-LES-Q-SF total scores were higher for HVs than rMDDs (95% CI, 2.27 to 10.69),

$t(37)=3.116$ ,  $p<0.01$ , reflecting a higher self-reported quality of life. SAS total scores were higher in HVs than rMDDs (95% CI, 1.23 to 11.43),  $t(37)=2.52$ ,  $p=0.02$ , reflecting a higher level of psychosocial and daily functioning (**Table 3.4**, see **Table 3.5** for mean rank values).

SRRS Hopeless Rumination ( $U=275.5$ ,  $p=0.01$ ), WSAS ( $U=295.0$ ,  $p<0.01$ ), MADRS ( $U=322.0$ ,  $p<0.01$ ) and BDI ( $U=264.5$ ,  $p=0.03$ ) scores were significantly higher in rMDDs than HVs. BAI scores were not significantly different between groups (**Table 3.4**).

**Table 3.4.** *Questionnaire score descriptive statistics and results for comparison of scores between healthy volunteers (HV) 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)	<u>275.5</u>	<u>0.01*</u>	<u>0.39</u>
APS	60.88 (18.38)	58.57 (19.92)	0.38	0.71	0.12
Q-LES-Q-SF Total Score	63.48 (5.87)	57.00 (7.11)	3.12	<0.01*	1.00
SAS Total Score	84.58 (6.04)	78.25 (9.52)	2.52	0.02*	0.81
WSAS Total Score	2.52 (4.18)	11.00 (9.66)	<u>295.0</u>	<u>&lt;0.01*</u>	<u>0.48</u>
MADRS Total Score	1.33 (1.93)	6.06 (3.40) <sup>a</sup>	<u>322.0</u>	<u>&lt;0.01*</u>	<u>0.70</u>
BAI Total Score	3.52 (3.49)	4.94 (4.52)	<u>222.5</u>	<u>0.35</u>	<u>0.15</u>
BDI Total Score	1.43 (1.91)	4.39 (5.08)	<u>264.5</u>	<u>0.03*</u>	<u>0.35</u>
NAART Full-Scale IQ	112.57(5.42)	11.55(5.58)	0.58	0.57	0.19

*Note.* Mann Whitney-U (non-parametric) test results are underlined

The effect sizes reported in this table are Cohen's  $r$  for the Mann-Whitney U results, calculated as  $r = \frac{z}{\sqrt{N}}$ , and Hedge's  $g$  for the t-test results,  $g = \frac{M_{HV} + M_{rMDD}}{S_{pooled}}$

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

Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire, maximum score = 80 (high life satisfaction), minimum score = 16 (low life satisfaction)

SAS = Social Adjustment Scale, maximum score = 100 (high psychosocial and daily functioning), minimum score = 0 (low psychosocial and daily functioning)

WSAS = Work and Social Adjustment Scale, maximum score = 40 (low psychosocial and daily functioning), minimum score = 0 (high psychosocial and daily functioning)

MADRS = Montgomery Asberg Depression Rating Scale, maximum score = 60 (high number and level of depressive symptoms), minimum score = 0 (no depressive symptoms)

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)

NAART = North American Adult Reading Test-Revised, maximum score = 127.8 (higher IQ [intelligence quotient]), minimum score = 80.2 (lower IQ)

<sup>a</sup>(n=17)

**Table 3.5.** *Questionnaire non-parametric descriptive statistics and data characteristics for healthy volunteers (HVs) and remitted depressed patients (rMDDs).*

Questionnaires	Distributions similar shape?	Mean Rank	
		HV (n=21)	rMDD (n=18)
SRRS Hopeless Rumination	N	15.88	24.81
WSAS Total Score	N	14.95	25.89
MADRS Total Score	N	12.67	27.94 <sup>a</sup>
BAI Total Score	N	18.40	21.86
BDI Total Score	N	16.40	24.19

*Note.*

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)

WSAS = Work and Social Adjustment Scale, maximum score = 40 (low psychosocial and daily functioning), minimum score = 0 (high psychosocial and daily functioning)

MADRS = Montgomery Asberg Depression Rating Scale, maximum score = 60 (high number and level of depressive symptoms), minimum score = 0 (no depressive symptoms)

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)

Y = yes, N = no

<sup>a</sup>(n=17)

### 3.3 eStroop Task

Only subjects with  $\geq 80\%$  accuracy scores (consistent with prior literature)<sup>27,87</sup> were included in the eStroop task analyses (18 rMDDs, 18 HVs). Descriptive statistics for accuracy and reaction time eStroop outcome measures are summarized in **Table 3.6**.

**Table 3.6.** *Emotional Stroop task descriptive statistics.*

Measure	Word Valence	Mean (SD)	
		HV (n=18)	rMDD (n=18)
Accuracy, proportion correct	Negative	0.99 (0.02)	0.98 (0.03)
	Neutral	0.98 (0.02)	0.97 (0.04)
	Positive	0.98 (0.02)	0.97 (0.04)
Reaction Time, ms	Negative	769.77 (100.00)	823.27 (89.47)
	Neutral	775.66 (97.27)	823.54 (97.84)
	Positive	767.70 (104.50)	821.41 (91.02)

#### 3.3.1 Accuracy

There was no main effect of valence [ $F(2,68)=2.74$ ,  $p=0.07$ , partial  $\eta^2=0.08$ ], group [ $F(1,34)=0.96$ ,  $p=0.33$ , partial  $\eta^2=0.03$ ], or valence x group interaction [ $F(2,68)=0.12$ ,  $p=0.89$ ] on accuracy.

#### 3.3.2 Reaction Time

Analyses were carried out on mean RT data for correct responses only. Mauchly's test of sphericity was met for the two-way interaction,  $\chi^2(2)=5.23$ ,  $p=0.07$ . There was no main effect of valence [ $F(2,68)=0.87$ ,  $p=0.43$ , partial  $\eta^2=0.03$ ], group [ $F(1,34)=2.62$ ,  $p=0.11$ , partial  $\eta^2=0.07$ ], or valence x group interaction [ $F(2,68)=0.34$ ,  $p=0.70$ ] on RT.

### 3.4 CANTAB Cognitive Tasks

Emotional recognition task median correct RT (all emotions) was significantly longer in rMDDs (1272.80 ms) than HVs (1051.30 ms). Rapid visual information

processing task median correct RT was significantly longer in rMDDs (24.22 ms) than HVs (15.25 ms). There were no significant differences between any of the other measures for any of the CANTAB tasks (see **Table 3.7** for t- and U-scores, p-values and effect sizes; see **Table 3.8** for median and mean rank for non-parametric tests only).

**Table 3.7.** Cambridge Neuropsychological Test Automated Battery (CANTAB) test score descriptive statistics and results for test score comparisons between healthy volunteers (HVs) and remitted depressed patients (rMDDs).

Task	Outcome Measure	Mean (SD)		t or U score	p-value	Effect size
		HV (n=21)	rMDD (n=18)			
RTI	Median Movement Time	243.00 (58.83)	246.64 (53.89)	<u>0.10</u>	<u>0.84</u>	<u>0.04</u>
	MDCRT	387.63 (36.99)	390.22 (42.42)	217.0	0.99	0.00
RVP	MDCRT	391.73 (37.32)	445.25 (76.22)	175.0	<b>0.01*</b>	0.40
	Probability of False Alarm	0.003 (0.003)	0.003 (0.002)	235.5	1.00	0.00
	Probability of Hit	0.956 (0.06)	0.93 (0.06)	241.5	0.06	0.31
DMS	MDCRT	2616.90 (881.94)	2826.83 (789.68)	226.0	0.29	0.18
	Percent Correct	89.25 (9.31)	88.50 (10.67)	211.5	0.90	0.02
SWM	Between Errors	8.65 (8.66)	8.89 (9.25)	227.5	0.97	0.01
	Double Errors	0.50 (1.15)	0.11 (0.32)	251.0	0.59	0.14
	Strategy Score	6.05 (2.98)	5.94 (3.28)	145.5	0.99	0.00
OTS	Mean Choices to Correct	1.35 (0.51)	1.40 (0.06)	246.5	0.05	0.32
	MDRT to 1 <sup>st</sup> Choice	10596.90 (4628.25)	11195.06 (5608.70)	195.0	0.68	0.07
	Mean Latency to Correct	19937.25 (10744.63)	23664.60 (8892.41)	230.0	0.15	0.24
	Problems Solved 1 <sup>st</sup> Choice	11.9 (2.73)	11.22 (2.13)	121.5	0.09	0.28
ERT	MDCRT Anger	1077.45 (262.15)	1405.33 (599.67)	179.0	0.11	0.26
	MDCRT Disgust	1084.70 (301.78)	1383.50 (489.01)	265.0	0.07	0.29
	MDCRT Fear	1492.45 (401.37)	1829.61 (698.75)	180.5	0.10	0.27
	MDCRT Happy	789.30 (243.65)	835.94 (233.77)	116.0	0.36	0.15
	MDCRT Sad	1182.85 (462.91)	1279.30 (425.36)	<u>-0.67</u>	<u>0.51</u>	<u>0.22</u>
	MDCRT Surprise	858.95 (268.72)	998.11 (296.94)	182.0	0.17	0.23
	MDRT All Emotions	1101.30 (303.93)	1355.47 (430.84)	161.0	<b>0.04*</b>	0.34
	Total Hits	59.65 (7.98)	56.78 (9.453)	179.0	0.32	0.16

*Note.* Independent samples t-test (parametric) results are underlined

The effect sizes reported in this table are Cohen's  $r$  for the Mann-Whitney U results, calculated as  $r = \frac{z}{\sqrt{N}}$ , and Hedge's  $g$  for the t-test results,  $g = \frac{M_{HV} + M_{rMDD}}{S_{pooled}}$

RTI = Reaction Time task, RVP = Rapid Visual Information Processing task, DMS = Delayed Matching to Sample task, SWM = Spatial Working Memory task, OTS = One Touch Stockings of Cambridge task, ERT = Emotional Recognition Task

MDCRT = median correct reaction time, MDRT = median reaction time

**Table 3.8.** *Cambridge Neuropsychological Test Automated Battery (CANTAB) test score non-parametric descriptive statistics and data characteristics for healthy volunteers (HVs) and remitted depressed patients (rMDDs).*

Task	Outcome Measure	Distributions similar shape?	Median or Mean Rank	
			HVs (n=21)	rMDD (n=18)
RTI	MDCRT	Y	378.50	386.30
RVP	MDCRT	N	<u>15.25</u>	<u>24.22</u>
	Probability of False Alarm	Y	0.002	0.002
	Probability of Hit	N	<u>22.70</u>	<u>15.94</u>
DMS	MDCRT	N	<u>17.65</u>	<u>21.56</u>
	Percent Correct	Y	1013.5	1331.5
SWM	Between Errors	Y	8.50	7.0
	Double Errors	Y	0.00	0
	Strategy Score	N	<u>19.55</u>	<u>19.44</u>
OTS	Mean Choices to Correct	Y	1.20	1.40
	MDRT to 1 <sup>st</sup> Choice	Y	9008.00	10358.50
	Mean Latency to Correct	N	<u>17.00</u>	<u>22.28</u>
	Problems Solved 1 <sup>st</sup> Choice	N	<u>22.43</u>	<u>16.25</u>
ERT	MDCRT Anger	N	<u>16.73</u>	<u>22.58</u>
	MDCRT Disgust	N	<u>16.43</u>	<u>22.92</u>
	MDCRT Fear	Y	1370.00	1667.00
	MDCRT Happy	N	<u>17.93</u>	<u>21.25</u>
	MDCRT Surprise	Y	873.50	913.50
	MDRT All Emotions	Y	1051.30	1272.80
	Total Hits	Y	58.50	57.50

*Note.* Mean rank values are underlined

RTI = Reaction Time task, RVP = Rapid Visual Information Processing task, DMS = Delayed Matching to Sample task, SWM = Spatial Working Memory task, OTS = One Touch Stockings of Cambridge task, ERT = Emotional Recognition Task

MDCRT = median correct reaction time, MDRT = median reaction time

Y = yes, N = no

### 3.5 Connectivity Analysis Results

In total, 18 rMDDs and 21 HVs were included in the resting-state functional connectivity analyses. A total of 18 rMDDs and 18 HVs were used in the task and task vs. rest analyses (3 controls were excluded due to missing task output data [N=2] or low task accuracy [N=1; 7.67% accuracy score]).

#### 3.5.1 Denoising Quality Control Checks

Mean global signal change, mean motion and number of valid scans were not found to differ between rMDDs vs. HVs during the task or rest ( $p < 0.05$ , two-tailed). One individual was identified as a maximum and mean motion outlier for the task scan. Including this individual in the analyses did not alter results (i.e., results did not differ with/without this individual), as such, this scan was retained. A handful (N=3) of individuals were also flagged as outliers for mean or maximum global signal change prior to denoising; however, the values were not extreme, and QC checks confirmed successful denoising of each of these scans. Following denoising, carpet plots and time courses of global signal for the rest and task conditions were normal for all subjects (including the three flagged global signal outliers), and were visibly smoother than pre-denoising. Inspection of associations between FC and the other QC measures yielded relatively good fits between the null distribution and post-denoising distributions. Inspection of the scatterplots between FC-distance was also greatly improved post-denoising (See **Appendix V** for all QC plots).

Power's  $FD^{110}$  was, on average,  $0.19 \pm 0.10$  mm for the rest scans and  $0.17 \pm 0.08$  mm for the task scans. Scans exceeding a FD threshold of 1.5 mm were identified as outliers and scrubbed from the data. On average,  $6.56 \pm 7.01$  rest scans (out of 180) and

12.83 ± 10.26 task scans (out of 242) were identified as outliers and subsequently scrubbed from the data per subject as part of the denoising procedures. There were no significant differences in number of outliers or FD between rMDDs and HVs for the rest or task scans ( $p > 0.05$ ).

### ***3.5.2 Sample Triple Network Connectivity Characteristics***

Please see **Table 3.9** for a summary of all the connectivity results for each intrinsic and between-network contrast.

#### *3.5.2.1 Default Mode Network Characteristics*

As was expected, intrinsic DMN connectivity was consistently positive across all ROIs (PCC, MPFC, LP[L], and LP[R]) at rest and during the task for the whole sample and rMDD and HV groups ( $p < 0.0001$ ). A whole-sample rest vs. task contrast revealed higher intrinsic DMN connectivity during the task compared to at-rest, LP(L)-PCC:  $t(35) = -2.25$ , LP(L)-MPFC:  $t(35) = -3.09$ ,  $p$ -FDR analysis-level=0.02. However, the inclusion of the antidepressant use covariate decreased the significance of this findings ( $p$ -FDR analysis level=0.09). No meaningful changes in significance or connectivity directionality were found when age was included as a covariate.

#### *3.5.2.2 Central Executive Network Characteristics*

Intrinsic CEN connectivity was also consistently positive across all ROIs (LPFC[L], LPFC[R], PPC[L], and PPC[R]) at rest and during the task for the whole sample and rMDD/HV groups ( $p < 0.0001$ ). Across the whole sample, there was higher intrinsic CEN connectivity at rest vs. during the task, PPC(L)-LPFC(R):  $t(35) = 3.34$ ,  $p$ -FDR analysis-level=0.01. However, the inclusion of the antidepressant use covariate rendered the whole-sample rest vs. task contrasts highly insignificant ( $p$ -FDR analysis-

level=0.80). No changes in significance or connectivity directionality were found when the age covariate was applied.

### 3.5.2.3 *Saliience Network Characteristics*

Again, as expected, intrinsic SN connectivity was consistently positive across all ROIs (AI[L], AI[R], RPFC[L], RPFC[R], ACC, SMG[L], and SMG[R]) at rest and during the task for the whole sample and rMDD/HV groups ( $p < 0.001$ ). A whole-sample rest vs. task contrast revealed higher intrinsic connectivity in the SN at rest vs. during the task, ACC-AI(L):  $t(35)=3.31$ ,  $p\text{-FDR analysis-level} < 0.05$ . The addition of the age and antidepressant covariates slightly decreased the significance of the results ( $p\text{-FDR analysis-level}=0.051$  and  $0.08$ , respectively) for the whole-sample rest vs. task contrast.

### 3.5.2.4 *Central Executive Network and Default Mode Network*

Contrary to expectations, CEN-DMN between-network ROI-to-ROI connectivity values were all positive and statistically significant ( $p\text{-FDR} < 0.05$ ) for the entire sample, as well as within the rMDD and control groups. No significant differences were found for rest vs. task DMN-CEN connectivity for the whole sample, rMDD or HV groups ( $p < 0.05$ ). No changes in significance or connectivity directionality were found when age or antidepressant use covariates of no interest were included.

### 3.5.2.5 *Central Executive Network and Saliience Network*

CEN-SN between-network ROI-to-ROI connectivity values were positively correlated during the task for the rMDD group only. No significant CEN-SN correlations were found at rest for the whole sample or rMDD/HV groups. Across the whole sample, higher CEN-SN connectivity was noted during the task vs. rest,  $\beta = -0.11$ ,  $t(35) = -3.31$ ,  $p\text{-FDR} < 0.01$ . No meaningful changes in significance or connectivity directionality were

found when age was included as a covariate. The addition of the antidepressant covariate rendered the task-based positive correlations insignificant in the rMDD group (p-FDR=0.16), and reduced significance slightly for the whole sample (p-FDR=0.05).

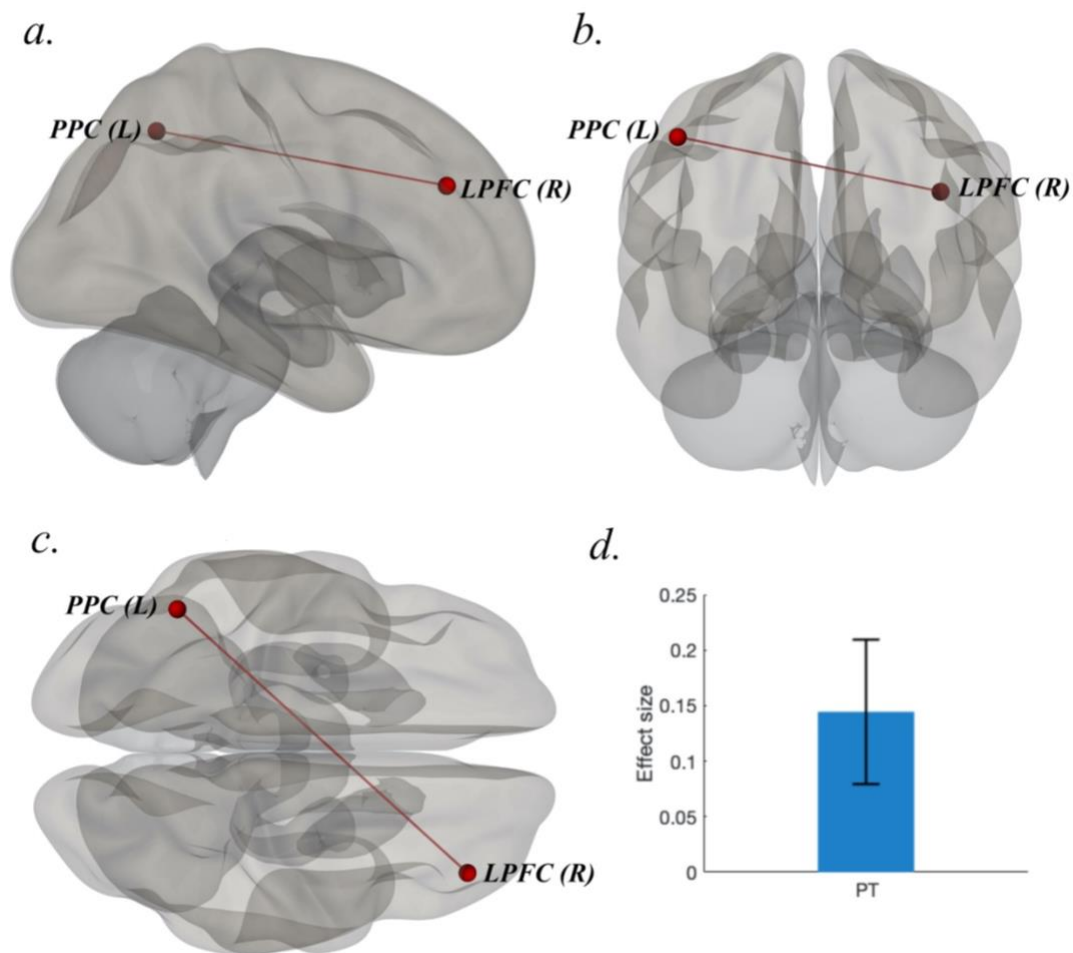
### 3.5.2.6 *Default Mode Network and Salience Network*

DMN-SN between-network ROI-to-ROI connectivity values were all negative and statistically significant (p-FDR<0.05) for the entire sample, as well as within the rMDD and control groups. No significant differences were found between rest vs. task DMN-SN connectivity for the whole sample or rMDD/HV subgroups (p<0.05). No changes in significance or connectivity directionality were found when age or antidepressant use covariates were included.

### 3.5.3 *Within-Network Connectivity Results*

None of the intrinsic DMN or SN connectivity contrasts (rest vs. task for rMDDs, rest vs. task for HVs, rMDD vs. HV at rest, rMDD vs. HV during the task, rest vs. task for rMDDs vs. HVs) were significant (p<0.05).

The paired t-test assessing rest vs. eStroop task within the rMDD group revealed significantly higher intrinsic CEN connectivity at rest (p-FDR analysis-level<0.01; **Figure 3.1**). This difference was specific to left PPC and right LPFC ROIs [ $\beta=0.14$ ,  $t(17)=3.86$ , p-FDR seed-level<0.01], and remained significant with the addition of age as a covariate (p-FDR seed-level<0.01). The inclusion of antidepressant use as a covariate slightly decreased significance (p-FDR seed-level=0.06). This CEN finding was not evident in the HV group.

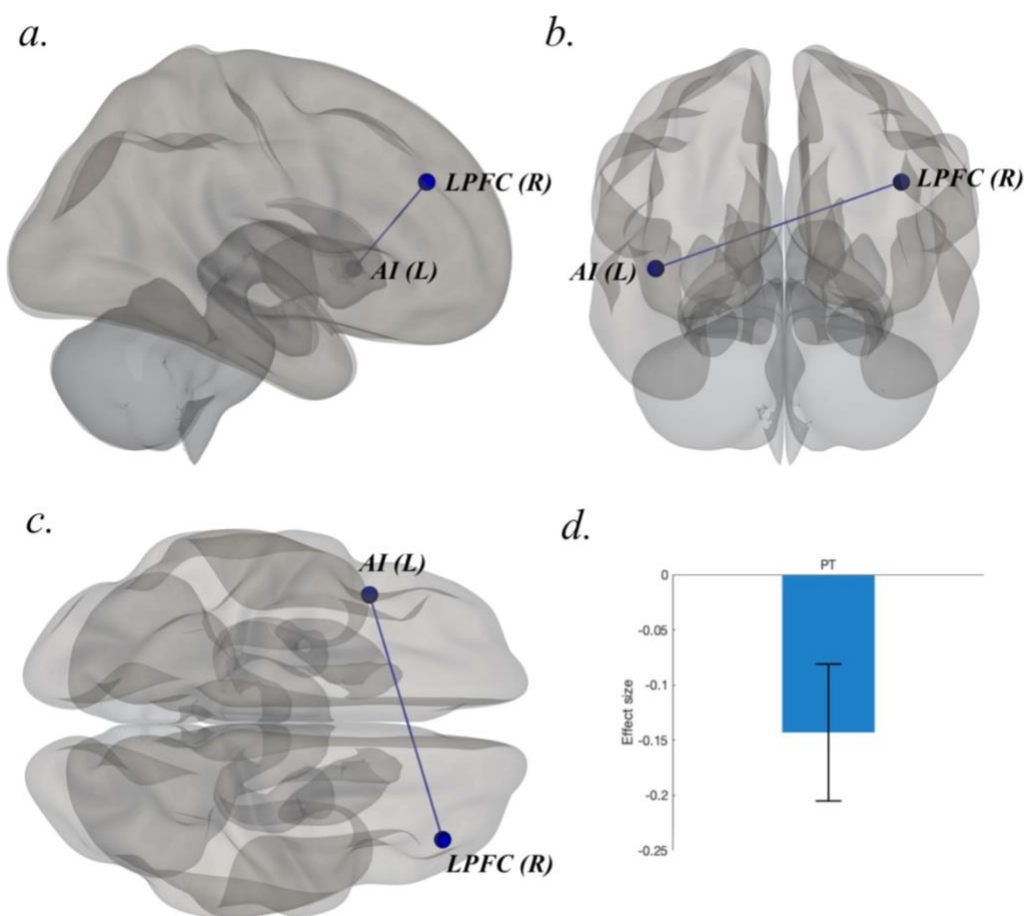


**Figure 3.1.** Visual representation of the statistically significant central executive network (CEN) rest>task results for the remitted major depressive disorder (rMDD) group. Three different views of the two nodes involved – the left posterior parietal cortex (PPC[L]) and right lateral prefrontal cortex (LPFC[R]) – are displayed; *a. Right, b. Posterior* and *c. Superior* views. *d. Effect size* of connectivity strength between PCC[L]-LPFC[R] for rest>task in the rMDD group (N=18, p-FDR seed-level<0.01).

### 3.5.4 Between-Network Connectivity Results

None of the DMN-CEN or SN-DMN between-network connectivity contrasts (rest vs. task for rMDDs, rest vs. task for HVs, rMDD vs. HV at rest, rMDD vs. HV during the task, rest vs. task for rMDDs vs. HVs) were significant ( $p < 0.05$ ).

The paired t-test within the rMDD group revealed more positive CEN-SN connectivity during the eStroop task vs. rest (p-FDR analysis-level=0.03; **Figure 3.2**). This was specific to connectivity between the right LPFC and left AI [ $\beta=-0.14$ ,  $t(17)=-4.01$ , p-FDR seed-level<0.01]; this remained significant with the addition of age as a covariate (p-FDR seed-level=0.02). The inclusion of antidepressant use as a covariate yielded non-significant results (p-FDR seed-level=0.14). This was not evident for the HV group.



**Figure 3.2.** Visual representation of the statistically significant central executive network (CEN) and salience network (SN) rest>task results for the remitted major depressive disorder (rMDD) group. the left prefrontal cortex (LPFC[R]) and left anterior insula (AI[L]) – are displayed above; *a. Right, b. Posterior and c. Superior views. d. Effect size of connectivity strength between AI[L]-LPFC[R] for rest>task in the rMDD group (N=18, p-FDR seed-level<0.01).*

### ***3.5.5 Exploratory Analysis – Main Effect of Antidepressants***

Given the effects of the inclusion of antidepressant use on some of the significant rest vs. task contrasts, exploratory analyses to elucidate the main effect of antidepressant usage were run. For each significant contrast described above, the main effect of antidepressant usage was explored. None of these analyses yielded significant results (data not shown).

**Table 3.9.** *DMN, CEN and SN Connectivity Contrast Results Summary (no covariates) for the whole sample and sub-samples; remitted depressed volunteers (rMDDs) & healthy volunteers (HVs) at rest, during the eStroop task, and at rest vs. during the task.*

Sample	Condition	Intra-network connectivity			Inter-network connectivity		
		DMN	CEN	SN	CEN-DMN	CEN-SN	DMN-SN
Whole Sample	Rest	+	+	+	+	<i>n.s.</i>	-
	Task	+	+	+	+	<i>n.s.</i>	-
	Rest>Task	-	+	+	<i>n.s.</i>	-	<i>n.s.</i>
rMDDs	Rest	+	+	+	+	<i>n.s.</i>	-
	Task	+	+	+	+	+	-
	Rest>Task	<i>n.s.</i>	+	<i>n.s.</i>	<i>n.s.</i>	-	<i>n.s.</i>
HVs	Rest	+	+	+	+	<i>n.s.</i>	-
	Task	+	+	+	+	<i>n.s.</i>	-
	Rest>Task	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>
rMDD>HV	Rest	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>
	Task	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>
	Rest>Task	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>	<i>n.s.</i>

*Note.* Findings with thick black box are those that differ between the samples.

DMN = default mode network, CEN = central executive network, SN = salience network

+ = positive findings, - = negative findings

n.s. = results were not statistically significant

### 3.6 CEN and DMN Connectivity Regressions

#### 3.6.1 CEN and DMN Connectivity, Rumination and Self-Reported Quality of Life in *rMDD* Participants

For all the listed significant results, there was homoscedasticity and normality of residuals. There were no outliers identified (i.e., there were no cases with standardized residuals greater than  $\pm 3$  SDs from the mean). All significant results (model outcomes and adjusted  $R^2$  values,  $p < 0.01$ ) are listed in **Table 3.10** and the associated correlation coefficients and false discovery rate corrected p-values are listed in **Table 3.11**.

**Table 3.10.** *DMN and CEN connectivity and self-reported quality of life and rumination questionnaire score regression model outcomes and % explained variance for the remitted depression (rMDD) group (n=18).*

Network	Condition	Scale	ROIs	Model Outcome	Adjusted $R^2$
DMN	Rest	WSAS	PCC-MPFC	F(1,16)=8.68, p=0.009	0.31
		WSAS	PCC-MPFC	F(1,16)=16.57, p=0.001	0.48
	Task	WSAS	PCC-LP(R)	F(1,16)=8.75, p=0.009	0.31
CEN	Task	SRRS HR	PPC(L)-LPFC(R)	F(1,16)=13.86, p=0.002	0.43

*Note.* Only statistically significant ( $\alpha=0.01$ ) results are listed in this table.

DMN = default mode network, CEN = central executive network

WSAS = Work and Social Adjustment Scale, SRRS HR = Stress Reactive Rumination Scale, hopeless rumination subscale

PCC = posterior cingulate cortex, MPFC = medial prefrontal cortex, LP(R) = right lateral parietal cortex, PPC(L) = left posterior parietal cortex, LPFC(R) = right lateral prefrontal cortex

**Table 3.11.** *DMN and CEN connectivity and self-reported quality of life and rumination questionnaire score regression coefficients and false discovery rate corrected p-values for the remitted depression (rMDD) group (n=18).*

Network	Condition	Scale	ROIs	Coefficients		CONN p-FDR (w/age covariate)
				$\beta_0$	$\beta_1$	
DMN	Rest	WSAS	PCC-MPFC	0.44	-0.01	0.03 (0.02)
	Task	WSAS	PCC-MPFC	0.61	-0.02	<0.01 (<0.01)
		WSAS	PCC-LP(R)	0.76	-0.02	0.03 (0.02)
CEN	Task	SRRS HR	PPC(L)-LPFC(R)	0.16	0.01	<0.01 (0.02)

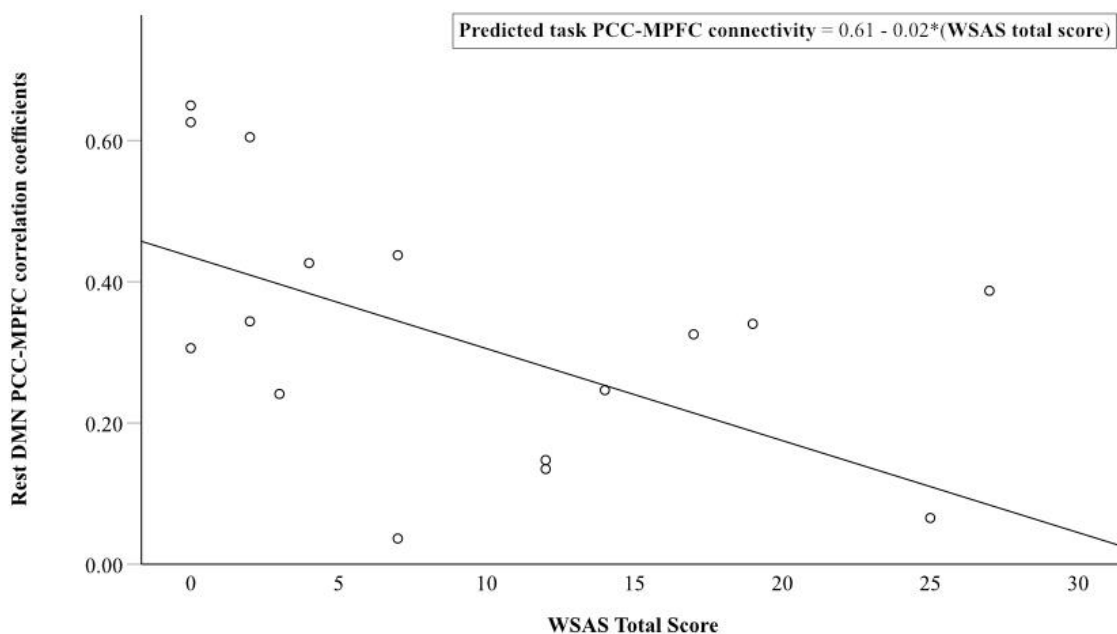
*Note.* Only statistically significant ( $\alpha=0.01$ ) results are listed in this table.

DMN = default mode network, CEN = central executive network

WSAS = Work and Social Adjustment Scale, SRRS HR = Stress Reactive Rumination Scale, hopeless rumination subscale

PCC = posterior cingulate cortex, MPFC = medial prefrontal cortex, LP(R) = right lateral parietal cortex, PPC(L) = left posterior parietal cortex, LPFC(R) = right lateral prefrontal cortex

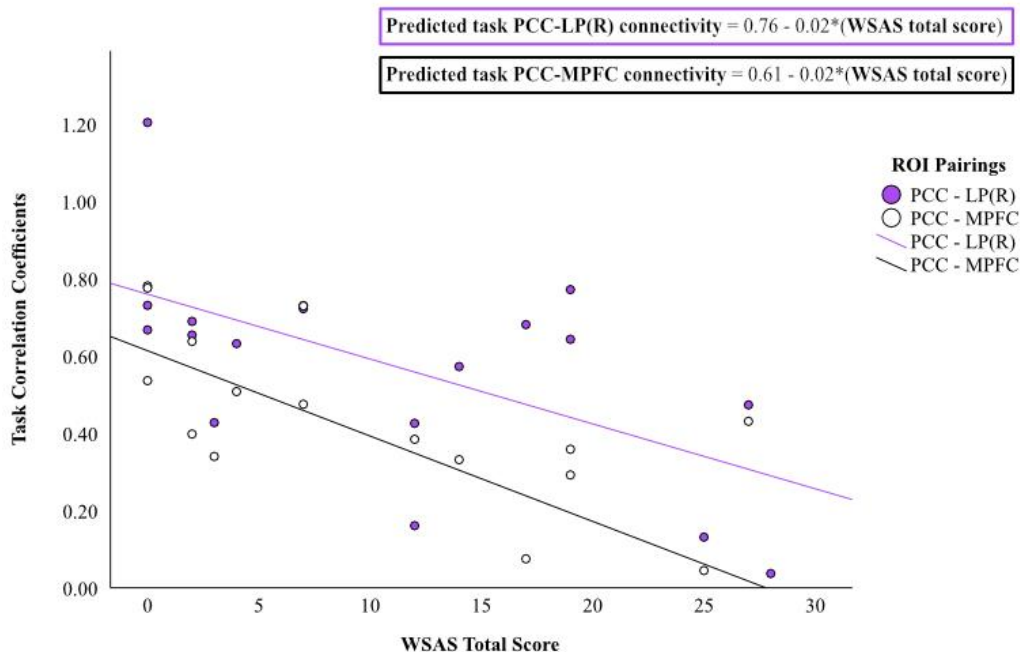
A linear regression established that WSAS total scores (self-reported psychosocial and daily functioning) negatively predicted connectivity within the DMN (PCC-MPFC) at rest,  $F(1,16)=8.68$ ,  $p<0.01$ , adjusted  $R^2 = 31.1\%$  (**Figure 3.3**, see **Table 3.11** for  $\beta_1$  values); in other words the higher the intrinsic DMN FC at rest, the lower the WSAS total scores (which reflect higher psychosocial and daily functioning). These results were followed up with two separate multiple regressions including age and antidepressant use as covariates; the results did not change [age:  $F(2,15)=5.01$ ,  $p=0.02$ , adjusted  $R^2=0.32$ ; antidepressant use:  $F(2,15)=4.20$ ,  $p=0.04$ , adjusted  $R^2=0.27$ ]. Only WSAS scores contributed significantly ( $p<0.05$ ) to these multiple regression predictions.



**Figure 3.3.** Scatterplot of Work and Social Adjustment Scale (WSAS) total scores (self-reported psychosocial and daily functioning) and default mode network (DMN) posterior cingulate cortex (PCC) – medial prefrontal cortex (MPFC) correlation coefficients at rest in the remitted major depression group. The linear regression indicated that WSAS total scores predicted PCC-MPFC connectivity at rest, and accounted for 31.1% of the explained variance (adjusted  $R^2$ ).

Two separate linear regressions indicated that WSAS total scores predicted connectivity within the DMN (PCC-MPFC [ $F(1,16)=16.57$ ,  $p<0.01$ ] and PCC-LP[R] [ $F(1,16)=8.75$ ,  $p<0.01$ ]) during the task, adjusted  $R^2 = 0.48$  (PCC-MPFC) and 0.31 (PCC-LP[R]) (**Figure 3.4**, see **Table 3.11** for  $\beta_1$  values); in other words the higher the intrinsic DMN FC during the task, the lower the WSAS total scores (reflecting higher psychosocial and daily functioning). These results were followed up with four separate multiple regressions including age and antidepressant use as covariates. The predictive relationship between WSAS total score and PCC-MPFC connectivity remained significant (age:  $F(2,15)=10.03$ ,  $p<0.01$ , adjusted  $R^2=0.52$ ; antidepressant use:  $F(2,15)=7.77$   $p<0.01$ , adjusted  $R^2=0.44$ ). The predictive relationship between WSAS total

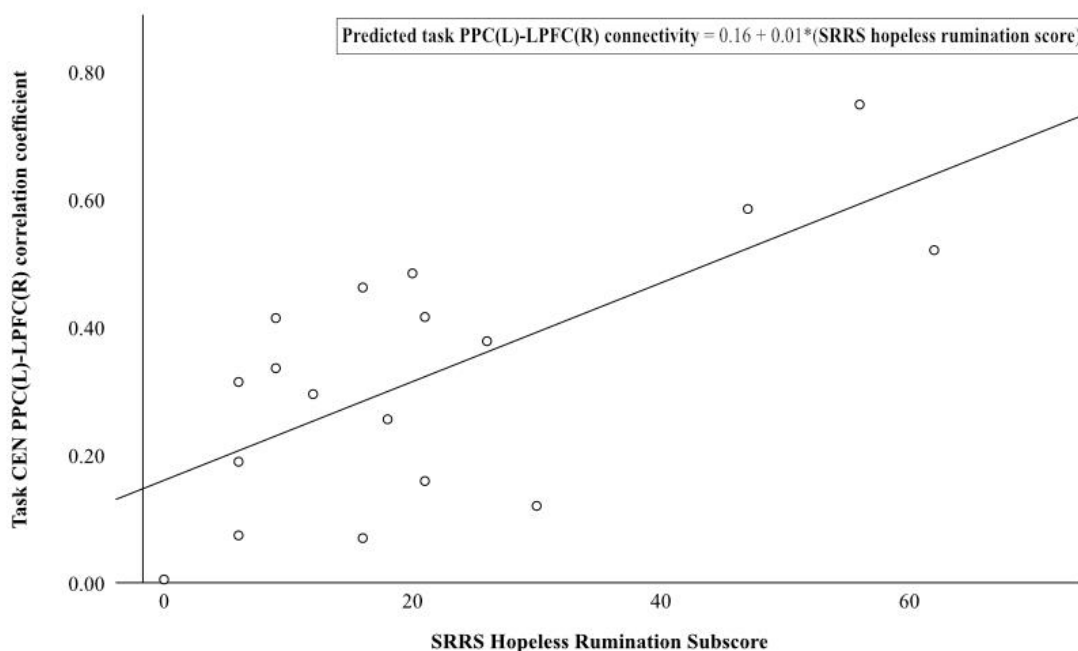
score and PCC-LP(R) connectivity also remained significant with the addition the covariates (age:  $F(2,15)=4.82$ ,  $p=0.02$ , adjusted  $R^2=0.31$ ; antidepressant use:  $F(2,15)=4.12$ ,  $p=0.04$ , adjusted  $R^2=0.27$ ). Only WSAS scores contributed significantly to these predictions,  $p<0.05$ .



**Figure 3.4.** Scatterplot of Work and Social Adjustment Scale (WSAS) total scores (self-reported psychosocial and daily functioning) and default mode network (DMN) posterior cingulate cortex (PCC) – right lateral parietal cortex (LP[R]) and PCC – medial prefrontal cortex (MPFC) correlation coefficients during the emotional Stroop task in the remitted major depression group. The linear regression indicated that WSAS total scores predicted PCC-LP(R) connectivity and MPFC connectivity during the task and accounted for 31.3% and 47.8% of the explained variance (adjusted  $R^2$ ), respectively.

A final linear regression indicated that scores from the hopeless rumination subscale of the SRRS predicted connectivity within the CEN (PPC[L]-LPFC[R]) during the task,  $F(1,16)=13.86$ ,  $p<0.01$ , adjusted  $R^2 = 0.43$  (**Figure 3.5**, see **Table 3.11** for  $\beta_1$  values); in other words the higher the intrinsic CEN functional connectivity, the higher the SRRS hopeless rumination scores (reflecting a greater tendency to engage in

hopeless, negative rumination in response to a stressful event). This remained significant when age was included as a covariate,  $F(2,15)=6.52$ ,  $p<0.01$ , adjusted  $R^2=0.39$ , or when antidepressant use was included as a covariate,  $F(2,15)=7.06$ ,  $p<0.01$ , adjusted  $R^2=0.42$ . Only hopeless rumination scores contributed significantly to the predictions,  $p<0.05$ . None of the other linear regression results were statistically significant ( $p>0.01$ ).



**Figure 3.5.** Scatterplot of Stress Reactive Rumination (SRRS) hopeless rumination subscores and central executive network (CEN) left posterior parietal cortex (PPC[L]) – right lateral prefrontal cortex (LPFC[R]) correlation coefficients during the emotional Stroop task in the remitted major depression group only. The linear regression indicated that SRRS hopeless rumination scores predicted PPC(L)-LPFC(R) connectivity during the task and accounted for 43.1% of the explained variance (adjusted  $R^2$ ).

### 3.6.2 CEN Connectivity and eStroop Task Performance

None of the linear regressions examining the predictive relationship between eStroop RT and CEN intrinsic connectivity were statistically significant ( $p>0.01$ ).

## Chapter 4: DISCUSSION

### 4.1 Summary

The main objective of this thesis was to compare resting-state and task (as well as task vs. resting-state) triple network connectivity profiles in remitted depressed patients (rMDDs) and healthy volunteers (HVs). A secondary objective was to explore relationships between DMN and CEN connectivity and daily functioning, quality of life, and rumination in the rMDD group. Our findings contribute to the body of research profiling triple network connectivity profiles in individuals in remission from MDD. Further, to our knowledge, these findings are novel in their contribution of profiling fMRI-indexed functional connectivity characteristics in rMDD during an eStroop task.

The HV and rMDD groups were well-matched on pertinent demographic features. On average, the rMDD participants had experienced ~3-4 major depressive episodes in their lifetimes, which is comparable with prior literature that has assessed network connectivity features in rMDD.<sup>58,111,112</sup> The rMDD group displayed higher levels of hopeless rumination compared to HVs, and displayed some degree of lingering depressive symptoms, despite not meeting clinical criteria for current depression. Furthermore, rMDDs reported lower psychosocial functioning and lower subjective quality of life compared to the HVs. This is consistent with previous findings of MDD symptoms and poor functional outcomes persisting into remission.<sup>6</sup>

There were no widespread findings of cognitive impairment in the rMDD sample as measured via the CANTAB cognitive battery, but there were some findings of an affective attentional bias and impaired processing speed. As hypothesized, there were no differences in accuracy between HV and rMDDs on the eStroop task. However, contrary

to our hypotheses, there was also no evidence of attentional bias towards negative stimuli during the eStroop task in the rMDD sample, nor was there significantly impaired processing speed in the rMDDs vs. HVs during the task.

Additionally, we also did not find any evidence of DMN hyperconnectivity and CEN hypoconnectivity at rest and during the task in the rMDD as compared to the HV group. In fact, no significant differences in connectivity between the rMDD and HV groups were found. There were, however, findings of higher intrinsic CEN and lower intra-network CEN-SN connectivity at rest vs. during the eStroop task that seemed driven by the rMDD group (i.e., these findings did not emerge in the HV subgroup). There were also findings of significantly positive CEN-SN connectivity in the rMDD group only. We also failed to replicate previous findings of negative correlations between the DMN and CEN, and actually found significant positive CEN-DMN correlations across the entire sample both at rest and during the task. Contrary to expectations (based on previous rest vs. visual attention task connectivity findings in healthy cohorts<sup>40</sup>), we also found significantly higher DMN connectivity during the eStroop task vs. at rest across the whole sample.

Finally, we noted a significant relationship between CEN and DMN connectivity, daily function and rumination in rMDD, but the directionality of these relationships were the opposite of what was hypothesized.

#### **4.2 Cognitive Impairment in rMDD**

There were no significant differences between rMDDs and HVs for most of the CANTAB tasks, with two exceptions. First, median correct RT was longer in rMDDs than HVs for the rapid visual information processing task. Second, median correct RT for

all emotional conditions was significantly longer in rMDDs vs. HVs during the emotional recognition task. These CANTAB findings suggest an attentional bias towards emotional faces and mild impairment in processing speed in the rMDD sample, consistent with previous findings in remitted depressed populations,<sup>8</sup> but there was no evidence of significant, broad-scale cognitive impairment. These modest findings are surprising given the significant self-reported cognitive, quality of life and psychosocial functioning impairments in our rMDD sample. However, it is important to note that the magnitude of previously reported cognitive dysfunction in rMDD samples tends to be moderate; for example, Cohen's *d* effect size estimates from one recent meta-analysis of CANTAB-assessed cognitive impairments ranged from -0.22 (small) to -0.61 (medium).<sup>8</sup> This means that impairments may not be statistically significant in smaller sample sizes like this study sample.

Another consideration when interpreting the relatively modest findings of cognitive impairment in the rMDD sample is the imperfect alignment of self-reported and objectively measured (i.e. behaviourally significant) cognitive impairments in rMDD. Importantly, smaller objectively-measured cognitive deficits do not necessarily correspond to better outcomes for patients. In fact, a 2019 study examining the difference between subjective and objective cognitive impairment in rMDD found that the combined presentation of high subjective complaints and low objective cognitive impairment was associated with lower quality of life, greater self-reported stress and increased socio-occupational problems.<sup>113</sup> The rMDD sample in this thesis may actually be representative of this subjective-objective cognitive impairment “mismatch” and associated poor outcomes, as indexed by the concurrent findings of modest objective

cognitive impairments, subjective complaints of cognitive impairment, and low psychosocial functioning and quality of life in the rMDD group. This noted, the subjective complaints of cognitive impairment in this thesis were only indexed by scores on a single questionnaire outcome question (IDS-SR, question #15); future studies should employ a full scale to measure subjective cognitive impairments more granularly. Furthermore, future work would benefit from mediation analyses to clarify the relationship between these features and medication status in remitted samples; this was not possible in the current sample due to insufficient power (however, we did use medication as a covariate in the current work to attempt to control for the effects in our findings). Future studies aiming to specifically examine the neurobiological origin of objective cognitive impairment in rMDD may also benefit from the utilization of demonstrated behavioural (i.e., objective) cognitive impairment as an inclusion criteria for volunteers (i.e. including a cognitive battery as part of the screening process).

Despite finding evidence of an emotional bias in the remitted sample during the CANTAB battery, there was no evidence of behavioral differences (RT, accuracy) between emotional conditions during the eStroop task. This suggests a lack of attentional bias towards emotionally-valenced words used in our eStroop task in the HV or rMDD samples, a finding that is inconsistent with prior findings of a negative bias in rMDD;<sup>32,33</sup> though consistent with data in HVs, which generally shows a lack of such a bias on the eStroop.<sup>33</sup> Furthermore, there was no evidence of impaired processing speed (longer RTs) in rMDDs vs. HVs. However, qualitative assessments of our data suggest longer (albeit insignificant) RTs in the rMDD cohort; a larger effect may have emerged in a larger sample size.

The lack of significant negative bias findings for the eStroop task for the rMDD cohort, in particular, may be explained, in part, by the choice of words. The emotional words were selected from the ANEW dataset to first maximize/minimize valence and then maximize arousal, with mean arousal values for negative ( $6.33 \pm 0.83$ ) and positive ( $6.23 \pm 0.82$ ) words that were well matched, but significantly below the peak arousal scale value of 9. The mean valence of the negative ( $1.98 \pm 0.28$ ) and positive ( $8.06 \pm 0.32$ ) words chosen were very close to the minimum and maximum values within the data (1.25-8.82), and were highly significantly ( $p < 0.0001$ ) different from the mean neutral ( $5.52 \pm 0.23$ ) word valence. However, we did not obtain sample-specific valence or arousal ratings, which may have revealed a less substantial distinction between the chosen negative and positive word valences and/or lower arousal scores in our sample. It has also been suggested that using disorder-congruent and/or self-relevant words may play an important role in eliciting attentional biases in MDD.<sup>114</sup> On the other hand, two recent meta-analyses found no difference in effect size between depression-specific and generally negative words<sup>32,33</sup> in MDD patients during the eStroop paradigm, suggesting that this aspect of word choice is less likely to have had an impact on the study results (though this is unclear in the context of remission from MDD).

Despite not seeing any behavioural evidence of group differences during the eStroop task, neural features may differ between rMDDs and HVs during the task, mirroring previous neural-behavioural eStroop findings in HVs<sup>30</sup>, and highlighting the benefit of neuroimaging in exploring putative cognitive-emotional dysfunctions. Presumably, compensatory neural activity can result in normal behavioural results in psychiatric illness.

### 4.3 Triple Network Connectivity Findings

The results of the quality control checks suggested successful denoising and relatively clean data that did not differ significantly between groups. As such, our connectivity findings were not likely driven by artefactual features (though, those can never be fully discounted).

There was significant positive whole-sample intrinsic connectivity in the DMN at rest and during the eStroop task, confirming an appropriate choice of network-specific ROIs. Contrary to our hypothesis, which was that the ‘task-negative’ DMN would have higher connectivity at rest than during the task, we found higher DMN connectivity during the eStroop task vs. at rest across the whole sample, and in the rMDD and HV samples. This effect may have been driven by an increase in self-referential processing during the presentation of the positive and/or negative words in the eStroop task, many of which could be interpreted in a self-referential way (eg. friendly, loved, rejected, failure). It stands to reason that the presentation of the negative and positive words by way of the eStroop task could increase DMN connectivity, given the known role of the DMN in self-referential processes,<sup>115</sup> and the relatively low cognitive demand of the task, which might allow for some degree of self-referential thought to occur without impairing task performance.

It is possible that increased DMN connectivity, indicative of increased self-referential thought, might have been most apparent during the negative vs. neutral and/or positive blocks in individuals with rMDD. This would make sense given the known propensity towards negative self-referential thought in clinical and sub-clinical depression,<sup>61</sup> especially in concert with the findings of increased hopeless rumination in

our rMDD study sample. Conversely, increased DMN connectivity might have been observed in the HVs during the positive vs. neutral and/or negative blocks, reflecting a higher level of self-relational thought when viewing/processing the positive words. To our knowledge, this study is the first to examine triple network connectivity during an eStroop task, so this interpretation is speculative, but there is behavioural data that supports this hypothesis. There is evidence that clinically depressed individuals rate negative words (eg. bleak, guilty) as being more self-referential and have greater recall for these negative words compared to non-depressed volunteers.<sup>116</sup> Conversely, non-depressed volunteers display higher self-referential scoring and recall of positive words (eg. loyal, organized).<sup>116,117</sup>

Given the relatively short length (2.4 min) of each of the affect-specific portions of the task (i.e. positive, negative, neutral), the task design was not optimal for comparing functional connectivity between affective categories in this study, as the absolute minimum suggested scan length for stable connectivity analyses is typically 5 min.<sup>118</sup> Future work should compare DMN connectivity in rMDD and HV groups between negative, neutral and positive eStroop blocks to explore this hypothesis, ideally via psychophysiological interactions (PPI) analysis.<sup>119</sup>

Contrary to what was hypothesized, we did not find any evidence of DMN hyperconnectivity at rest or during the task in the rMDDs vs. HVs. However, this finding is not completely unprecedented given the mixed literature. The sample characteristics, preprocessing methods, ROI definition techniques and cognitive tasks tend to vary depending on the study, which might account for the mixed findings. In particular, a recent meta-analysis of functional connectivity findings in MDD found that intrinsic

DMN hyperconnectivity was more likely in unmedicated vs. medicated MDD.<sup>49</sup> As such, the mixed-medication status of our study sample might have contributed to the lack of significant group differences. Further, it is possible that altered DMN connectivity features in rMDD are subtle (and perhaps more likely in some subsamples; for example, adolescent-onset rMDD)<sup>59</sup>, and we were underpowered to capture and assess these differences. Furthermore, DMN connectivity alterations may exist with different DMN nodes (many are identified in the literature) or other brain regions outside of the triple network model. These analyses are beyond the scope of this thesis, and the sample is likely underpowered for such broad-scale, undirected analyses; nevertheless, future studies may benefit from whole-brain voxel-wise connectivity analyses.

There was significant positive whole-sample intrinsic connectivity in the CEN at rest and during the eStroop task, again confirming an appropriate choice of network-specific ROIs. Contrary to expectations, however, we did not find any evidence of CEN hypoconnectivity at rest in the rMDD group. Also contrary to our hypotheses, there were no significant CEN connectivity differences in HVs compared to rMDDs. We did, however, find higher intrinsic CEN connectivity at rest vs. during the eStroop task in the rMDDs; this was not found in HVs. The findings of higher CEN connectivity at rest vs. during the task was also found in the whole-sample analysis. These findings may also be due, in part, to the choice of task: the CEN is generally associated with cognitive control processes, which may not be optimally engaged during the eStroop task (it is a task with relatively low cognitive load and, as was mentioned above, may have elicited self-referential processes to a greater degree than was anticipated). We would still expect to see relatively higher CEN connectivity during the task vs. at rest, but the majority of the

literature has focused on CEN activity, not connectivity *per se* during tasks, which are not necessarily directly related.<sup>119</sup> Furthermore, no study, to our knowledge, has examined rest vs. task connectivity profiles during an eStroop task, so perhaps the CEN is differentially engaged during this task as opposed to non-affective cognitive tasks.

There was significant positive whole-sample intrinsic connectivity in the SN at rest and during the eStroop task, again confirming an appropriate choice of network-specific ROIs. Findings of higher SN connectivity at rest vs. during the task were significant for the whole sample contrast, but not the subgroups (i.e. HVs or rMDDs). The lack of findings at a subgroup level may simply be a consequence of the subgroup sample sizes being underpowered (they were both ‘trending’ in line with the whole sample results, data not shown). Given the fact that the SN and CEN generally coactivate,<sup>37</sup> this finding ties in with the findings of higher intrinsic CEN connectivity at rest vs. during the eStroop task in the whole sample, and could be explained via a similar mechanism (i.e. perhaps the eStroop task does not optimally engage the CEN, and therefore does not simultaneously engage the SN, which makes sense given their typical pattern of co-activation).

There were also findings of a significant positive CEN-SN connectivity during the task in the remitted group only, and higher CEN-SN connectivity during the task vs. at rest in the rMDDs and the whole sample; this was not found in the HV subgroup (p-FDR=0..50). Given the relative paucity of data on CEN-SN connectivity during rMDD (these analyses were exploratory in nature) it is not possible to compare these data with existing literature. It is possible that the higher observed CEN-SN during the task in the rMDD group might reflect greater switching between the CEN/DMN via the SN (hence

the increased CEN-SN connectivity), in order to keep up with the task demands and achieve a similar accuracy and RT to the HVs. However, this is highly speculative and requires further study to confirm.

Interestingly, all of these rMDD sample-specific CEN findings were altered by the inclusion of antidepressant usage as a covariate. Though no significant main effect or interaction with antidepressant use emerged for any of these contrasts (perhaps due to power), it is possible that these findings are, at least to a certain extent, altered by antidepressant medication, given the mixed-medication status of the sub-group using antidepressants. Regardless, findings would likely be easier to interpret in an unmedicated sample or a larger sample with clearly demarcated medication classes.

Contrary to expectations, we found significant positive (vs. the hypothesized negative) connectivity between the CEN and DMN for the entire sample, as well as within the rMDD and HV groups both at rest and during the eStroop task. While surprising, this finding could perhaps be partially explained by the methodology used. First, most studies assessing CEN-DMN connectivity have used activity analyses to create ‘task-positive’ and ‘task-negative’ masks<sup>38</sup>, ICA for extracting networks,<sup>56,76</sup> or seed-to-voxel analyses.<sup>46,49,54</sup> Here, we used an ROI-to-ROI approach, which makes direct comparisons with previous literature difficult. The impetus for an ROI-to-ROI approach was to streamline analyses and enable a more for a more robust replication design. Second, the popularity of global signal regression may have overestimated the degree of negative CEN-DMN correlations in past literature (we did not use global signal regression in this thesis, but rather a denoising alternative called aCompCor). A recent meta-analysis failed to find strong evidence of a negative task-positive (dorsal attention

network)/task-negative (DMN) network correlation in the absence of global signal regression, finding instead weak negative correlations or even positive correlations when global signal regression was not applied.<sup>120</sup> The authors of that study posited that the negative correlation between the dorsal attention network and DMN may in fact be state-dependent. It is possible that the CEN-DMN correlations are similarly transient/task-dependent, and negative correlations may only emerge under certain conditions.

There were also findings of significant negative whole-sample, and within group (both rMDD and HV) DMN-SN connectivity during the task and at rest. In the context of prior findings of decreased resting-state DMN-SN connectivity in MDD<sup>49,84</sup> and rMDD<sup>85</sup> relative to HVs, perhaps this strong pairing across all groups is simply indicative of a relatively normal DMN-SN connectivity profile in our sample, though this is speculative.

#### **4.4 The Relationship Between Connectivity, Daily Function and Rumination in**

##### **rMDD**

Contrary to our hypotheses, lower psychosocial and daily functioning scores were associated with lower DMN connectivity at rest and during the task in the rMDD group (these relations were only assessed in the rMDD cohort because of the lack of variability in HV questionnaire scores and specific interest in the variability of symptoms within the rMDD group and the associated connectivity alterations). It is possible that lower intrinsic connectivity in the DMN, regardless of condition, was indicative of a potential ‘breakdown’ of network function (i.e. more “disorganized” function/suboptimal levels of intrinsic DMN activity) that was associated with poorer functioning. Interestingly, a recent (2020) study also linked diminished DMN connectivity in MDD to greater social dysfunction; as such, this finding is not completely at odds with prior literature.<sup>121</sup>

Unexpectedly, a greater tendency to engage in hopeless rumination was associated with increased intrinsic CEN connectivity during the task in the rMDD group. Interestingly, there was one study that similarly associated poor outcomes (increased depression symptom severity, anhedonia, fatigue, poor cognitive function) with higher CEN connectivity within a group of late-life depressed individuals.<sup>122</sup> Research in healthy cohorts have found that CEN connectivity increases as a function of cognitive demand during tasks.<sup>83</sup> It is possible that the CEN hyperconnectivity during the task is indicative of compensatory reactivity to increased rumination, i.e. the rMDD participants with relatively higher CEN connectivity during the task found the task more cognitively demanding because of competing resources. This putative explanation could account for why this relation emerged during the task, in particular.

#### **4.5 Limitations**

The sample size limits the statistical power for more granular analyses (e.g. subgroups), and therefore the interpretation of the thesis results. Similarly, the mixed-medication status (44.4% medicated) of the rMDD group might account for some of the variability in the findings. Ideally, the research should be replicated with a larger sample size in the future to ensure adequate statistical power for more granular assessments. Some studies of remitted depression have used medication-free samples to subvert the confounding factor of antidepressant medication.<sup>53,57,59,123</sup> However, given the fact that remitted depressed individuals tend to be on maintenance medication (the Canadian Network for Mood and Anxiety Treatments evidence-based guidelines for clinicians suggest maintenance treatment for at least 2 years for recurrent remitted depression),<sup>124</sup> the inclusion of medicated individuals may be an important factor when studying this

population for: a) practical recruitment issues and b) to accurately represent the general rMDD population. Ideally, future research should be conducted with an adequate sample size to compare cognitive impairment and associated connectivity profiles in rMDD across clearly demarcated medication classes (to truly assess whether/and what kind of medication may influence outcomes).

Further, though the sex distributions were balanced between the rMDD and HV groups, and the inclusion of sex as a covariate of no-interest did not change the connectivity results, the lack of sex and/or gender-based analyses is a notable limitation of this thesis. Given the known gender/sex differences in MDD prevalence, symptomology, disease course<sup>125</sup> and fMRI connectivity features,<sup>126</sup> future studies would benefit from sex and/or gender-based analyses, which might reveal differential triple network alterations in males vs. females. Another potential limitation is the inclusion of both right- and left-handed participants (though only N=4 left-handed participants were included, N=2 rMDD and N=2 HV, and handedness was included as a covariate of no interest to control for these effects), which may have muddied the neuroimaging results for the emotional Stroop task, in particular, given previous evidence of language network lateralization and connectivity differences associated with handedness.<sup>127</sup>

Further, despite relatively well-established prior findings of rMDD group differences and the fact that it reliably tests affective cognition, the eStroop task is not a particularly cognitively-demanding task. Given the relatively low magnitude of cognitive dysfunction in rMDD, rest vs. task connectivity differences may have been better elucidated (in this sample) by a more demanding cognitive task and perhaps a more salient emotional task (or a more challenging version of an emotion-cognitive task).

Indeed, research in healthy cohorts has suggested that intrinsic DMN connectivity is modulated by cognitive load (i.e. DMN connectivity decreases as cognitive load increases).<sup>83</sup> There is actually some experimental evidence suggesting that the use of an alternate task may have been more effective at eliciting a group effect with smaller sample sizes like the one used in this thesis. According to a comparative quantitative review by Pekham et al., the dot probe task may be a more discriminatory measure of biased attention to negative information in depression than the eStroop task (i.e. the effect size was much larger for the dot probe task vs. the eStroop).<sup>128</sup> There are also different variants of the eStroop task that might create more intense emotional interference, and are more effortful. For example, the ‘word-face’ version of the task, where emotional words are overlaid on an emotional face and the participant must identify the emotional facial expression, or the ‘priming’ version of the task, where each word trial is primed with an emotional or neutral picture,<sup>129</sup> might have elicited more pronounced effects. Furthermore, given that cognitive impairments have been found across many domains in rMDD, including memory, processing speed, semantic fluency and executive function,<sup>8,10,11</sup> future studies should explore triple network alterations during tasks in other (ie., non-emotional) affected cognitive domains.

The interpretation of the ROI-to-ROI functional connectivity analyses could be aided by concurrent activity analyses, and/or by the use of complementary alternate functional connectivity analyses such as seed-to-voxel assessments. Though the ROI-to-ROI analysis was justifiably employed with replicability in mind and in order to address very specific hypotheses with regards to the triple network model, the results could certainly be complemented by seed-to-voxel analyses. As was mentioned earlier in the

discussion, future rMDD studies would benefit from affect-specific PPI eStroop task analyses to determine whether the self-referential affect-specific hypothesis is supported by the data. Finally, though these analyses were beyond the scope of this thesis, future analyses of this thesis data should include concurrent EEG-fMRI connectivity analyses, which would benefit from the superior temporal resolution of EEG (2 ms timescale) in concert with the excellent spatial resolution of fMRI.

#### **4.6 Conclusions and Future Directions**

Our rMDD sample presented with subjective complaints of cognitive impairment in concentration and decision making, and some mild objective impairments as indexed by an attentional bias towards emotional faces and longer processing speed. The rMDD individuals also reported significantly lower quality of life and psychosocial functioning, in line with previous literature.

We failed to replicate previous reports of DMN hyperconnectivity and CEN hypoconnectivity in rMDD participants. We did, however, find evidence of altered intrinsic CEN and CEN-SN connectivity between the rest and task conditions that seemed driven by the rMDD sample, and at least partially affected by antidepressant status. The findings were at odds with previous literature in many cases, something that may be explained by a combination of factors, including the relatively low cognitive load and potentially self-referential nature of the eStroop task, the sample size, the mixed-medication status of the remitted sample, and the choice of ROIs, to name a few. Future research would benefit from a larger sample size and the use of an unmedicated sample or clearly demarcated medication classifications. Furthermore, comparisons of connectivity during tasks with different cognitive loads (ex. 1-back, 2-back, 3-back as in

the N-back working memory task), across affective categories (negative, neutral, positive) and/or probing different types of cognition might help explain some of the findings.

It is also important to note that the CEN task connectivity and CEN/DMN/SN rest vs. task connectivity analyses conducted in this thesis are rare in the literature, but arguably important to examine within the context of the triple network model. The hypothesis that aberrant network function underlies cognitive dysfunction in remitted and acutely ill MDD patients relies in no small part on aberrant network function during task completion. The literature has historically focused on CEN activity during tasks; these findings could be complemented by CEN connectivity analyses, given the emerging evidence that the relationship between regional activation and functional connectivity is not linear.<sup>119</sup> Future studies would benefit from complementary task-based connectivity and activity analyses.

This thesis contributes to the growing body of work on triple network connectivity alterations in rMDD, and contributes novel findings and hypotheses with regards to self-referential processes elicited by the eStroop task via the rest vs. task and task-based connectivity analyses. Furthermore, the lack of widespread objective cognitive impairments and/or connectivity alterations in rMDD may suggest some degree of concurrent behavioural and neural cognitive recovery after remission. From a clinical perspective, these results suggest that objective measures of cognition largely recover in remission (or, perhaps were never objectively that impaired in this cohort). These findings in combination with the self-reported attentional difficulties in this cohort suggest that in some individuals, cognitive impairments in remission might be mostly an

‘attributional’ problem (i.e. a distorted negative appraisal of one’s own cognitive function). As such, psychological interventions in such individuals might be appropriate. Further, our data suggesting that remitted patients are cognitively similar to never-depressed individuals (using objective indices) might help reassure rMDD patients, and be integrated as part of a treatment plan. Though future work is required to confirm this recovery, these findings are good news for individuals with MDD with regards to functional recovery post-remission, and may help inform and aid psychological interventions.

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## Appendix I: Phone Screens (rMDD followed by HV)

### SCREENING SCRIPT – CDP-Choline & MDD Remitted Study rMDD VERSION

The following is intended as a guide. You do not need to read it word-for-word.

Hello (INSERT INDIVIDUAL'S NAME)

My name is (FIRST NAME) and I am a(n) (POSITION) from the Clinical EEG Lab at the Royal. I am calling about our study on the effects of a natural supplement on cognitive performance, which you had expressed an interest in participating in.

**\*\*OR\*\***

Thank you for calling us to find out more about our research.

---

Do you have a moment so that I can explain the study to you?

The purpose of our study is to examine the effects of a natural supplement called CDP-choline on cognitive performance. We will be using a series of cognitive tasks administered on an iPad to measure your performance. There are no risks associated with CDP-choline as it is a substance that occurs naturally in the body and is found in many foods.

There is a second, optional arm of the study that involves brain imaging. If you choose to participate in this, we will measure your brain activity using two methods. The first method is called EEG – it involves placing passive electrodes on your head to measure brain electrical activity. We will also measure your brain structure and function with the use of a magnetic resonance imaging (fMRI) machine.

If you choose to participate, you would come to our laboratory 3 times – with each visit lasting ~3-4 hours. These visits will occur over a period of 2-3 weeks.

During these visits, you will be required to fill out several questionnaires and complete a few cognitive tasks – if you choose to participate in the brain imaging arm, we will also record EEG and MRI data. You will be compensated \$30/session, with an additional 30\$/session if you participate in the brain imaging. The total compensation for participating without imaging will be \$90 for three sessions. If you qualify and choose to participate in the neuroimaging part of the study, the total compensation will be \$150 for three sessions. All testing will be carried out at the Royal Hospital on Carling.

Are you still interested in participating in this study and continuing with the screen?

**[IF NO]:** Thank you very much for your time.

**[IF YES – still interested]:**

Is this a good time to do the phone screen – it may take ~15-30 minutes?

**[IF NO]:** Set up a time to call back:

Date: \_\_\_\_\_ Time: \_\_\_\_\_

**[IF YES]:** Before having you visit, we need to ask you some questions to determine if you are eligible for the study. It is possible that some of these questions may make you feel uncomfortable or distressed. If this happens, let me know, and we can stop the screen at any time, or take a break. You also have the right to

refuse to answer any questions. I also want to assure you that the information collected during this phone screen is confidential. The information will be destroyed if you do not qualify for the study or choose not to participate. If you do qualify, this information will be kept in a safe place.

**[IF NO]:** Thank you very much for your time.

**[IF YES]:** Before we start, do you have any questions about the study?

*The following information may have been obtained before the screen (e.g. from e-mail or phone message).*

Name: \_\_\_\_\_ Sex: M or F (circle) Age & DOB: \_\_\_\_\_ (18-65 yrs)

Employment: \_\_\_\_\_ Highest Level of Education: \_\_\_\_\_

Height: \_\_\_\_\_ Weight: \_\_\_\_\_ **Exclude if BMI >38kg/m<sup>2</sup>** Handedness: L R  
Both

Telephone: \_\_\_\_\_ E-Mail: \_\_\_\_\_

Heard about study via: \_\_\_\_\_

### **GENERAL MEDICAL**

I am going to start off by asking you a few questions about your physical health.

Have you been diagnosed with or are you currently being treated for any major physical medical problems or chronic medical conditions?

YES NO

[IF YES]: Which ones? \_\_\_\_\_

Are you currently taking any medication for any chronic health problems? (e.g. high blood pressure, cholesterol, thyroid, diabetes)

YES NO

[IF YES]: Which ones/how long? \_\_\_\_\_

**Any thyroid issues should be stabilized for at least 3 months**

Do you have any major allergies to food or medication?

YES NO

[IF YES]: Which ones? \_\_\_\_\_

Do you have a history of any neurological or neuromuscular problems? (e.g. stroke, epilepsy, brain cysts, migraines, MS).

YES NO

[IF YES]: Which ones? \_\_\_\_\_

Do you have any major motor impairments? (e.g. cerebral palsy, physical disability, muscular dystrophy)

YES NO

[IF YES]: Which ones? \_\_\_\_\_

Have you ever had a concussion?

YES NO

[IF YES]: Were you unconscious/ if so, how long were you unconscious? \_\_\_\_\_

Have you ever been diagnosed with a development problem? (e.g. autism)

YES NO

[IF YES]: Which ones? \_\_\_\_\_

Have you ever been diagnosed with or struggled with major learning disabilities? (e.g. pronounced reading problems, dyslexia)

YES NO

[IF YES]: Which ones? \_\_\_\_\_

### **FURTHER MEDICAL – STUDY COMPATIBILITY - NEUROIMAGING**

Do you have any issues with back pain?

YES NO

[IF YES]: Would this impede you from sitting up straight or lying still for prolonged periods of time?

YES NO

Have you ever had an EEG done or have previously participated in an EEG study?

YES NO

[IF YES]: What for/when? \_\_\_\_\_

Have you ever had an MRI done or participated in aMRI study?

YES NO

[IF YES]: What for/when? \_\_\_\_\_

Do you have any metal in your body? (e.g. pacemakers, surgical/aneurysm clips, prosthetic valves, metal plates/screws, pins, cochlear implants, braces, etc.?)

YES NO

[IF YES]: What for/when? \_\_\_\_\_

Do you wear eyeglasses/contacts?

YES NO

[IF YES]: Inquire about whether they can wear their contact lenses to testing

[IF NO]: Inquire about glasses prescription (we have MR-compatible glasses)

Are you colour blind?

YES NO

[IF YES]: **Exclude**

### **MENTAL HEALTH SECTION**

**EXCLUDE REMITTED MDD PATIENTS if they are currently experiencing major symptoms of depression or report being in a major depressive episode (MDE). Ideally, we want to recruit those**

**who are not on an antidepressant, however, individuals in remission taking an antidepressant may be accepted. Exclude if their primary diagnosis is anything but MDD.**

I am now going to ask you some questions about your mental health

**DEPRESSION – STUDY SPECIFIC**

Have you ever been diagnosed with major depressive disorder (MDD)

YES NO

[IF YES]: When? By whom (GP, psychologist)? Was this your primary diagnosis? \_\_\_\_\_

**(Exclude patient if MDD was not their primary diagnosis)**

[IF YES]: Approx. how many major depressive episodes (i.e. depressive periods lasting 2+ weeks) have you experienced in your lifetime? \_\_\_\_\_

[IF <2]: **Exclude**

Would you say that you are currently experiencing a major depressive episode?

YES NO

[IF YES]: **Exclude**

[IF NO]: When was your most recent major depressive episode and how long did it last?

\_\_\_\_\_ **(Exclude if last MDE was less than 3 months ago or more than 4 years ago)**

Have you ever taken medication for depression?

YES NO

[IF YES]: Are you currently taking these medications? \_\_\_\_\_

[IF YES]: How long have you been taking this medication? \_\_\_\_\_

**[If they have taken medication for depression, but are not currently]** When did you stop? \_\_\_\_\_

**Inventory for Depressive Symptomatology item #15, Concentration/Decision Making:**

*For the past 7 days, how would you rate your concentration and decision making?*

0 = There is no change in my usual capacity to concentrate or make decisions.

1 = I occasionally feel indecisive or find that my attention wanders.

2 = Most of the time, I struggle to focus my attention or to make decisions.

3 = I cannot concentrate well enough to read or cannot make even minor decisions.

**At this point – administer the BDI over the phone. Exclude if score is  $\geq 20$**

*Beck Depression Inventory-II (BDI-II): Adapted General Screening Questions (feelings within past 2 weeks)*

<p>On a scale of 0-3, how often would you rate your sadness? _____</p> <p><b>0 = I do not feel sad</b></p> <p><b>1 = I feel sad much of the time</b></p> <p><b>2 = I am sad all the time</b></p> <p><b>3 = I am so sad that I can't stand it</b></p> <p>On a scale of 0-3, how would you rate past failures? _____</p>	<p>On a scale of 0-3, how would you rate your pessimism? _____</p> <p><b>0 = I am not discouraged about my future</b></p> <p><b>1 = I feel more discouraged about my future than I used to be</b></p> <p><b>2 = I do not expect things to work out for me</b></p> <p><b>3 = I feel my future is hopeless and will only get worse</b></p>
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<p><b>0 = I do not feel like a failure</b>  <b>1 = I have failed more than I should have</b>  <b>2 = As I look back, I see a lot of failures</b>  <b>3 = I feel I am a total failure as a person</b></p> <p>On a scale of 0-3, how would you rate any guilty feelings that you have? _____  <b>0 = I don't feel particularly guilty</b>  <b>1 = I feel guilty over many things I have done or should have done</b>  <b>2 = I feel quite guilty most of the time</b>  <b>3 = I feel guilty all of the time</b></p> <p>On a scale of 0-3, how would you rate your feelings of self-dislike? _____  <b>0 = I feel the same about myself as ever</b>  <b>1 = I have lost confidence in myself</b>  <b>2 = I am disappointed in myself</b>  <b>3 = I dislike myself</b></p> <p>On a scale of 0-3, how would you rate suicidal thoughts or wishes? _____  <b>0 = I don't any have any thoughts of killing myself</b>  <b>1 = I have thoughts of killing myself, but I would not carry them out</b>  <b>2 = I would like to kill myself</b>  <b>3 = I would kill myself if I had the chance</b></p>	<p>On a scale of 0-3, how would you rate recent loss of pleasure? _____  <b>0 = I get as much pleasure as I ever did from the things I enjoy</b>  <b>1 = I don't enjoy things as much as I used to</b>  <b>2 = I get very little pleasure from the things I used to enjoy</b>  <b>3 = I can't get any pleasure from the things I used to enjoy</b></p> <p>On a scale of 0-3, how you would rate punishment feelings? _____  <b>0 = I don't feel like I am being punished</b>  <b>1 = I feel I may be punished</b>  <b>2 = I expect to be punished</b>  <b>3 = I feel I am being punished</b></p> <p>On a scale of 0-3, how critical do you find you are of yourself? _____  <b>0 = I don't criticize or blame myself more than usual</b>  <b>1 = I am more critical of myself than I used to be</b>  <b>2 = I criticize myself for all of my faults</b>  <b>3 = I blame myself for everything bad that happens</b></p> <p>On a scale of 0-3, how you rate recent crying? _____  <b>0 = I don't cry any more than I used to</b>  <b>1 = I cry more than I used to</b>  <b>2 = I cry over every little thing</b>  <b>3 = I feel like crying, but I can't</b></p>
<p>On a scale of 0-3, how would you rate your agitation? _____  <b>0 = I am no more restless or wound up than usual</b>  <b>1 = I feel more restless or wound up than usual</b>  <b>2 = I am so restless or agitated that it's hard to stay still</b>  <b>3 = I am so restless or agitated that I have to keep moving or doing something</b></p> <p>On a scale of 0-3, how would you rate loss of interest? _____  <b>0 = I have not lost interest in other people or activities</b>  <b>1 = I am less interested in other people or things than before</b></p>	<p>On a scale of 0-3, how would you rate your irritability? _____  <b>0 = I am no more irritable than usual</b>  <b>1 = I am more irritable than usual</b>  <b>2 = I am much more irritable than usual</b>  <b>3 = I am irritable all the time</b></p> <p>On a scale of 0-3, how would you rate recent changes in appetite? _____  <b>0 = I have not experienced any change in my <u>appetite</u></b>  <b>1a = My appetite is somewhat less than usual</b>  <b>1b = My appetite is somewhat greater than usual</b>  <b>2a = My appetite is much less than before</b>  <b>2b = My appetite is much greater than usual</b></p>

<p><b>2 = I have lost most of my interest in other people or things</b>  <b>3 = It's hard to get interested in anything</b></p> <p>On a scale of 0-3, how would rate your indecisiveness? _____</p> <p><b>0 = I make decisions about as well as ever</b>  <b>1 = I find it more difficult to make decisions than usual</b>  <b>2 = I have much greater difficulty in making decisions than I used to</b>  <b>3 = I have trouble making any decisions</b></p> <p>On a scale of 0-3, how would you rate your feelings of worthlessness? _____</p> <p><b>0 = I do not feel I am worthless</b>  <b>1 = I don't consider myself as worthwhile and useful as I used to</b>  <b>2 = I feel more worthless as compared to other people</b>  <b>3 = I feel utterly worthless</b></p> <p>On a scale of 0-3, how would you rate loss of energy? _____</p> <p><b>0 = I have as much energy as ever</b>  <b>1 = I have less energy than I used to have</b>  <b>2 = I don't have enough energy to do very much</b>  <b>3 = I don't have enough energy to do anything</b></p> <p>On a scale of 0-3, how would you rate recent changes in your sleeping pattern? _____</p> <p><b>0 = I have not experienced any change in my sleeping pattern</b>  <b>1a = I sleep somewhat more than usual</b>  <b>1b = I sleep somewhat less than usual</b></p> <p><b>2a = I sleep a lot more than usual</b>  <b>2b = I sleep a lot less than usual</b></p> <p><b>3a = I sleep most of the day</b>  <b>3b = I wake up 1-2 hours early and can't get back to sleep</b></p>	<p><b>3a = I have no appetite at all</b>  <b>3b = I crave food all the time</b></p> <p>On a scale of 0-3, how you would rate your concentration? _____</p> <p><b>0 = I can concentrate as well as ever</b>  <b>1 = I can't concentrate as well as usual</b>  <b>2 = It's hard to keep my mind on anything for very long</b>  <b>3 = I find I can't concentrate on anything</b></p> <p>On a scale of 0-3, how tired or fatigued are you? _____</p> <p><b>0 = I am no more tired or fatigued than usual</b>  <b>1 = I get more tired or fatigue more easily than usual</b>  <b>2 = I am too tired or fatigued to do a lot of the things I used to do</b>  <b>3 = I am too tired or fatigued to do most of the things I used to do</b></p> <p>On a scale of 0-3, how you rate loss of interest in sex? _____</p> <p><b>0 = I have not noticed any recent change in my interest in sex</b>  <b>1 = I am less interested in sex than I used to be</b>  <b>2 = I am much less interested in sex now</b>  <b>3 = I have lost interest in sex completely</b></p>
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END OF BDI-II

Have you ever been diagnosed with any other mental health issues?

YES NO

[IF YES]: What/when/secondary diagnoses? \_\_\_\_\_

**(Exclude patient if any secondary diagnosis other than anxiety)**

Have you taken medication for this disorder?

YES NO

[IF YES]: Which medications? Are you currently taking these medications? \_\_\_\_\_

### The following are SCID-adapted questions

#### MANIA

Was there a period in your life when, for at least one week:

-You were so happy/excited/energized that other people thought you were not your normal self and/or this was abnormal for you?

YES NO [IF YES]

Details? \_\_\_\_\_

-You were extremely irritable or angry for most of the time (for at least a week)? Did you fight or argue with people outside of your family? YES NO [IF YES]

Details? \_\_\_\_\_

[IF YES TO ABOVE] During this time:

Did you feel you had special talents or abilities?	Yes	No
[IF YES] What kinds talents/abilities _____		
Became impulsive in a way that was highly unusual for you (e.g. spent a lot of money, had sexual indiscretions)?	Yes	No
Needed significantly less sleep but did not feel tired?	Yes	No
[IF YES TO ANY OF ABOVE] Are you currently experiencing any of these feelings?	Yes	No

[IF YES] to any of above: **INELIGIBLE** (\*please use discretion – ask about context\*)

#### ANXIETY DISORDERS

##### Panic

-Have you ever had a panic attack, when you suddenly felt frightened or suddenly developed a lot of physical symptoms?

YES NO [IF YES]

Details? \_\_\_\_\_

[IF YES TO ABOVE]

-Have these attacks ever come on completely out of the blue – in situations where you don't expect to be nervous or uncomfortable?

YES NO [IF YES]

Details? \_\_\_\_\_

-Just before you began having panic attacks, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

YES NO [IF YES]

Details? \_\_\_\_\_

##### Agoraphobia

-Were you ever afraid of going out of the house alone, being in crowds, standing in a line or traveling on buses or trains?

YES NO [IF YES]

Details? \_\_\_\_\_

[IF YES TO ABOVE]

If YES: What were you afraid would happen?

-Does participant mention anxiety about being in place/situation from escape may be difficult or embarrassing or in which help may not be available in the event of panic-like symptoms?

YES NO [IF YES]

Details? \_\_\_\_\_

-Just before you began having these fears, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

YES NO [IF YES]

Details? \_\_\_\_\_

### **Social Phobia**

-Is there anything that you have been afraid to do or felt uncomfortable doing in front of other people, like speaking, eating or writing?

YES NO [IF YES]

Details? \_\_\_\_\_

### **[IF YES TO ABOVE]**

-If YES to "Public Speaking": Do you think that you are more uncomfortable than most people who are in a similar situation?

YES NO [IF YES]

Details? \_\_\_\_\_

IF YES: What were you afraid would happen?  
\_\_\_\_\_

-Does participant mention that exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic-attack?

YES NO [IF YES]

Details? \_\_\_\_\_

IF YES: Just before you began having these fears, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

YES NO [IF YES]

Details? \_\_\_\_\_

### **GAD**

-In the last six months, have you been particularly nervous or anxious?

YES NO [IF YES]

Details? \_\_\_\_\_

### **[IF YES TO ABOVE]**

IF YES: What do you worry about?  
\_\_\_\_\_

-During the past six months, would you say that you are worrying more often than not?

YES NO [IF YES]

Details? \_\_\_\_\_

-When you are worrying, do you find it difficult to stop?

YES NO [IF YES]

Details? \_\_\_\_\_

When you're feeling anxious or nervous, do you feel:

\_\_\_ Restless \_\_\_ Frequently tired \_\_\_ Trouble concentrating/Mind goes blank \_\_\_ Irritable  
\_\_\_ Tense muscles \_\_\_ Sleep disturbance

(3 of the above must be present)

### **PSYCHOSIS**

-Delusions: Have you ever had a time in your life when you believed people were following you, out to get you, trying to hurt you or that you had special powers?

YES NO [IF YES]

Details? \_\_\_\_\_

[IF YES TO ABOVE]

-Were you convinced they were talking about you or did you think it might have been your imagination?

YES NO [IF YES]

Details? \_\_\_\_\_

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-What about receiving special messages from the TV, radio, or newspaper, or from the way things were arranged around you?

YES NO [IF YES]

Details? \_\_\_\_\_

-What about anyone going out of their way to give you a hard time, or trying to hurt you?

YES NO [IF YES]

Details? \_\_\_\_\_

-Did you ever feel that you were especially important in some way, or that you had special powers to do things that other people couldn't do?

YES NO [IF YES]

Details? \_\_\_\_\_

-Did you ever feel that someone or something outside yourself was controlling your thoughts or actions against you will?

YES NO [IF YES]

Details? \_\_\_\_\_

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### **Auditory Hallucinations**

-Did you ever hear things that other people couldn't hear, such as noises, or the voices of people whispering or talking? (Were you awake at the time?)

YES NO [IF YES]

Details? \_\_\_\_\_

[IF YES TO ABOVE]

If YES: What did you hear? How often did you hear it?

If VOICES: Did they comment on what you were doing or thinking? \_\_\_\_\_

How many voices did you hear? Were they talking to each other? \_\_\_\_\_

### **Visual Hallucinations**

-Did you ever have visions or see things that other people couldn't see? (Were you awake at the time?)

YES NO [IF YES]

Details? \_\_\_\_\_

### **Other Symptoms**

*(The following items are rated based on observations)*

Catatonic behaviour, Grossly disorganized behaviour, Grossly inappropriate affect or Disorganized speech

NO YES: \_\_\_\_\_

Affective flattening

NO YES: \_\_\_\_\_

[IF YES] to any of above: **INELIGIBLE** (\*please use discretion – ask about context\* If unsure, ask Dr.

Natalia Jaworska

**\*Try and get as much detail as possible with regards to past or present medications relevant to mental health**

**DRUG AND ALCOHOL USE**

I'm now going to ask you some questions about your substance use. Can you let me know whether you consume the following?

Coffee/tea/energy drinks: YES NO \_\_\_\_\_ times per day/week **(exclude if >4 cups/day regularly)**

Smoker: YES NO Since When?\_\_\_\_\_ Trying to quit? \_\_\_\_\_  
Cigarettes per day/week \_\_\_\_\_

Do you use vaporizers or e-cigarettes? YES NO  
IF YES: How long? \_\_\_\_\_  
IF YES: How frequently throughout the day? \_\_\_\_\_

Are you able to go without for a 3 hour period? YES NO **(Exclude)**

Have you ever been a smoker? YES NO

**Alcohol**

How many drinks do you have per day/week? \_\_\_\_\_ **(Exclude if >than 3 units a day)**

Have you ever been treated for alcohol dependence?

YES NO

[IF YES] How long ago? \_\_\_\_\_

**(Exclude if they currently have a substance abuse problem or have within the past year.)**

**Drug and Medicine Use**

Have you ever become dependent on a prescribed medication or taken a lot more than you were supposed to?

YES NO

[IF YES]: Details? \_\_\_\_\_

Have you ever used street drugs or marijuana?

YES NO

[IF NO]: Skip the drug related section below

Have you ever used any of the following?

Circle the name of each drug ever used (or write in name if other)	Period of heaviest use (age or date, and duration) and describe pattern of use	Level of use
<b>Sedatives - hypnotics – anxiolytics:</b>		
Quaalude, Seconal, Valium, Xanax, Librium, barbiturates, Miltown, Ativan, Dalmane, Halcion, Restoril, or other :		1 2 3
_____		
<b>Cannabis:</b> marijuana, hashish , THC, or other: _____		1 2 3

<b>Stimulants:</b> amphetamine, "speed", crystal meth, dexadrine, Ritalin, "ice", or other: _____	1 2 3
<b>Opioids:</b> heroin, morphine, opium, Methadone, Darvon, codein, Percodan, Demerol, Dilaudid, unspecified or other: _____	1 2 3
<b>Cocaine:</b> intranasal, IV, freebase, crack, "speedball", unspecified or other: _____	1 2 3
<b>Hallucinogens/PCP:</b> LSD, mescaline, peyote, psilocybin, STP, mushrooms, PCP ("angel dust"), Extasy, MDMA, or other: _____	1 2 3
<b>Other:</b> steroids, "glue", paint, inhalants, nitrous oxide ("laughing gas"), amyl or butyl nitrate ("popers"), nonprescription sleep or diet pills, unknown, or other: _____	1 2 3

*Family Interview for Genetic Studies (FIGS): Adapted General Screening Questions*

We're almost done, I'm just going to ask you some questions about your family, specifically your immediate family – these include your parents, siblings, offspring/children and spouses. I'd like you to keep these particular individuals in mind as we go through the questions:

-Was/is anyone in your immediate family adopted?

YES NO [IF YES]

Details? \_\_\_\_\_

-Was/does anyone in your family have a developmental disability?

YES NO [IF YES]

Details? \_\_\_\_\_

Did/does anyone:

-Have problems with their nerves or emotions? ...to the extent that they had to take medicine e.g. lithium or see a doctor for it?

YES NO [IF YES]

Details? \_\_\_\_\_

-Feel very low for a couple of weeks or more, or have a diagnosis of depression?

YES NO [IF YES]

Details? \_\_\_\_\_

-Attempt or complete suicide?

YES NO [IF YES]

Details? \_\_\_\_\_

-Seem over-excited (or manic) day and night, or have a diagnosis of mania?

YES NO [IF YES]

Details? \_\_\_\_\_

-Have visions, hear voices, or have beliefs that seem strange or unreal?

YES NO [IF YES]

Details? \_\_\_\_\_

-Have unusual or bizarre behavior, or have a diagnosis of schizophrenia?

YES NO [IF YES]

Details? \_\_\_\_\_

This study will require you to abstain from nicotine for 3 hours before you session and caffeine for 6 hours before your session (decaf coffee is fine). Abstinence from alcohol and over-the-counter drugs (with the exception of prescribed medications) is also required from midnight the night before your visit until your session is complete. We also ask that you abstain from street drugs for two weeks prior to testing dates and will ask you to provide a urine sample during the screening session to confirm abstinence. Do you think this would be a problem?

YES NO

[IF YES]: Ask them if they would like to be contacted for future studies and thank them for their time.

You will also need to abstain from having any **eggs or peanut products** before the sessions (as these are naturally high in CDP-choline) and restrict yourself to a light meal before your session. Do you think this would be a problem?

YES NO

[IF YES]: Ask them if they would like to be contacted for future studies and thank them for their time.

As mentioned, our testing occurs at the Royal Hospital on Carling (1145 Carling Ave) – do you know where it is? Do you foresee any difficulties in getting to/from the test sessions? \_\_\_\_\_

Will you require any reimbursement for bus tickets or parking?

YES NO

Do you think you will have some scheduling conflicts that might prevent you from being tested at a particular time? (exams, going home, vacations, employment) \_\_\_\_\_

Is there a day of the week and/or time that would work well for you to come in for the testing? (preferably morning/early afternoon): \_\_\_\_\_

Based on this preliminary screen, you seem like you may qualify for study participation. However, I will need to review this interview with one of the researchers and we will contact you shortly via email about your participation. Is that alright?

Do you have any further questions?

**Finally, there are many ongoing studies in the lab at this moment – do you consent to having your contact information stored in a secure database to be contacted for future research?**

YES NO

**SCREENING SCRIPT – CDP-Choline & MDD Remitted Study**  
**HEALTHY VOLUNTEER VERSION**

**The following is intended as a guide. You do not need to read it word-for-word.**

Hello (INSERT INDIVIDUAL'S NAME)

My name is (FIRST NAME) and I am a(n) (POSITION) from the Clinical EEG Lab at the Royal. I am calling about our study on the effects of a natural supplement on cognitive performance, which you had expressed an interest in participating in.

**\*\*OR\*\***

Thank you for calling us to find out more about our research.

---

Do you have a moment so that I can explain the study to you?

The purpose of our study is to examine the effects of a natural supplement called CDP-choline on cognitive performance. We will be using a series of cognitive tasks administered on an iPad to measure your performance. There are no risks associated with CDP-choline as it is a substance that occurs naturally in the body and is found in many foods.

There is a second, optional arm of the study that involves brain imaging. If you choose to participate in this, we will measure your brain activity using two methods. The first method is called EEG – it involves placing sensors on your head to measure brain electrical activity. We will also measure your brain structure and function with the use of amagnetic resonance imaging (fMRI) machine.

If you choose to participate, you would come to our laboratory 2 times – with each visit lasting ~2-4 hours. These visits will occur over a period of 2-3 weeks.

During these visits, you will be required to fill out several questionnaires and complete a few cognitive tasks – if you choose to participate in the brain imaging arm, we will also record EEG and MRI data. You will be compensated \$30/session, with an additional 30\$/session if you participate in the brain imaging. All testing will be carried out at the Royal Hospital on Carling.

Are you still interested in participating in this study and continuing with the screen?

**[IF NO]:** Thank you very much for your time.

**[IF YES – still interested]:**

Is this a good time to do the phone screen – it may take ~15-30 minutes?

**[IF NO]:** Set up a time to call back:

Date: \_\_\_\_\_ Time: \_\_\_\_\_

**[IF YES]:** Before having you visit, we need to ask you some questions to determine if you are eligible for the study. It is possible that some of these questions may make you feel uncomfortable or distressed. If this happens, let me know, and we can stop the screen at any time, or take a break. You also have the right to refuse to answer any questions. I also want to assure you that the information collected during this phone screen is confidential. The information will be destroyed if you do not qualify for the study or choose not to participate. If you do qualify, this information will be kept in a safe place. Keeping in mind that some of the questions I will ask are quite personal, is it alright if I proceed?

**[IF NO]:** Thank you very much for your time.

**[IF YES]:** Before we start, can you tell me your current age? **(18-65 years of age for inclusion)**

*The following information may have been obtained before the screen (e.g. from e-mail or phone message).*

Name: \_\_\_\_\_ Sex: M or F (circle) Age: \_\_\_\_\_ (18-65 yrs) DOB:  
\_\_\_\_\_

Employment: \_\_\_\_\_ Highest Level of Education: \_\_\_\_\_

Height: \_\_\_\_\_ Weight: \_\_\_\_\_ **Exclude if BMI >38kg/m<sup>2</sup>** Handedness: L R  
Both

Telephone: \_\_\_\_\_ E-Mail: \_\_\_\_\_

## GENERAL MEDICAL

I am going to start off by asking you a series of questions about your physical health.

Have you been diagnosed with or are you currently being treated for any major medical problems or chronic medical conditions?

YES NO

[IF YES]: Which ones? \_\_\_\_\_

Are you currently taking any medication for any chronic health problems? (e.g. high blood pressure, cholesterol, thyroid, diabetes)

YES NO

[IF YES]: Which ones/how long? \_\_\_\_\_

**Any thyroid issues should be stabilized for at least 3 months**

Do you have any major allergies to food or medication?

YES NO

[IF YES]: Which ones? \_\_\_\_\_

Do you have a history of any neurological or neuromuscular problems? (e.g. stroke, epilepsy, brain cysts, migraines, MS).

YES NO

[IF YES]: Which ones? \_\_\_\_\_

Do you have any major motor impairments? (e.g. cerebral palsy, physical disability, muscular dystrophy)

YES NO

[IF YES]: Which ones? \_\_\_\_\_

Have you ever had a concussion?

YES NO

[IF YES]: How long were you unconscious? \_\_\_\_\_

Have you ever been diagnosed with a development problem? (e.g. autism)

YES NO

[IF YES]: Which ones? \_\_\_\_\_

Have you ever been diagnosed with or struggled with major learning disabilities? (e.g. pronounced reading problems, dyslexia)

YES NO

[IF YES]: Which ones? \_\_\_\_\_

---

### **FURTHER MEDICAL – STUDY COMPATIBILITY - NEUROIMAGING**

Do you have any issues with back pain?

YES NO

[IF YES]: Would this impede you from sitting up straight or lying still for prolonged periods of time?

YES NO

Have you ever had an EEG done or have previously participated in an EEG study?

YES NO

[IF YES]: What for/when? \_\_\_\_\_

Have you ever had a MRI done or participated in a MRI study?

YES NO

[IF YES]: What for/when? \_\_\_\_\_

Do you have any metal in your body? (e.g. pacemakers, surgical/aneurysm clips, prosthetic valves, metal plates/screws, pins, cochlear implants, braces, etc.?)

YES NO

[IF YES]: What for/when? \_\_\_\_\_

Have you had x-rays, nuclear medicine tests or radiation doses (e.g. CTs, PET scans) during the past year?

YES NO

[IF YES]: What for/when? \_\_\_\_\_

Do you wear eyeglasses/contacts?

YES NO

[IF YES]: Inquire about whether they can wear their contact lenses to testing

[IF NO]: Inquire about glasses prescription (we have MR-compatible glasses)

Are you colour blind?

YES NO

[IF YES]: **Exclude**

### **MENTAL HEALTH SECTION**

**EXCLUDE Healthy Controls: if they have a history of psychiatric disorders or are currently exhibiting symptoms of a psychiatric disorder.**

I am now going to ask you some questions about your mental health

#### **DEPRESSION – STUDY SPECIFIC**

Have you ever been diagnosed with major depressive disorder (MDD)

YES NO

[IF YES]: When? Was this your primary diagnosis? \_\_\_\_\_

**(Exclude as Healthy Control IF YES – may be eligible for experimental group)**

[IF YES]: Approx. how many major depressive episodes have you experienced in your lifetime? \_\_\_\_\_

[IF <2]: **Exclude**

Would you say that you are currently experiencing a major depressive episode?

YES NO

[IF YES]: **Exclude**

[IF NO]: When was your most recent major depressive episode and how long did it last? \_\_\_\_\_

(**Exclude if last MDE was less than 3 months ago or more than 4 years ago**)

Have you ever taken medication for depression?

YES NO

[IF YES]: Are you currently taking these medications? \_\_\_\_\_

[IF YES]: How long have you been taking this medication? \_\_\_\_\_

**[If they have taken medication for depression, but are not currently]** When did you stop? \_\_\_\_\_

#### **Inventory for Depressive Symptomatology item #15, Concentration/Decision Making:**

*For the past 7 days, how would you rate your concentration and decision making?*

0 = There is no change in my usual capacity to concentrate or make decisions.

1 = I occasionally feel indecisive or find that my attention wanders.

2 = Most of the time, I struggle to focus my attention or to make decisions.

3 = I cannot concentrate well enough to read or cannot make even minor decisions.

**At this point – administer the BDI over the phone. Exclude if score is  $\geq 20$**

*Beck Depression Inventory-II (BDI-II): Adapted General Screening Questions (feelings within past 2 weeks)*

<p>On a scale of 0-3, how often would you rate your sadness? _____</p> <p><b>0 = I do not feel sad</b></p> <p><b>1 = I feel sad much of the time</b></p> <p><b>2 = I am sad all the time</b></p> <p><b>3 = I am so sad that I can't stand it</b></p> <p>On a scale of 0-3, how would you rate past failures? _____</p> <p><b>0 = I do not feel like a failure</b></p> <p><b>1 = I have failed more than I should have</b></p> <p><b>2 = As I look back, I see a lot of failures</b></p> <p><b>3 = I feel I am a total failure as a person</b></p> <p>On a scale of 0-3, how would you rate any guilty feelings that you have? _____</p> <p><b>0 = I don't feel particularly guilty</b></p> <p><b>1 = I feel guilty over many things I have done or should have done</b></p> <p><b>2 = I feel quite guilty most of the time</b></p>	<p>On a scale of 0-3, how would you rate your pessimism? _____</p> <p><b>0 = I am not discouraged about my future</b></p> <p><b>1 = I feel more discouraged about my future than I used to be</b></p> <p><b>2 = I do not expect things to work out for me</b></p> <p><b>3 = I feel my future is hopeless and will only get worse</b></p> <p>On a scale of 0-3, how would you rate recent loss of pleasure? _____</p> <p><b>0 = I get as much pleasure as I ever did from the things I enjoy</b></p> <p><b>1 = I don't enjoy things as much as I used to</b></p> <p><b>2 = I get very little pleasure from the things I used to enjoy</b></p> <p><b>3 = I can't get any pleasure from the things I used to enjoy</b></p>
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<p><b>3 = I feel guilty all of the time</b></p> <p>On a scale of 0-3, how would you rate your feelings of self-dislike? _____</p> <p><b>0 = I feel the same about myself as ever</b>  <b>1 = I have lost confidence in myself</b>  <b>2 = I am disappointed in myself</b>  <b>3 = I dislike myself</b></p> <p>On a scale of 0-3, how would you rate suicidal thoughts or wishes? _____</p> <p><b>0 = I don't any have any thoughts of killing myself</b>  <b>1 = I have thoughts of killing myself, but I would not carry them out</b>  <b>2 = I would like to kill myself</b>  <b>3 = I would kill myself if I had the chance</b></p>	<p>On a scale of 0-3, how you would rate punishment feelings? _____</p> <p><b>0 = I don't feel like I am being punished</b>  <b>1 = I feel I may be punished</b>  <b>2 = I expect to be punished</b>  <b>3 = I feel I am being punished</b></p> <p>On a scale of 0-3, how critical do you find you are of yourself? _____</p> <p><b>0 = I don't criticize or blame myself more than usual</b>  <b>1 = I am more critical of myself than I used to be</b>  <b>2 = I criticize myself for all of my faults</b>  <b>3 = I blame myself for everything bad that happens</b></p> <p>On a scale of 0-3, how you rate recent crying? _____</p> <p><b>0 = I don't cry any more than I used to</b>  <b>1 = I cry more than I used to</b>  <b>2 = I cry over every little thing</b>  <b>3 = I feel like crying, but I can't</b></p>
<p>On a scale of 0-3, how would you rate your agitation? _____</p> <p><b>0 = I am no more restless or wound up than usual</b>  <b>1 = I feel more restless or wound up than usual</b>  <b>2 = I am so restless or agitated that it's hard to stay still</b>  <b>3 = I am so restless or agitated that I have to keep moving or doing something</b></p> <p>On a scale of 0-3, how would you rate loss of interest? _____</p> <p><b>0 = I have not lost interest in other people or activities</b>  <b>1 = I am less interested in other people or things than before</b>  <b>2 = I have lost most of my interest in other people or things</b>  <b>3 = It's hard to get interested in anything</b></p> <p>On a scale of 0-3, how would your indecisiveness? _____</p> <p><b>0 = I make decisions about as well as ever</b>  <b>1 = I find it more difficult to make decisions than usual</b></p>	<p>On a scale of 0-3, how would you rate your irritability? _____</p> <p><b>0 = I am no more irritable than usual</b>  <b>1 = I am more irritable than usual</b>  <b>2 = I am much more irritable than usual</b>  <b>3 = I am irritable all the time</b></p> <p>On a scale of 0-3, how would you rate recent changes in appetite? _____</p> <p><b>0 = I have not experienced any change in my appetite</b>  <b>1a = My appetite is somewhat less than usual</b>  <b>1b = My appetite is somewhat greater than usual</b>  <b>2a = My appetite is much less than before</b>  <b>2b = My appetite is much greater than usual</b></p> <p><b>3a = I have no appetite at all</b>  <b>3b = I crave food all the time</b></p> <p>On a scale of 0-3, how you would rate your concentration? _____</p> <p><b>0 = I can concentrate as well as ever</b>  <b>1 = I can't concentrate as well as usual</b></p>

<p><b>2 = I have much greater difficulty in making decisions than I used to</b>  <b>3 = I have trouble making any decisions</b></p> <p>On a scale of 0-3, how would you rate your feelings of worthlessness? _____  <b>0 = I do not feel I am worthless</b>  <b>1 = I don't consider myself as worthwhile and useful as I used to</b>  <b>2 = I feel more worthless as compared to other people</b>  <b>3 = I feel utterly worthless</b></p> <p>On a scale of 0-3, how would you rate loss of energy? _____  <b>0 = I have as much energy as ever</b>  <b>1 = I have less energy than I used to have</b>  <b>2 = I don't have enough energy to do very much</b>  <b>3 = I don't have enough energy to do anything</b></p> <p>On a scale of 0-3, how would you rate recent changes in your sleeping pattern? _____  <b>0 = I have not experienced any change in my sleeping pattern</b>  <b>1a = I sleep somewhat more than usual</b>  <b>1b = I sleep somewhat less than usual</b></p> <p><b>2a = I sleep a lot more than usual</b>  <b>2b = I sleep a lot less than usual</b></p> <p><b>3a = I sleep most of the day</b>  <b>3b = I wake up 1-2 hours early and can't get back to sleep</b></p>	<p><b>2 = It's hard to keep my mind on anything for very long</b>  <b>3 = I find I can't concentrate on anything</b></p> <p>On a scale of 0-3, how tired or fatigued are you? _____  <b>0 = I am no more tired or fatigued than usual</b>  <b>1 = I get more tired or fatigued more easily than usual</b>  <b>2 = I am too tired or fatigued to do a lot of the things I used to do</b>  <b>3 = I am too tired or fatigued to do most of the things I used to do</b></p> <p>On a scale of 0-3, how you rate loss of interest in sex? _____  <b>0 = I have not noticed any recent change in my interest in sex</b>  <b>1 = I am less interested in sex than I used to be</b>  <b>2 = I am much less interested in sex now</b>  <b>3 = I have lost interest in sex completely</b></p>
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END OF BDI-II

Have you ever been diagnosed with any other mental health issues?

YES NO

[IF YES]: What/when/secondary diagnoses? \_\_\_\_\_

**(Exclude if there is diagnosis)**

Have you taken medication for this disorder?

YES NO

[IF YES]: Are you currently taking these medications? \_\_\_\_\_

**The following are SCID-adapted questions**

### **MANIA**

Was there a period in your life when, for at least one week:

-You were so happy/excited/energized that other people thought you were not your normal self and/or this was abnormal for you?

YES NO [IF YES]

Details? \_\_\_\_\_

-You were extremely irritable or angry for most of the time (for at least a week)? Did you fight or argue with people outside of your family? YES NO [IF YES]

Details? \_\_\_\_\_

[IF YES TO ABOVE] During this time:

Did you feel you had special talents or abilities?	Yes	No
[IF YES] What kinds talents/abilities _____		
Became impulsive in a way that was highly unusual for you (e.g. spent a lot of money, had sexual indiscretions)?	Yes	No
Needed significantly less sleep but did not feel tired?	Yes	No
[IF YES TO ANY OF ABOVE] Are you currently experiencing any of these feelings?	Yes	No

[IF YES] to any of above: **INELIGIBLE** (\*please use discretion – ask about context\*)

## ANXIETY DISORDERS

### Panic

-Have you ever had a panic attack, when you suddenly felt frightened or suddenly developed a lot of physical symptoms?

YES NO [IF YES]

Details? \_\_\_\_\_

[IF YES TO ABOVE]

-Have these attacks ever come on completely out of the blue – in situations where you don't expect to be nervous or uncomfortable?

YES NO [IF YES]

Details? \_\_\_\_\_

-Just before you began having panic attacks, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

YES NO [IF YES]

Details? \_\_\_\_\_

### Agoraphobia

-Were you ever afraid of going out of the house alone, being in crowds, standing in a line or traveling on buses or trains?

YES NO [IF YES]

Details? \_\_\_\_\_

[IF YES TO ABOVE]

If YES: What were you afraid would happen?

-Does participant mention anxiety about being in place/situation from escape may be difficult or embarrassing or in which help may not be available in the event of panic-like symptoms?

YES NO [IF YES]

Details? \_\_\_\_\_

-Just before you began having these fears, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

YES NO [IF YES]

Details? \_\_\_\_\_

### Social Phobia

-Is there anything that you have been afraid to do or felt uncomfortable doing in front of other people, like speaking, eating or writing?

YES NO [IF YES]

Details? \_\_\_\_\_

[IF YES TO ABOVE]

-If YES to "Public Speaking": Do you think that you are more uncomfortable than most people who are in a similar situation?

YES NO [IF YES]

Details? \_\_\_\_\_

IF YES: What were you afraid would happen?

-Does participant mention that exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic-attack?

YES NO [IF YES]

Details? \_\_\_\_\_

IF YES: Just before you began having these fears, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

YES NO [IF YES]

Details? \_\_\_\_\_

### GAD

-In the last six months, have you been particularly nervous or anxious?

YES NO [IF YES]

Details? \_\_\_\_\_

[IF YES TO ABOVE]

IF YES: What do you worry about?

-During the past six months, would you say that you are worrying more often than not?

YES NO [IF YES]

Details? \_\_\_\_\_

-When you are worrying, do you find it difficult to stop?

YES NO [IF YES]

Details? \_\_\_\_\_

When you're feeling anxious or nervous, do you feel:

\_\_\_ Restless \_\_\_ Frequently tired \_\_\_ Trouble concentrating/Mind goes blank \_\_\_ Irritable

\_\_\_ Tense muscles \_\_\_ Sleep disturbance

(3 of the above must be present)

### PSYCHOSIS

-Delusions: Have you ever had a time in your life when you believed people were following you, out to get you, trying to hurt you or that you had special powers?

YES NO [IF YES]

Details? \_\_\_\_\_

[IF YES TO ABOVE]

-Were you convinced they were talking about you or did you think it might have been your imagination?

YES NO [IF YES]

Details? \_\_\_\_\_

-What about receiving special messages from the TV, radio, or newspaper, or from the way things were arranged around you?

YES NO [IF YES]

Details? \_\_\_\_\_

-What about anyone going out of their way to give you a hard time, or trying to hurt you?

YES NO [IF YES]

Details? \_\_\_\_\_

-Did you ever feel that you were especially important in some way, or that you had special powers to do things that other people couldn't do?

YES NO [IF YES]

Details? \_\_\_\_\_

-Did you ever feel that someone or something outside yourself was controlling your thoughts or actions against you will?

YES NO [IF YES]

Details? \_\_\_\_\_

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### **Auditory Hallucinations**

-Did you ever hear things that other people couldn't hear, such as noises, or the voices of people whispering or talking? (Were you awake at the time?)

YES NO [IF YES]

Details? \_\_\_\_\_

### **[IF YES TO ABOVE]**

If YES: What did you hear? How often did you hear it?

\_\_\_\_\_

If VOICES: Did they comment on what you were doing or thinking? \_\_\_\_\_

How many voices did you hear? Were they talking to each other? \_\_\_\_\_

### **Visual Hallucinations**

-Did you ever have visions or see things that other people couldn't see? (Were you awake at the time?)

YES NO [IF YES]

Details? \_\_\_\_\_

### **Other Symptoms**

*(The following items are rated based on observations)*

Catatonic behaviour, Grossly disorganized behaviour, Grossly inappropriate affect or Disorganized speech

NO YES: \_\_\_\_\_

Affective flattening

NO YES: \_\_\_\_\_

**[IF YES] to any of above: INELIGIBLE** (\*please use discretion – ask about context\* If unsure, ask Dr.

Natalia Jaworska

**\*Try and get as much detail as possible with regards to past or present medications relevant to mental health**

### **DRUG AND ALCOHOL USE**

I'm now going to ask you some questions about your substance use. Can you let me know whether you consume the following?

Coffee/tea/energy drinks: YES NO \_\_\_\_\_ times per day/week (**exclude if >4 cups/day regularly**)

Smoker: YES NO Since When? \_\_\_\_\_ Trying to quit? \_\_\_\_\_  
Cigarettes per day/week \_\_\_\_\_

Do you use vaporizers or e-cigarettes? YES NO  
IF YES: How long? \_\_\_\_\_  
IF YES: How frequently throughout the day? \_\_\_\_\_

Are you able to go without for a 3 hour period? YES NO (**Exclude**)

Have you ever been a smoker? YES NO

### Alcohol

How many drinks do you have per day/week? \_\_\_\_\_ (**Exclude if >than 3 units a day**)

Have you ever been treated for alcohol dependence?

YES NO

[IF YES] How long ago? \_\_\_\_\_

**(Exclude if they currently have a substance abuse problem or have within the past year.)**

### Drug and Medicine Use

Have you ever become dependent on a prescribed medication or taken a lot more than you were supposed to?

YES NO

[IF YES]: Details? \_\_\_\_\_

Have you ever used street drugs? (including marijuana)

YES NO

[IF NO]: Skip the drug related section below

Have you ever used any of the following?

Circle the name of each drug ever used (or write in name if other)	Period of heaviest use (age or date, and duration) and describe pattern of use	Level of use
<b>Sedatives - hypnotics – anxiolytics:</b> Quaalude, Seconal, Valium, Xanax, Librium, barbiturates, Miltown, Ativan, Dalmane, Halcion, Restoril, or other : _____		1 2 3
<b>Cannabis:</b> marijuana, hashish , THC, or other: _____		1 2 3
<b>Stimulants:</b> amphetamine, “speed”, crystal meth, dexadrine, Ritalin, “ice”, or other: _____		1 2 3

<b>Opioids:</b> heroin, morphine, opium, Methadone, Darvon, codein, Percodan, Demerol, Dilaudid, unspecified or other:	1 2 3
<hr/>	
<b>Cocaine:</b> intranasal, IV, freebase, crack, “speedball”, unspecified or other:	1 2 3
<hr/>	
<b>Hallucinogens/PCP:</b> LSD, mescaline, peyote, psilocybin, STP, mushrooms, PCP (“angel dust”), Extasy, MDMA, or other:	1 2 3
<hr/>	
<b>Other:</b> steroids, “glue”, paint, inhalants, nitrous oxide (“laughing gas”), amyl or butyl nitrate (“popers”), nonprescription sleep or diet pills, unknown, or other:	1 2 3

*Family Interview for Genetic Studies (FIGS): Adapted General Screening Questions*

We’re almost done, I’m just going to ask you some questions about your family, specifically your immediate family – these include your parents, siblings, offspring/children and spouses. I’d like you to keep these particular individuals in mind as we go through the questions:

-Was/is anyone in your immediate family adopted?

YES NO [IF YES]

Details? \_\_\_\_\_

-Was/does anyone in your family have a developmental disability?

YES NO [IF YES]

Details? \_\_\_\_\_

Did/does anyone:

-Have problems with their nerves or emotions? ...to the extent that they had to take medicine e.g. lithium or see a doctor for it?

YES NO [IF YES]

Details? \_\_\_\_\_

-Feel very low for a couple of weeks or more, or have a diagnosis of depression?

YES NO [IF YES]

Details? \_\_\_\_\_

-Attempt or complete suicide?

YES NO [IF YES]

Details? \_\_\_\_\_

-Seem over-excited (or manic) day and night, or have a diagnosis of mania?

YES NO [IF YES]

Details? \_\_\_\_\_

-Have visions, hear voices, or have beliefs that seem strange or unreal?

YES NO [IF YES]

Details? \_\_\_\_\_

-Have unusual or bizarre behavior, or have a diagnosis of schizophrenia?

YES NO [IF YES]

Details? \_\_\_\_\_

Are you interested in participating in the imaging arm of the study?

YES NO

[IF YES]: **Administer BIC pre-screening form**

This study will require you to abstain from nicotine for 3 hours before you session and caffeine for 6 hours before your session (decaf coffee is fine). Abstinence from alcohol and over-the-counter drugs (with the exception of prescribed medications) is also required from midnight the night before your visit until your session is complete. We will also ask that you abstain from street drugs for two weeks prior to any testing dates. Do you think this would be a problem?

YES NO

[IF YES]: Ask them if they would like to be contacted for future studies and thank them for their time.

You will also need to abstain from having any **eggs or peanut products** before the sessions (as these are naturally high in CDP-choline) and restrict yourself to a light meal before your session. Do you think this would be a problem?

YES NO

[IF YES]: Ask them if they would like to be contacted for future studies and thank them for their time.

As mentioned, our testing occurs at the Royal Hospital on Carling (1145 Carling Ave) – do you know where it is? Do you foresee any difficulties in getting to/from the test sessions? \_\_\_\_\_

Will you require any reimbursement for bus tickets or parking?

YES NO

Do you think you will have some scheduling conflicts that might prevent you from being tested at a particular time? (exams, going home, vacations, employment) \_\_\_\_\_

**If participant seems PERFECT for the study (i.e., no red flags):**

Based on this preliminary screen, you seem like a great candidate for the study. Do you have any questions and are you still interested in participating?

[IF YES]: Great! I would like to tentatively schedule you to come in for your first session, although I must first review your file with my supervisor.

Is there a date/time that would work for you (preferably morning/early afternoon): \_\_\_\_\_

Alright, I will email or call you to confirm an appointment date as soon as possible.

Thank you.

**If participant DOES NOT seem perfect for the study/there are some concerns:**

Based on this preliminary screen, you seem like you may qualify for study participation. However, I will need to review this interview with one of the researchers and we will contact you shortly about your participation.

Is that alright?

Do you have any further questions?

**Finally, there are many ongoing studies in the lab at this moment – do you consent to having your contact information stored in a secure database to be contacted for future research?**

YES NO

## Appendix II: Questionnaires

Williams & Kobak

### Structured Interview Guide for the Montgomery-Åsberg Depression Rating Scale (SIGMA)

PT'S INITIALS: \_\_\_\_\_ PT'S ID: \_\_\_\_\_ INTERVIEWER: \_\_\_\_\_ TIME BEGAN SIGMA: \_\_\_\_\_ DATE: \_\_\_\_\_

OVERVIEW: I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF WEEK)? IF OUT-PATIENT: Have you been working? (What kind of work do you do?) IF NOT: Why not?

#### In the past week, have you been feeling sad or unhappy?

(Depressed at all?) IF YES: Can you describe what this has been like for you?

(IF UNKNOWN: How bad has that been?)

IF DEPRESSED: Does the feeling lift at all if something good happens

How much does your mood lift? Does the feeling ever go away completely?

(What things have made you feel better?)

How often did you feel (depressed/OWN EQUIVALENT) this past week?

(IF UNKNOWN: How many days this week did you feel that way? How much of each day?)

In the past week, how have you been feeling about the future? (Have you been discouraged or pessimistic?) What have your thoughts been? How

(discouraged or pessimistic) have you been? How often have you felt

that way? Do you think things will ever get better for you?

#### IF ACKNOWLEDGES DEPRESSED MOOD, TO GET CONTEXT ASK:

How long have you been feeling this way?

#### RATING BASED ON OBSERVATION DURING INTERVIEW AND THE FOLLOWING QUESTIONS.

In the past week, do you think you have looked sad or depressed to other

people? Did anyone say you looked sad or down?

How about when you've looked in the mirror? Did you look gloomy or

depressed?

IF YES: How sad or depressed do you think you have looked?

How much of the time over the past week do you think you have looked

depressed or down?

IF APPEARANCE WAS DEPRESSED IN PAST WEEK: Have you been able

to laugh or smile at all during the past week? IF YES: How hard has it been

for you to laugh or smile, even if you weren't feeling happy inside?

#### Have you felt tense or edgy in the past week? Have you felt anxious or nervous?

IF YES: Can you describe what that has been like for you? How bad has it been? (Have you felt panicky?)

What about feeling fearful that something bad is about to happen?

How hard has it been to control these feelings? (What has it taken to help

you feel calmer? Has anything worked to calm you down?)

How much of the time have you felt this way over the past week?

**How has your sleeping been in the past week?** (How many hours have you been sleeping, compared with usual?)

**Have you had trouble falling asleep?** (How long has it been taking you to fall asleep this past week?)

**Have you been able to stay asleep through the night?** (Have you been waking up at all in the middle of the night? How long does it take you to go back to sleep?)

**Has your sleeping been restless or disturbed?**

**How has your appetite been this past week?**

(What about compared with your usual appetite?)

Have you been less interested in food? (How much less?)

Does food taste as good as usual? IF LESS: How much less?

Have you had to force yourself to eat?

Have other people had to urge you to eat?

**1. REPORTED SADNESS.** Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0 Occasional sadness in keeping with the circumstances

1

2 Sad or low but brightens up without difficulty

3

4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances

5

6 Continuous or unvarying sadness, misery or despondency

**2. APPARENT SADNESS.** Representing despondency, gloom and despair. (More than just ordinary transient low spirits) reflected in speech, facial expressions and posture. Rate by depth and inability to brighten up.

0 No sadness

1

2 Looks dispirited but does brighten up without difficulty

3

4 Appears sad and unhappy most of the time

5

6 Looks miserable all the time. Extremely despondent

**3. INNER TENSION.** Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension amounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 Placid. Only fleeting inner tension

1

2 Occasional feelings of edginess and ill-defined discomfort

3

4 Continuous feelings of inner tension or intermittent panic which the patient can master with some difficulty

5

6 Unrelenting dread or anguish. Overwhelming panic

**4. REDUCED SLEEP.** Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0 Sleeps as usual

1

2 Slight difficulty dropping off to sleep or slightly reduced, light, or fitful sleep

3

4 Sleep reduced or broken by at least 2 hours

5

6 Less than 2 or 3 hours sleep

**5. REDUCED APPETITE.** Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

0 Normal or increased appetite

1

2 Slightly reduced appetite

3

4 No appetite. Food is tasteless

5

6 Needs persuasion to eat at all

## Appendix (continued)

<p><b>Have you had trouble concentrating or collecting your thoughts in the past week?</b> (How about at home or at work?) IF YES: Can you give me some examples? (Have you been able to concentrate on reading a newspaper or magazine? Do you need to read things over and over again?)</p> <p>How often has that happened in the past week? Has this caused any problems for you? IF YES: Can you give me some examples?</p> <p>Has your trouble concentrating been so bad at any time in the past week that it has been difficult to follow a conversation? (IF YES: How bad has that been? How often has that happened this past week?)</p> <p>NOTE: ALSO CONSIDER BEHAVIOUR DURING INTERVIEW.</p>	<p><b>6. CONCENTRATION DIFFICULTIES.</b> Representing difficulties in collecting one's thoughts amounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.</p> <p>0 No difficulties in concentration</p> <p>1</p> <p>2 Occasional difficulties in collecting one's thoughts</p> <p>3</p> <p>4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation</p> <p>5</p> <p>6 Unable to read or converse without great difficulty</p>
<p><b>Have you had any trouble getting started at things in the past week?</b> IF YES: What things?</p> <p><b>Have you had to push yourself to do things?</b> IF YES: What things? How hard have you had to push yourself? Are you OK once you get started or is it still more of an effort to get something done? What about getting started at simple routine everyday things (like getting dressed)?</p> <p><b>Have you done everyday things more slowly than usual?</b> (Have you been sluggish?) IF YES: Like what, for example? How bad has that been?</p>	<p><b>7. LASSITUDE.</b> Representing a difficulty getting started, or slowness initiating and performing everyday activities.</p> <p>0 Hardly any difficulty in getting started. No sluggishness</p> <p>1</p> <p>2 Difficulties in starting activities</p> <p>3</p> <p>4 Difficulties in simple routine activities, which are carried out with effort</p> <p>5</p> <p>6 Complete lassitude. Unable to do anything without help</p>
<p><b>Have you been less interested in things around you, or in activities you used to enjoy?</b> IF YES: What things? How bad has that been? How much less interested in those things are you now compared with before?</p> <p>Have you been less able to enjoy the things you usually enjoy? Has there been any change in your ability to feel emotions? (Do you feel things less intensely than you used to, things like anger, grief, pleasure?) IF YES: Can you tell me more about that? (IF UNKNOWN: Are you able to feel any emotions at all?)</p> <p>How do you feel towards your family and friends? Is that different from usual? IF REDUCED: Do you feel less than you used to towards them?</p>	<p><b>8. INABILITY TO FEEL.</b> Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.</p> <p>0 Normal interest in the surroundings and in other people</p> <p>1</p> <p>2 Reduced ability to enjoy usual interests</p> <p>3</p> <p>4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances</p> <p>5</p> <p>6 The experience of being emotionally paralysed, inability to feel anger, grief or pleasure, and a complete or even painful failure to feel for close relatives and friends</p>
<p><b>Have you been putting yourself down, or feeling that you're a failure in some way, over the past week?</b> (Have you been blaming yourself for things that you've done, or not done?) IF YES: What have your thoughts been? How often have you felt that way?</p> <p><b>Have you been feeling guilty about anything in the past week? What about feeling as if you have done something bad or sinful?</b> IF YES: What have your thoughts been? How often have you felt that way?</p> <p>ALSO CONSIDER RESPONSES TO QUESTIONS ABOUT PESSIMISM FROM ITEM 1.</p>	<p><b>9. PESSIMISTIC THOUGHTS.</b> Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.</p> <p>0 No pessimistic thoughts</p> <p>1</p> <p>2 Fluctuating ideas of failure, self-reproach or self-depreciation</p> <p>3</p> <p>4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future</p> <p>5</p> <p>6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakeable</p>
<p><b>This past week, have you felt like life isn't worth living?</b> IF YES: Tell me about that. IF NO: What about feeling as if you're tired of living?</p> <p><b>This week, have you thought that you would be better off dead?</b> IF YES: Tell me about that.</p> <p><b>Have you had thoughts of hurting or even killing yourself this past week?</b> IF YES: What have you thought about? How often have you had these thoughts? How long have they lasted? Have you actually made plans? IF YES: What are these plans? Have you made any preparations to carry out these plans? (Have you told anyone about it?)</p>	<p><b>10. SUICIDAL THOUGHTS.</b> Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparation for suicide. Suicidal attempts should not in themselves influence this rating.</p> <p>0 Enjoys life or takes it as it comes</p> <p>1</p> <p>2 Weary of life. Only fleeting suicidal thoughts</p> <p>3</p> <p>4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention</p> <p>5</p> <p>6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide</p>

TOTAL MADRS SCALE SCORE: \_\_\_\_\_

Date \_\_\_\_\_

ID# \_\_\_\_\_

**HANDEDNESS INVENTORY**

Please indicate your preferences in the use of hands in the following activities by putting + in the appropriate column. Where the preference is so strong that you would never try to use the other hand unless absolutely forced to, put ++. In any case you are really indifferent put + in both columns.

Some of the activities require both hands. In these cases the part of the task or object for which hand preference is wanted is indicated in brackets.

Please try to answer all the questions and only leave a blank if you have no experience at all of the object or task.

<b>Task</b>	<b>Left</b>	<b>Right</b>
Writing		
Drawing		
Throwing		
Scissors		
Toothbrush		
Knife (without fork)		
Spoon		
Broom (upper hand)		
Striking match (match)		
Opening box (lid)		
Which foot do you prefer to kick with?		
Which eye do you use when using only one? (E.g. taking picture with a camera.)		

L.Q. \_\_\_\_\_ (Leave this space blank)

### Beck Anxiety Inventory (BAI)

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not At All	Mildly but it didn't bother me much	Moderately - it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling hot	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Wobbliness in legs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Unable to relax	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fear of worst happening	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dizzy or lightheaded	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Heart pounding/racing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Unsteady	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Terrified or afraid	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nervous	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling of choking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hands trembling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shaky / unsteady	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fear of losing control	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Difficulty in breathing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fear of dying	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Scared	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Indigestion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Faint / lightheaded	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Face flushed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hot/cold sweats	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>


**Beck Depression  
Inventory**
**Baseline**

V 0477

CRTN: \_\_\_\_\_ CRF number: \_\_\_\_\_

Page 14

patient initials: \_\_\_\_\_

**BDI-II**

Date: \_\_\_\_\_

Name: \_\_\_\_\_ Marital Status: \_\_\_\_\_ Age: \_\_\_\_\_ Sex: \_\_\_\_\_

Occupation: \_\_\_\_\_ Education: \_\_\_\_\_

**Instructions:** This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

**1. Sadness**

- 0 I do not feel sad.
- 1 I feel sad much of the time.
- 2 I am sad all the time.
- 3 I am so sad or unhappy that I can't stand it.

**2. Pessimism**

- 0 I am not discouraged about my future.
- 1 I feel more discouraged about my future than I used to be.
- 2 I do not expect things to work out for me.
- 3 I feel my future is hopeless and will only get worse.

**3. Past Failure**

- 0 I do not feel like a failure.
- 1 I have failed more than I should have.
- 2 As I look back, I see a lot of failures.
- 3 I feel I am a total failure as a person.

**4. Loss of Pleasure**

- 0 I get as much pleasure as I ever did from the things I enjoy.
- 1 I don't enjoy things as much as I used to.
- 2 I get very little pleasure from the things I used to enjoy.
- 3 I can't get any pleasure from the things I used to enjoy.

**5. Guilty Feelings**

- 0 I don't feel particularly guilty.
- 1 I feel guilty over many things I have done or should have done.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

**6. Punishment Feelings**

- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

**7. Self-Dislike**

- 0 I feel the same about myself as ever.
- 1 I have lost confidence in myself.
- 2 I am disappointed in myself.
- 3 I dislike myself.

**8. Self-Criticalness**

- 0 I don't criticize or blame myself more than usual.
- 1 I am more critical of myself than I used to be.
- 2 I criticize myself for all of my faults.
- 3 I blame myself for everything bad that happens.

**9. Suicidal Thoughts or Wishes**

- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

**10. Crying**

- 0 I don't cry anymore than I used to.
- 1 I cry more than I used to.
- 2 I cry over every little thing.
- 3 I feel like crying, but I can't.

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Subtotal Page 1

**Continued on Back**

 0154018392  
NR15645



V 0477

**Beck Depression  
Inventory**

CRTN: \_\_\_\_\_ CRF number: \_\_\_\_\_

Page 15

patient inits: \_\_\_\_\_

**Baseline**
**11. Agitation**

- 0 I am no more restless or wound up than usual.
- 1 I feel more restless or wound up than usual.
- 2 I am so restless or agitated that it's hard to stay still.
- 3 I am so restless or agitated that I have to keep moving or doing something.

**12. Loss of Interest**

- 0 I have not lost interest in other people or activities.
- 1 I am less interested in other people or things than before.
- 2 I have lost most of my interest in other people or things.
- 3 It's hard to get interested in anything.

**13. Indecisiveness**

- 0 I make decisions about as well as ever.
- 1 I find it more difficult to make decisions than usual.
- 2 I have much greater difficulty in making decisions than I used to.
- 3 I have trouble making any decisions.

**14. Worthlessness**

- 0 I do not feel I am worthless.
- 1 I don't consider myself as worthwhile and useful as I used to.
- 2 I feel more worthless as compared to other people.
- 3 I feel utterly worthless.

**15. Loss of Energy**

- 0 I have as much energy as ever.
- 1 I have less energy than I used to have.
- 2 I don't have enough energy to do very much.
- 3 I don't have enough energy to do anything.

**16. Changes in Sleeping Pattern**

- 0 I have not experienced any change in my sleeping pattern.
- 1a I sleep somewhat more than usual.
- 1b I sleep somewhat less than usual.
- 2a I sleep a lot more than usual.
- 2b I sleep a lot less than usual.
- 3a I sleep most of the day.
- 3b I wake up 1-2 hours early and can't get back to sleep.

**17. Irritability**

- 0 I am no more irritable than usual.
- 1 I am more irritable than usual.
- 2 I am much more irritable than usual.
- 3 I am irritable all the time.

**18. Changes in Appetite**

- 0 I have not experienced any change in my appetite.
- 1a My appetite is somewhat less than usual.
- 1b My appetite is somewhat greater than usual.
- 2a My appetite is much less than before.
- 2b My appetite is much greater than usual.
- 3a I have no appetite at all.
- 3b I crave food all the time.

**19. Concentration Difficulty**

- 0 I can concentrate as well as ever.
- 1 I can't concentrate as well as usual.
- 2 It's hard to keep my mind on anything for very long.
- 3 I find I can't concentrate on anything.

**20. Tiredness or Fatigue**

- 0 I am no more tired or fatigued than usual.
- 1 I get more tired or fatigued more easily than usual.
- 2 I am too tired or fatigued to do a lot of the things I used to do.
- 3 I am too tired or fatigued to do most of the things I used to do.

**21. Loss of Interest in Sex**

- 0 I have not noticed any recent change in my interest in sex.
- 1 I am less interested in sex than I used to be.
- 2 I am much less interested in sex now.
- 3 I have lost interest in sex completely.

Subtotal Page 2

Subtotal Page 1

Total Score

NR15645

34567890112 ABCDE

Name: \_\_\_\_\_

Date: \_\_\_\_\_

**Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form  
(Q-LES-Q-SF)**

Taking everything into consideration, during the past week how satisfied have you been with your.....

	Very Poor	Poor	Fair	Good	Very Good
.....physical health?	1	2	3	4	5
.....mood?	1	2	3	4	5
.....work?	1	2	3	4	5
.....household activities?	1	2	3	4	5
.....social relationships?	1	2	3	4	5
.....family relationships?	1	2	3	4	5
.....leisure time activities?	1	2	3	4	5
.....ability to function in daily life?	1	2	3	4	5
.....sexual drive, interest and/or performance?*	1	2	3	4	5
.....economic status?	1	2	3	4	5
.....living/housing situation?*	1	2	3	4	5
.....ability to get around physically without feeling dizzy or unsteady or falling?*	1	2	3	4	5
.....your vision in terms of ability to do work or hobbies?*	1	2	3	4	5
.....overall sense of well being?	1	2	3	4	5
.....medication? (If not taking any, check here _____ and leave item blank.)	1	2	3	4	5
.....How would you rate your overall life satisfaction and contentment during the past week?	1	2	3	4	5

\*If satisfaction is very poor, poor or fair on these items, please UNDERLINE the factor(s) associated with a lack of satisfaction.



## social adjustment scale (sas-m)

<p><i>this questionnaire asks about how you have been during the last two weeks at work, spare time activities and in family life – please read each statement and then put a tick (✓) in the box to the right to indicate how much the statement has applied to you <u>during the last two weeks</u></i></p>		1 = not at all	2 = occasionally	3 = about half the time	4 = most of the time	5 = all the time
<p><b><u>work outside the home:</u></b> the following questions are about how things have been in your job (full or half-time – if you do <b>not</b> have a job go straight on to the next section) – over the last 2 weeks have you:</p>						
1.	missed any time from work?*					
2.	been doing your job well?					
3.	felt ashamed of how you have been doing your work?*					
4.	got angry with or argued with people at work?*					
5.	felt upset, worried or uncomfortable at work?*					
6.	been finding your work interesting?					
<p><b><u>housework:</u></b> the following questions are about how the housework has been – over the last 2 weeks have you:</p>						
7.	done the necessary housework each day?					
8.	been doing the housework each day?					
9.	felt ashamed of how you have been doing the housework?*					
10.	got angry with or argued with salespeople/tradesmen/neighbours?*					
11.	felt upset, worried or uncomfortable while doing the housework?*					
12.	found the housework boring, unpleasant or a drudge?*					
<p><b><u>social and leisure activities:</u></b> the following questions are about your friends and what you have been doing in your spare time – over the last 2 weeks have you:</p>						
13.	been in touch with any of your friends?					
14.	been able to talk about your feelings openly with your friends?					
15.	done things socially with your friends (e.g. visiting, entertaining, going out together)?					
16.	spent your available time on hobbies or spare time interests?					
17.	got angry with or argued with your friends?*					
18.	been offended or had your feelings hurt by your friends?*					
19.	felt ill at ease, tense or shy when with people?*					
20.	felt lonely and wished for companionship?*					
21.	felt bored in your free time?*					

*note that on this & the next page, scores for starred questions are reversed – 5, 4, 3, 2, 1*

**cont.**

<b>extended family:</b> the following questions are about your extended family, i.e. parents, or brothers, sisters, in-laws, and children not living at home (please do <b>not</b> include your partner or children living at home) – over the last 2 weeks have you:		1	2	3	4	5
22.	got angry with or argued with any of your relatives?*					
23.	made an effort to keep in touch with your relatives?					
25.	been able to talk about your feelings openly with you relatives?					
26.	depended on your relatives for help, advice or friendship?					
27.	been feeling that you have let your relatives down at any time?*					
28.	been feeling that your relatives have let you down at any time?*					
<b>marital:</b> the following questions are about how things have been between you and your partner. If you are <b>not</b> living with your partner or living with a person in a steady relationship, go straight on to the next section. Over the past 2 weeks have you:						
29.	got angry with each other or argued with one another?*					
30.	been able to talk about your feelings/problems with your partner?					
31.	been making most of the decisions at home yourself?					
32.	tended to give in and let your partner have their own way when there was a disagreement?*					
33.	and your partner shared the responsibility for practical matters that have arisen?					
34.	had to depend on your partner to help you?*					
35.	been feeling affectionate towards your partner?					
36.	and your partner had sexual relations/? About how many times?					
37.	had any problems during sexual intercourse (e.g. pain or difficulty with climax)?*					
38.	enjoyed your sexual relations with your partner?					
<b>parental:</b> the following questions are about how things have been with your children (if you do <b>not</b> have children living at home go straight to the next section) – over the last 2 weeks?						
39.	been interested in your children's activities, e.g. school/friends/etc?					
40.	been able to talk to and listen to your children?					
41.	been shouting at or arguing with your children?*					
42.	been feeling affectionate towards your children?					
<b>family unit:</b> the following questions are about how things have been with your immediate family, that is your partner and children at home. If you do <b>not</b> have an immediate family, please ignore this section. Over the past 2 weeks have you:						
43.	been worrying more than necessary about things happening to your family?*					
44.	been feeling that you have let your immediate family down at all?*					
45.	been feeling that your immediate family has let you down at all?*					

	actual	ideal	%		actual	ideal	%
outside work	=			marital	=		
housework	=			parental	=		
social & leisure	=			family unit	=		
extended family	=			total score	=		

---



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### social adjustment scale (sas-m)

Serenity Programme™ - [serene.me.uk](http://serene.me.uk) - Work and Social Adjustment Scale - WSAS

## Work and Social Adjustment Scale (WSAS)

Identifier

Date

People's problems sometimes affect their ability to do certain day-to-day tasks in their lives. To rate your problems look at each section and determine on the scale provided how much your problem impairs your ability to carry out the activity. This assessment is not intended to be a diagnosis. If you are concerned about your results in any way, please speak with a qualified health professional.

If you're retired or choose not to have a job for reasons unrelated to your problem, tick here

	0	1	2	3	4	5	6	7	8
	Not at all		Slightly		Definitely		Markedly		Very severely
1	Because of my [problem] my <b>ability to work</b> is impaired. '0' means 'not at all impaired' and '8' means very severely impaired to the point I can't work.								<input type="text"/>
2	Because of my [problem] my <b>home management</b> (cleaning, tidying, shopping, cooking, looking after home or children, paying bills) is impaired.								<input type="text"/>
3	Because of my [problem] my <b>social leisure activities</b> (with other people e.g. parties, bars, clubs, outings, visits, dating, home entertaining) are impaired.								<input type="text"/>
4	Because of my [problem], my <b>private leisure activities</b> (done alone, such as reading, gardening, collecting, sewing, walking alone) are impaired.								<input type="text"/>
5	Because of my [problem], my ability to form and maintain <b>close relationships</b> with others, including those I live with, is impaired.								<input type="text"/>

Total WSAS score =

The maximum score of the WSAS is 40, lower scores are better. Privacy - please note - this form does not transmit any information about you or your assessment scores. If you wish to keep your results, either print this document or save this file locally to your computer. If you click 'save' before closing, your results will be saved in this document. These results are intended as a guide to your health and are presented for educational purposes only. They are not intended to be a clinical diagnosis. If you are concerned in any way about your health, please consult with a qualified health professional.

### Appendix III: CANTAB Task Details

**Reaction Time (RTI; 3 min):** a measure of motor and mental response speeds. During this task, participants must keep their finger on a button at the bottom of the screen and wait for one of the five icons oriented at the top of the screen to turn yellow. When this happens, participants must release the button at the bottom of the screen and touch the yellow icon as quickly as possible.

*Median Movement Time:* the median time taken for a subject to release the response button and select the target stimulus after it flashed yellow on screen. Calculated across correct, assessed trials in which the stimulus could appear in any one of five locations. Measured in milliseconds.

*Median Correct Reaction Time (MDCRT):* the median duration it took for a subject to release the response button after the presentation of a target stimulus. Calculated across correct, assessed trials in which the stimulus could appear in any one of five locations. Measured in milliseconds.

**Rapid Visual Information Processing (RVP; 7 min):** a measure of sustained and selective attention and processing speed. During this task, digits between 2-9 appear in a pseudo-randomized order within a white outline at the center of the screen, at a rate of 100 digits/minute. Participants are asked to detect a target sequence of three numbers (for example 2-4-6) and respond as quickly and accurately as possible to the target sequence via a button press.

*Median Correct Reaction Time (MDCRT):* the median response latency on trials where the subject responded correctly. Calculated across all assessed trials.

*Probability of False Alarm:* the number of sequence presentations that were false alarms divided by the number of sequence presentations that were false alarms plus the number of sequence presentations that were correct rejections:  $(\text{False Alarms} \div (\text{False Alarms} + \text{Correct Rejections}))$ .

*Probability of Hit:* the number of target sequences during assessment blocks that were correctly responded to within the time allowed, divided by the number of target sequences during assessment blocks.  $(\text{Correct hits} \div \text{total number of sequences})$ .

**Delayed Matching to Sample (DMS; 7 min):** a measure of visual matching ability and short-term visual recognition memory. During this task, a complex, non-verbal, abstract visual pattern (the “sample pattern”) is displayed in a red box at the top of the screen. After the sample pattern has been displayed, four similar patterns (the “choice patterns”) appear in four white boxes at the bottom of the screen. The sample pattern is covered up with a solid red box before the choice patterns appear. In some trials, the choice patterns appear immediately after the sample pattern is covered up, whereas in other there is a slight delay (4 or 12 seconds) before the choice patterns show up.

*Median Correct Reaction Time (MDCRT):* the median latency between the presentation of the response stimuli options and the subject selecting the correct box on their first attempt. Calculated across all correct assessed trials (simultaneous and all delays).

*Percent Correct:* the percentage of assessment trials containing a delay during which the subject chose the correct box on their first box choice. Calculated across all assessed trials containing a delay.

**Spatial Working Memory (SWM; 4 min):** assesses working memory, specifically indexing short-term information storage and the updating and manipulation of that information to guide action. It measures executive function via the assessment of strategy use. During the task, 4, 6 or 8 coloured boxes appear on the screen. Clicking on each box will either reveal a blank space or a yellow token. After a token is found, a new token will appear in a different coloured box. After a token has been found in a box, it will not appear in that box again for the rest of the trial, so participants must use their memory and the process of elimination to find all of the tokens and fill up an empty column on the right side of the screen. The number of searchable boxes on the screen slowly increases from 4 to 6 to 8, thereby increasing the difficulty of the task as the trials progress. To discourage the use of stereotyped search strategies, the colour and positioning of the boxes are changed from trial to trial.

*Between Errors:* The number of times the subject incorrectly revisits a box in which a token has previously been found. Calculated across all assessed four, six and eight token trials.

*Double Errors:* The number of times a subject commits an error that is both a within error and a between error. Calculated across all assessed four, six and eight token trials.

*Strategy Score (6-8 boxes):* The number of times a subject begins a new search pattern from the same box they started with previously. If they always begin a search from the same starting point we infer that the subject is employing a planned strategy for finding the tokens. Therefore a low score indicates high strategy use (1 = they always begin the search from the same box), a high score indicates that they are beginning their searches from many different boxes. Calculated across assessed trials with 6 tokens or more.

**One Touch Stockings of Cambridge (OTS; 10 min):** a measure of executive function, specifically probing the domains of spatial planning and the working memory. During the task, two displays with three coloured balls (blue, green and red) are presented. The balls are arranged in such a way that they appear to be stacked in stockings or socks suspended from a beam. The task involves figuring out the minimum number of moves required to move the balls in the lower display so as to exactly match the arrangement in the upper display. This work must be done in the participants head (not by actually moving the balls on the screen) and their answer must be indicated by selecting the appropriate box displayed at the bottom of the screen.

*Mean Choices to Correct:* The mean number of box selections it took a subject before they chose the correct box. Calculated across all correct assessed trials.

*Median Latency to First Choice:* The median latency, measured from the appearance of the stocking balls until the first box choice was made by the subject. Calculated across all assessed trials where the subject's first response was correct.

*Mean Latency to Correct:* The mean latency, measured from the appearance of the stocking balls until the correct box choice was made by the subject. Calculated across all assessed trials.

*Problems Solved on First Choice:* The total number of assessed trials where the subject chose the correct answer on their first attempt. Calculated across all assessed trials.

**Emotion Recognition Task (ERT; 6-10 min):** measures ability to identify six basic emotional facial expressions (sadness, happiness, fear, anger, disgust or surprise) along a continuum of expression magnitude. During this task, computer morphed composite images from real individuals are displayed on the screen for 200ms, then immediately covered up with a static display to prevent residual processing. Each face is expressing one of six emotions (sadness, happiness, fear, anger, disgust or surprise), and following the image display, the participant must select the emotion the face displayed from the six options.

*Median Correct Reaction Time (MDRCT) Anger:* The median latency for a subject to correctly select the emotion 'Anger' after being presented with a face stimulus showing Anger. Calculated across all assessed trials.

*Median Correct Reaction Time (MDRCT) Disgust:* The median latency for a subject to correctly select the emotion 'Disgust' after being presented with a face stimulus showing Disgust. Calculated across all assessed trials.

*Median Correct Reaction Time (MDRCT) Fear:* The median latency for a subject to correctly select the emotion 'Fear' after being presented with a face stimulus showing Fear. Calculated across all assessed trials.

*Median Correct Reaction Time (MDRCT) Happiness:* The median latency for a subject to correctly select the emotion 'Happiness' after being presented with a face stimulus showing Happiness. Calculated across all assessed trials.

*Median Correct Reaction Time (MDRCT) Sadness:* The median latency for a subject to correctly select the emotion 'Sadness' after being presented with a face stimulus showing Sadness. Calculated across all assessed trials.

*Median Correct Reaction Time (MDRCT) Surprise:* The median latency for a subject to correctly select the emotion 'Surprise' after being presented with a face stimulus showing Surprise. Calculated across all assessed trials.

*Median Reaction Time (MDRCT) All Emotions:* The overall median latency for a subject to select an emotion word after being presented with a stimulus. Calculated across all assessed trials.

*Total Hits:* The total number of correct responses (emotion selection) the subject made across all assessed trials.

### Appendix IV: List of ANEW Words used in eStroop Task

**Table 1.** Negative word list for eStroop task divided by block number. Word length (# letters), and Self-Assessment Manikin (SAM) rated mean valence (1 = unhappy, 9 = happy) and arousal (1 = calm/unaroused, 9 = excited/aroused) values are listed. All valence and arousal values are from the Affective Norms for English Words stimulus collection, compiled by the University of Florida's Centre for the Study of Emotion and Attention.

Block #	Word	Length	Valence	Arousal
1	suicide	7	1.25	5.73
	failure	7	1.7	4.95
	terrified	9	1.72	7.86
	nightmare	9	1.91	7.59
	distressed	10	1.94	6.4
	dead	4	1.94	5.73
	prison	6	2.05	5.7
	accident	8	2.05	6.26
	detest	6	2.17	6.06
	victim	6	2.18	6.06
	roach	5	2.35	6.64
	putrid	6	2.38	5.74
	2	rape	4	1.25
terrorist		9	1.69	7.27
disaster		8	1.73	6.33
killer		6	1.89	7.86
disloyal		8	1.93	6.56
jail		4	1.95	5.49
burial		6	2.05	5.08
maggot		6	2.06	5.28
thief		5	2.13	6.89
hostage		7	2.2	6.76
anger		5	2.34	7.63
rage		4	2.41	8.17
3	funeral	7	1.39	4.94
	grief	5	1.69	4.78
	abuse	5	1.8	6.83
	hurt	4	1.9	5.85
	terrible	8	1.93	6.27
	cruel	5	1.97	5.68
	assault	7	2.03	7.51
	vomit	5	2.06	5.75
	pain	4	2.13	6.5
	debt	4	2.22	5.68
	crash	5	2.31	6.95
mad	3	2.44	6.76	

4	rejected	8	1.5	6.37
	betray	6	1.68	7.24
	rabies	6	1.77	6.1
	pollute	7	1.85	6.08
	misery	6	1.93	5.17
	poison	6	1.98	6.05
	despise	7	2.03	6.28
	war	3	2.08	7.49
	hate	4	2.12	6.95
	divorce	7	2.22	6.33
	violent	7	2.29	6.89
enraged	7	2.46	7.97	
5	cancer	6	1.5	6.42
	poverty	7	1.67	4.87
	ulcer	5	1.78	6.12
	slave	5	1.84	6.21
	drown	5	1.92	6.57
	hatred	6	1.98	6.66
	afraid	6	2	6.67
	stress	6	2.09	7.45
	demon	5	2.11	6.76
	crucify	7	2.23	6.47
	insult	6	2.29	6
	injury	6	2.49	5.69
6	murderer	8	1.53	7.47
	torture	7	1.56	6.1
	tragedy	7	1.78	6.24
	mutilate	8	1.82	6.41
	morgue	6	1.92	4.84
	upset	5	2	5.86
	bankrupt	8	2	6.21
	trauma	6	2.1	6.33
	bomb	4	2.1	7.15
	fearful	7	2.25	6.33
	fat	3	2.28	4.81
	shamed	6	2.5	4.88

**Table 2.** Positive word list for eStroop task divided by block number. Word length (# letters), and Self-Assessment Manakin (SAM) rated mean valence (1 = unhappy, 9 = happy) and arousal (1 = calm/unaroused, 9 = excited/aroused) values are listed. All valence and arousal values are from the Affective Norms for English Words stimulus collection, compiled by the University of Florida's Centre for the Study of Emotion and Attention.

<b>Block #</b>	<b>Word</b>	<b>Length</b>	<b>Valence</b>	<b>Arousal</b>
1	love	4	8.72	6.44
	mother	6	8.39	6.13
	win	3	8.38	7.72
	joyful	6	8.22	5.98
	happy	5	8.21	6.49
	proud	5	8.03	5.56
	sexy	4	8.02	7.36
	caress	6	7.84	5.14
	beauty	6	7.82	4.95
	rescue	6	7.7	6.53
	riches	6	7.7	6.17
triumphant	10	8.82	6.78	
2	triumph	7	7.8	5.78
	affection	9	8.39	6.21
	cash	4	8.37	7.37
	baby	4	8.22	5.53
	promotion	9	8.2	6.44
	passion	7	8.03	7.26
	diploma	7	8	5.67
	sunrise	7	7.86	5.06
	wedding	7	7.82	5.97
	honest	6	7.7	5.32
	desire	6	7.69	7.35
money	5	7.59	5.7	
3	paradise	8	8.72	5.12
	friendly	8	8.43	5.11
	comedy	6	8.37	5.85
	kiss	4	8.26	7.32
	graduate	8	8.19	7.25
	beach	5	8.03	5.53
	engaged	7	8	6.77
	party	5	7.86	6.69
	truth	5	7.8	5
	savior	6	7.73	5.8
	honor	5	7.66	5.9
adventure	9	7.6	6.98	
4	loved	5	8.64	6.38
	champion	8	8.44	5.85

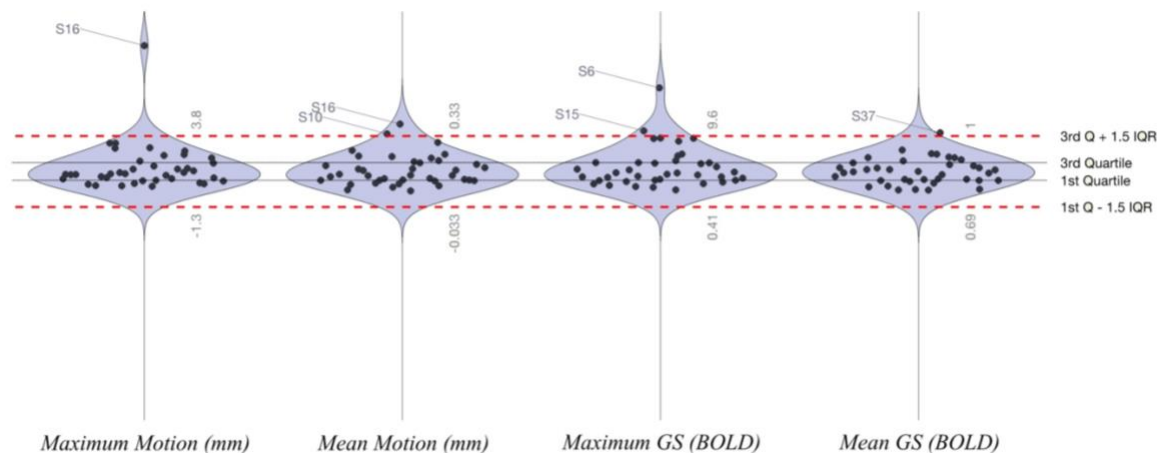
	orgasm	6	8.32	8.1
	delight	7	8.26	5.44
	lucky	5	8.17	6.53
	thrill	6	8.05	8.02
	ecstasy	7	7.98	7.38
	liberty	7	7.98	5.6
	luxury	6	7.88	4.75
	friend	6	7.74	5.74
	family	6	7.65	4.8
	intimate	8	7.61	6.98
5	joy	3	8.6	7.22
	laughter	8	8.45	6.75
	romantic	8	8.32	7.59
	pleasure	8	8.28	5.74
	music	5	8.13	5.32
	sex	3	8.05	7.36
	aroused	7	7.97	6.63
	merry	5	7.9	5.9
	trophy	6	7.78	5.39
	admired	7	7.74	6.11
	food	4	7.65	5.92
	cute	4	7.62	5.53
6	miracle	7	8.6	7.65
	humor	5	8.56	5.5
	victory	7	8.32	6.63
	success	7	8.29	6.11
	cheer	5	8.1	6.12
	joke	4	8.1	6.74
	fame	4	7.93	6.55
	diamond	7	7.92	5.53
	spring	6	7.76	5.67
	pretty	6	7.75	6.03
	leader	6	7.63	6.27
	profit	6	7.63	6.68

**Table 3.** Neutral word list for eStroop task divided by block number. Word length (# letters), and Self-Assessment Manakin (SAM) rated mean valence (1 = unhappy, 9 = happy) and arousal (1 = calm/unaroused, 9 = excited/aroused) values are listed. All valence and arousal values are from the Affective Norms for English Words stimulus collection, compiled by the University of Florida's Centre for the Study of Emotion and Attention.

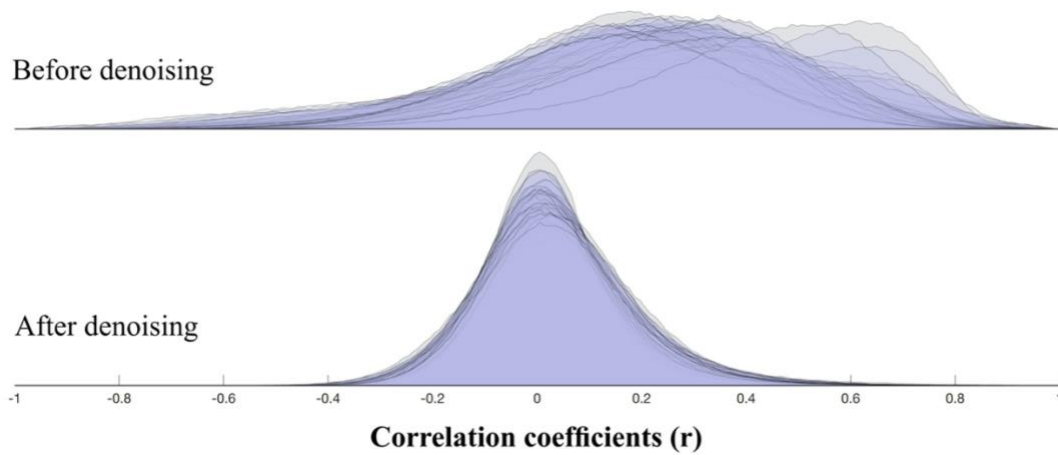
<b>Block #</b>	<b>Word</b>	<b>Length</b>	<b>Valence</b>	<b>Arousal</b>
1	taxi	4	5	3.41
	cord	4	5.1	3.54
	kerchief	8	5.11	3.43
	phase	5	5.17	3.98
	locker	6	5.19	3.38
	material	8	5.26	4.05
	hairpin	7	5.26	3.27
	poster	6	5.34	3.93
	arm	3	5.34	3.59
	lantern	7	5.57	4.05
	cow	3	5.57	3.49
	plant	5	5.98	3.62
	2	hydrant	7	5.02
appliance		9	5.1	4.05
part		4	5.11	3.82
column		6	5.17	3.62
context		7	5.2	4.22
office		6	5.24	4.08
item		4	5.26	3.24
sphere		6	5.33	3.88
industry		8	5.3	4.47
bathroom		8	5.55	3.88
quiet		5	5.58	2.82
village		7	5.92	4.08
3		foot	4	5.02
	trunk	5	5.09	4.18
	elbow	5	5.12	3.81
	statue	6	5.17	3.46
	engine	6	5.2	3.98
	headlight	9	5.24	3.81
	ankle	5	5.27	4.16
	butter	6	5.33	3.17
	wagon	5	5.37	3.98
	museum	6	5.54	3.6
	windmill	8	5.6	3.74
	lamb	4	5.89	3.36
	4	inhabitant	10	5.05
machine		7	5.09	3.82

	door	4	5.13	3.8
	umbrella	8	5.16	3.68
	paper	5	5.2	2.5
	cork	4	5.22	3.8
	building	8	5.29	3.92
	fabric	6	5.3	4.14
	banner	6	5.4	3.83
	avenue	6	5.5	4.12
	ketchup	7	5.6	4.09
	privacy	7	5.88	4.12
5	cabinet	7	5.05	3.43
	chair	5	5.08	3.15
	journal	7	5.14	4.05
	month	5	5.15	4.03
	pencil	6	5.22	3.14
	table	5	5.22	2.92
	passage	7	5.28	4.36
	chin	4	5.29	3.31
	violin	6	5.43	3.49
	glacier	7	5.5	4.24
	lightbulb	9	5.61	4.1
	prairie	7	5.75	3.41
6	barrel	6	5.05	3.36
	serious	7	5.08	4
	utensil	7	5.14	3.57
	clock	5	5.14	4.02
	kettle	6	5.22	3.22
	street	6	5.22	3.39
	patent	6	5.29	3.5
	finger	6	5.29	3.78
	elevator	8	5.44	4.16
	basket	6	5.45	3.63
	jelly	5	5.66	3.7
	key	3	5.68	3.7

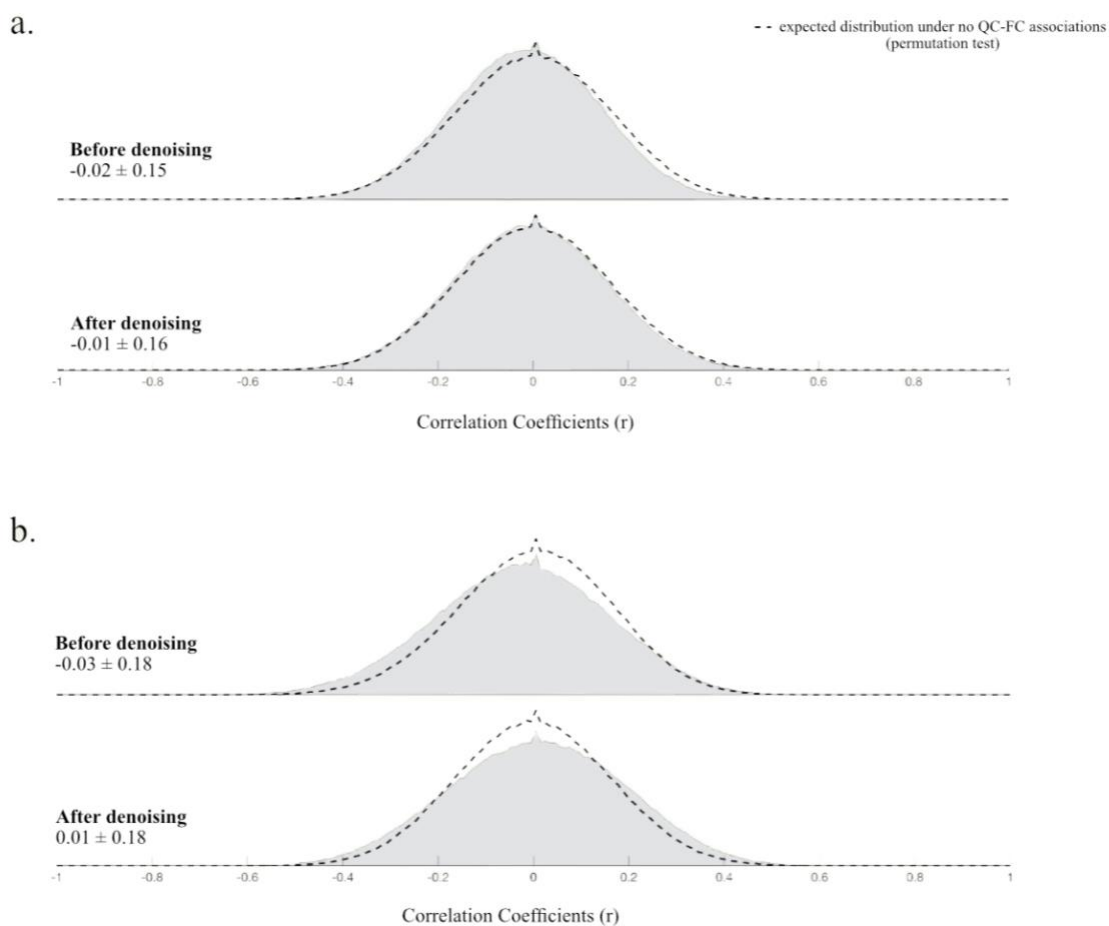
## Appendix V: Denoising Quality Control Figures



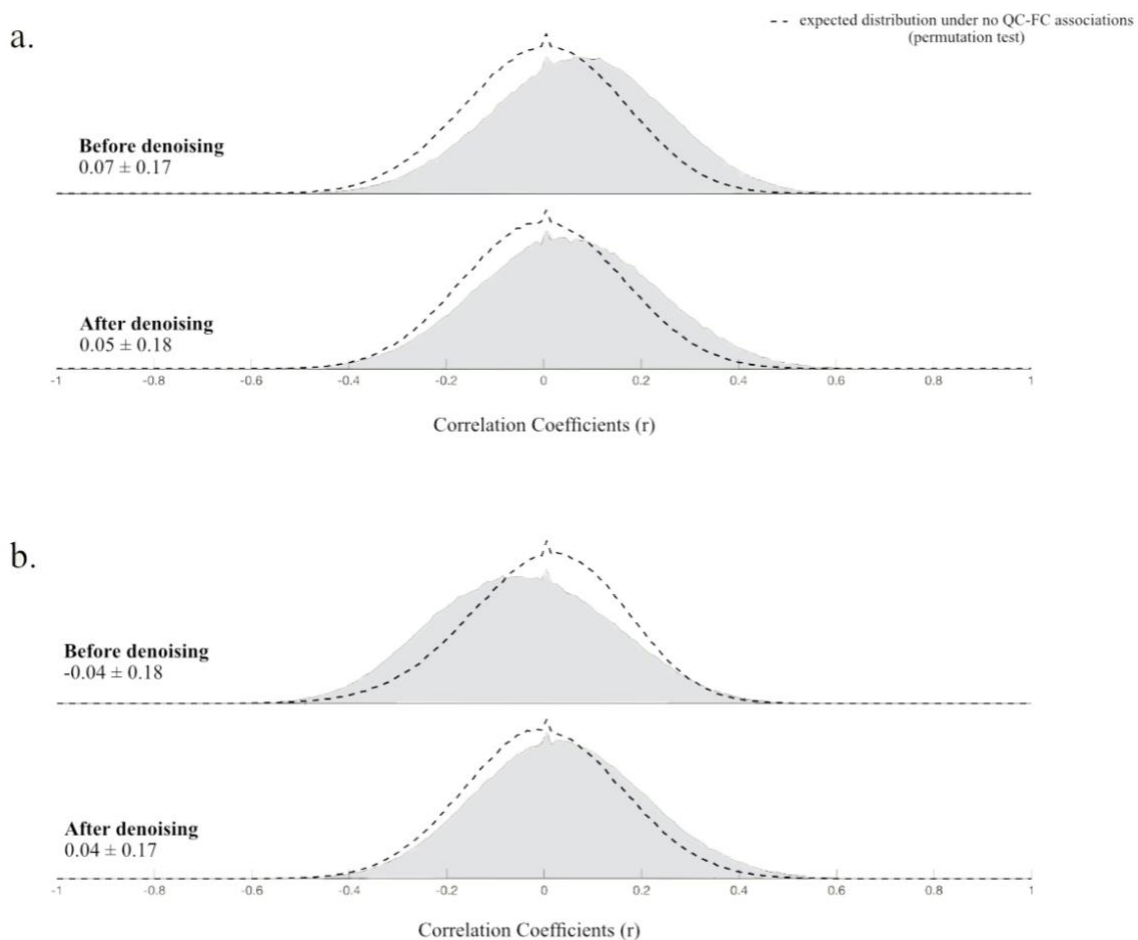
**Figure 1.** Histogram of subject-wise values for maximum motion (mm), mean motion (mm), maximum global signal (GS) change (whole-brain BOLD signals) and mean global signal (GS) change (whole-brain BOLD signals) prior to denoising, calculated across the rest and task conditions. Outliers (subject values outside the 3<sup>rd</sup>/1<sup>st</sup> quartile  $\pm$  1.5 inter-quartile range [IQR],  $n=6$ ) are identifiable when they fall outside the red dashed line. S16 was identified as an outlier on maximum motion (10.44 mm) and mean motion (0.39 mm). S10 was identified as a mean motion outlier (0.34 mm, 0.01 mm above IQR range). S15 (10.3) and S6 (15.9) were identified as maximum GS change outliers, and S37 (1.05) was identified as a mean GS change outlier.



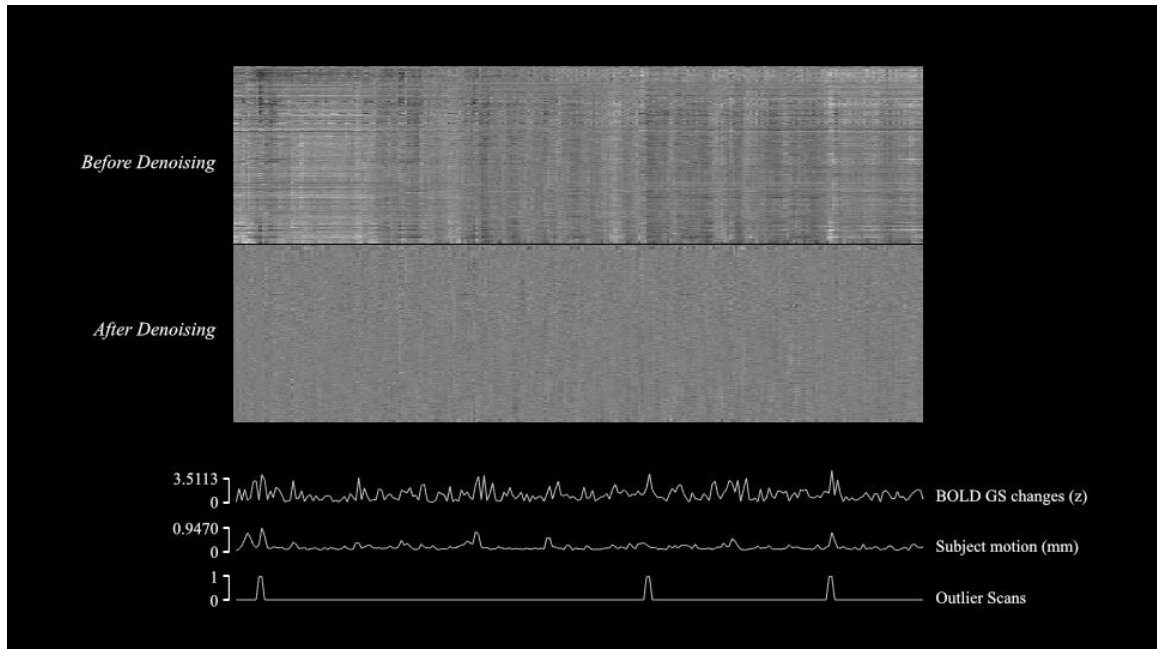
**Figure 2.** Functional connectivity correlation coefficient distributions between randomly selected pairs of points in the brain before and after denoising. Each grey outline of a distribution represents one individual's data (18 rMDDs and 21 HVs), with separate distributions generated for the rest and task conditions for each individual, both of which are displayed.



**Figure 3.** Distribution of the correlation coefficients ( $r$ ) for the relationship between *a.* mean global signal change and *b.* maximum global signal change and functional connectivity across all subjects before and after denoising. Functional connectivity values used in this figure are representative of correlation coefficients between randomly selected pairs of voxels in the brain. Mean  $\pm$  standard deviations values for the correlation coefficients corresponding to each condition are listed to the left of each distribution under the before/after denoising labels. The expected null distribution (in the case of no associations between global signal changes and functional connectivity) are indicated via the dashed line, and the sample distributions appear in grey.

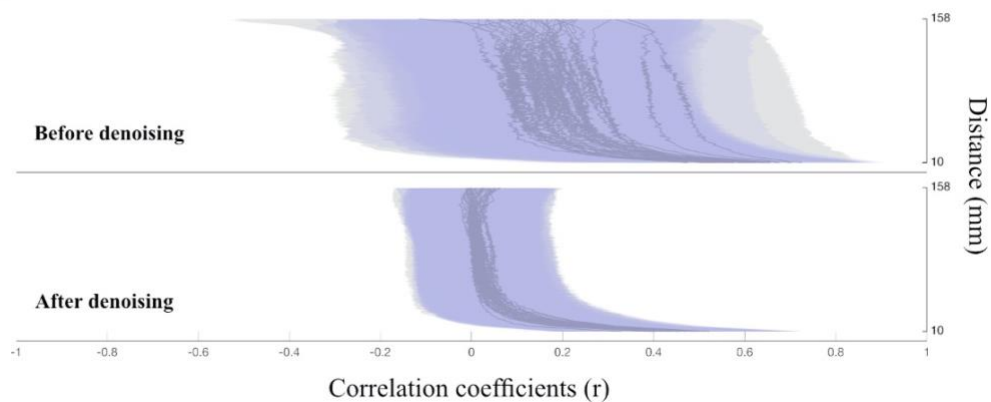


**Figure 4.** Distribution of the correlation coefficients ( $r$ ) for the relationship between *a.* mean motion ( $mm$ ) and *b.* maximum motion ( $mm$ ) and functional connectivity across all subjects before and after denoising. Functional connectivity values used in this figure are representative of correlation coefficients between randomly selected pairs of voxels in the brain. Mean  $\pm$  standard deviations values for the correlation coefficients corresponding to each condition are listed to the left of each distribution under the before/after denoising labels. The expected null distribution (in the case of no associations between global signal changes and functional connectivity) are indicated via the dashed line, and the sample distributions appear in grey.

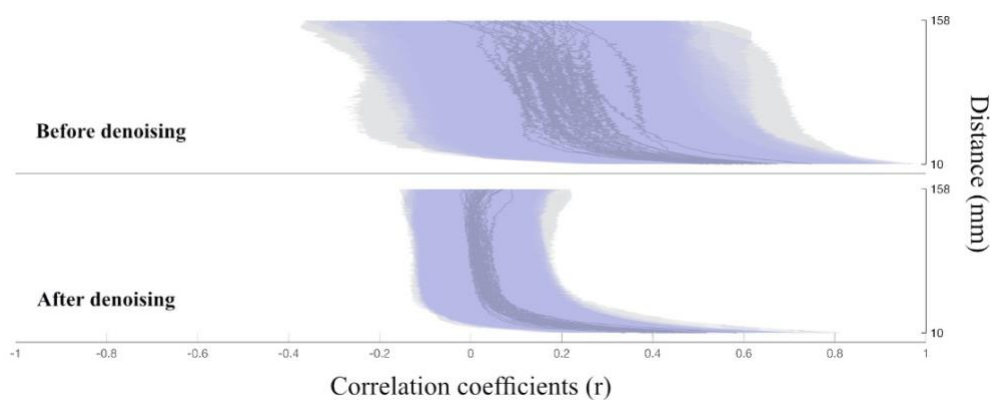


**Figure 5.** A randomly selected subject-specific plot of global signal before and after denoising, as well as the associated subject's z-normalized global signal changes, framewise composite motion (mm) and outlier scans across time before denoising during the eStroop task (*top*). Carpet plots are two-dimensional representations of global signal in the brain, wherein each column represents an individual volume, and each row is an individual voxel in that volume. Outliers were defined as scans exceeding a framewise displacement composite movement threshold of 1.5 mm or a z-normalized differenced mean image intensity threshold of 3 standard deviations from the mean.

*a. Rest*



*b. Task*



**Figure 6.** Whole-sample subject-wise plots of functional connectivity correlation coefficients ( $r$ ) vs. distance (mm) before and after denoising *a. At rest* and *b. During the eStroop task*. Each individual grey line represents data from a single subject. Both groups (rMDD and HV) are represented in this figure.