RESTING-STATE FUNCTIONAL CONNECTIVITY AND DEPRESSION: TOWARD NEURAL MECHANISMS OF DEPRESSION, RUMINATION, AND EMOTION DYSREGULATION

By

LAURA MARIE LESNEWICH

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ABSTRACT OF THE THESIS

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By LAURA MARIE LESNEWICH

Thesis Director:

Marsha E. Bates

Depressive disorders are heterogeneous and their diagnoses have poor reliability. There is a need to understand the biological mechanisms of depression to improve assessment, diagnosis, and treatment. The default mode network (DMN), central executive network (CEN), and salience network (SN) are large-scale neural networks that have been implicated in depression. The present study examined how resting-state functional connectivity within and between these three networks is associated with individual differences in depression severity as well as rumination and emotion dysregulation, two transdiagnostic features associated with depression. Data were collected via functional magnetic resonance imaging (fMRI) using a standard resting-state paradigm. Resting-state data for n = 59 participants were analyzed using independent component analysis. Functional connectivity values between core nodes of the DMN, CEN, and SN were calculated using Pearson correlation, and these connectivity values were correlated to continuous measures of depression severity, rumination, and emotion dysregulation across the whole sample. Functional connectivity between the right dorsolateral prefrontal cortex (CEN) and paracingulate gyrus (CEN)

was positively correlated ($p < 0.05$) to depression severity. Functional connectivity between the left dorsolateral prefrontal cortex (CEN) and left inferior parietal lobule (DMN) was negatively correlated ($p < 0.05$) to depression severity. These associations were no longer significant after correction for multiple comparisons. Each pair of brain regions was additionally correlated to a distinct pattern of rumination and emotion dysregulation scores. If replicated, the present findings could add knowledge about how resting-state functional connectivity varies with individual differences in depression severity and related constructs.

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Introduction

Depression is a debilitating mental health condition that affects approximately 30% of U.S. individuals in their lifetime (Kessler, Petukhova, Sampson, Zalavsky, & Wittchen, 2012). Depression is marked by a prolonged period of negative emotionality, attenuated behavioral flexibility, and functional impairment. The economic burden of depression in the U.S. was estimated to be over $200 billion in 2010 and is growing each year (Greenberg et al., 2015). Depression is also associated with an increased risk for chronic health problems (Strine et al., 2008) and death by suicide (Lesage et al., 1994). Researchers have developed a number of evidence-based treatments for depression across various disciplines, including anti-depressant pharmacotherapy, electroconvulsive therapy, transcranial magnetic stimulation, and psychotherapy, such as cognitive-behavioral therapy and behavioral activation (Barlow, 2014). However, up to one third of depressed individuals in treatment fail to achieve remission after multiple treatment attempts, and 10-20% of depressed patients are classified as treatment resistant (Holtzheimer & Mayberg, 2011; Rush et al., 2006). There is a clear need for more research on the factors that contribute to the etiology and maintenance of depression in order to improve assessment and locate new targets for treatment.

Accurate diagnosis is thought to be one prerequisite to successful mental health treatment. Diagnosis can prove to be difficult, however, for conditions such as depression that have a variety of clinical presentations and wide range of severity. The gold standard for mental health diagnosis in the U.S. is the Diagnostic and Statistical Manual of Mental Disorders, which is currently in its fifth edition (DSM-5; APA, 2013). The DSM-5 defines each disorder by a set of symptom criteria, which are self-reported by the patient.

Thus, clinicians rely heavily on subjective data provided by their clients as well as their own clinical judgment to make diagnoses. It is well established, however, that actuarial prediction is superior to subjective clinical judgment (Dawes, Faust, and Meehl, 1989; Goldberg, 1970; Wiggins, 1973). Indeed, in a recent DSM-5 field trial, researchers found the interrater reliability of the major depressive disorder diagnosis to be "questionable" with a kappa of only .25 (Regier et al., 2013). Thus, most mental healthcare professionals do not agree on the presence or absence of major depressive disorder, which is arguably the clearest presentation of clinical depression. Other depressive disorders defined in the DSM-5 have been questioned for their validity as distinct diagnoses, including persistent depressive disorder (Rhebergen & Graham, 2013) and disruptive mood dysregulation disorder (Evans et al., 2017). The need for objective, evidence-based methods to inform diagnosis and treatment is clear.

To this end, much research in the last few decades has focused on identifying biological mechanisms of psychological disorders (Jones & Mendell, 1999; Sanislow et al., 2010; Singh & Rose, 2009). A biological mechanism can be defined as a physiological process that explains or contributes to a pattern of behavior, disease/disorder state, or other measureable outcome. In general, mechanisms can explain how and/or why psychological disorders develop and how and/or why interventions produce change (Kazdin, 2007). Findings from mechanisms research have the potential to tailor individual treatment, predict prognosis, and even improve treatment outcomes (Kazdin, 2007; Singh & Rose, 2009). For example, an understanding of underlying mechanisms could help clinicians distinguish between two presentations of depression,

plan the most effective course of depression treatment, or predict which individuals will respond to specific forms of antidepressant treatment.

The present study focused on functional connectivity in the brain, a mechanism proposed to be involved in depression (Schneider & Prvulovic, 2013), in young adults with a range of depression severity. The goal was to identify potential neural mechanisms associated with various clinical features of depression. To this end, we examined functional connectivity of three major neural networks and how functional connectivity relates to individual differences in depression severity, rumination, and emotion dysregulation.

The following sections describe the construct of depression, summarize two neural models of depression, define resting-state functional connectivity, and characterize three neural networks and their patterns of connectivity in depressed individuals.

Heterogeneity of Depression

Depression is a polythetic construct. For example, it is possible for two individuals diagnosed with major depressive disorder to share no common symptoms as they are defined in the DSM-5. Of the nine diagnostic criteria listed in the DSM-5, no single criterion is necessary for diagnosis (APA, 2013). Individuals with major depression must endorse one of the first two criteria, depressed mood or markedly diminished pleasure, but neither symptom is necessary in its own right. Three additional criteria can be satisfied with one of two opposing symptoms, i.e. insomnia or hypersomnia, psychomotor agitation or retardation, and significant weight loss or weight gain. The remaining four criteria, i.e. feelings of worthlessness/excessive guilt, fatigue, diminished concentration, and suicidality, are not specific to major depression. Persistent

depressive disorder (i.e. dysthymia) is similarly polythetic, needing two out of six symptoms for diagnosis. Importantly, symptoms that define depressive disorders are not unique to this diagnostic class. Bipolar, anxiety, neurodevelopmental, and trauma-related disorders share symptoms with depression. This heterogeneity and non-specificity in subjective symptom presentation presents difficulties in assessment and treatment.

The depression literature emphasizes the importance of investigating additional constructs related to depression beyond its diagnostic criteria in order to explain individual differences in various presentations of depression (Beck & Haigh, 2014; Joormann & Gotlib, 2010; Nolen-Hoeksema, 2000). Rumination and emotion dysregulation are two such transdiagnostic constructs. Rumination is defined as the tendency to focus on symptoms of distress and their possible causes and consequences, typically in a pervasive and repetitive manner (Nolen-Hoeksema,Wisco, & Lyubomirsky, 2008). Rumination is conceptualized as a response style to distress, highlighting its behavioral nature despite its cognitive content (Nolen-Hoeksema, 1991). Importantly, the act of rumination does not lead to adaptive behavior, such as problem solving. Rather, ruminators tend to focus on their own distress without taking steps to change their affect or environment. Rumination has been shown to exacerbate depressive symptoms and negative thinking and impair protective processes such as problem solving and social support (Nolen-Hoeksema et al., 2008). Rumination also has been shown to predict the onset of depressive episodes (Nolen-Hoeksema, 2000).

Emotion regulation is defined as behavior aimed at monitoring, evaluating, and modifying the intensity or length of emotional experiences (Thompson, 1994). Thus, emotion regulation may serve to attenuate, maintain, or enhance emotional arousal

(Thompson, 1994). Emotion regulation is achieved through one or more behavioral strategies, which may be adaptive (e.g. self-disclosure and reappraisal) or maladaptive (e.g. suppression and catastrophizing; Joormann & Gotlib, 2010). Emotion dysregulation is a hallmark of depression, which is characterized by heightened negative affect and diminished positive affect (Joormann & Gotlib, 2010). Depressed individuals tend to employ maladaptive emotion regulation strategies over adaptive ones, thus maintaining or exacerbating their symptoms.

The heterogeneous nature of depressive symptoms and features suggests it may be more useful to examine depression dimensionally rather than categorically and highlights the need to understand the various biological mechanisms involved in this disorder (Brakowski et al., 2017). Such an approach mirrors the National Institutes of Health Research Domain Criteria (RDoC), which de-emphasize the utility of categorical diagnoses in favor of continuous measurement of psychiatric symptoms with the goal of discerning biological mechanisms of mental health conditions (Insel et al., 2010; Sanislow et al., 2010). The present study was guided by the RDoC framework to examine depressive symptoms, rumination, and emotion dysregulation as continuous measures in relation to resting-state brain function. This approach facilitates the direct investigation of individual variability in depression presentations and severity as they relate to neural functioning.

Neural Models of Depression

Neural models suggest that a subjective, symptom-driven classification system is insufficient for accurate diagnosis of depressive disorders, which contributes to deleterious effects on treatment and prognosis (Holtzheimer & Mayberg, 2011).

Furthermore, by its very nature, a symptom-driven classification system leads to difficulty testing the factors that contribute to the etiology and maintenance of depression. In light of these problems, researchers have developed testable models of depression that are based on objective biological correlates rather than on subjective symptoms. Two such neural models that have had considerable impact on the depression literature are the limbic-cortical dysregulation model and the triple network model.

The limbic-cortical dysregulation model of depression is a widely cited theory based on the collective findings of positron emission tomography (PET) research (Mayberg 1997; Mayberg, 2003). This theory was one of the first attempts to account for all depressive symptoms in a single neural model. Mayberg hypothesized that depression is due to a "functional lesion" of the brain, or a dysregulation of larger systems, rather than a failure of localized brain regions (Mayberg, 2003). Specifically, this three-component model is comprised of limbic, cortical, and sub-cortical brain systems that may underlie the heterogeneous symptoms of depression. The cortical (dorsal) component includes the dorsomedial frontal cortex, prefrontal cortex, premotor cortex, parietal cortex, and the anterior and posterior cingulate cortices (Mayberg, 2003). This component was hypothesized to be involved in the cognitive elements of depression, including difficulties with attention, executive functioning, psycho-motor slowing, rumination, and sense of self (Mayberg, 1997). The limbic (ventral) component includes the medial orbitofrontal cortex, subgenual cingulate cortex, hypothalamus, hippocampus, insula, and amygdala (Mayberg, 2003). This component was hypothesized to relate to disturbances in reward, i.e. anhedonia, sleep, appetite, and sex (Mayberg, 1997). The subcortical (rostral) component includes the rostral anterior cingulate cortex, striatum,

thalamus, and brain stem (Mayberg, 2003). This component was theorized to be involved in the emotional salience of external stimuli and serve a regulatory "gating" role between the cortical and limbic components (Mayberg, 1997). The model as a whole posits that depression arises out of impaired control of the limbic component by the cortical component via dysregulation in the subcortical gating mechanism.

The triple network model is a transdiagnostic theory that has had considerable influence on the understanding of psychopathology as a whole, including depression (Menon, 2011). It is based primarily on the findings of resting-state fMRI research. Like Mayberg, Menon argues psychopathology results from dysfunction of networks rather than of discrete anatomical regions. He proposes three brain networks are involved in psychopathology: the default mode network (DMN), the central executive network (CEN), and the salience network (SN). These networks, described in further detail in a later section, are involved in self-referential thought, executive functioning, and emotional processing, respectively. The model emphasizes the role of the SN, which determines the motivating importance (i.e. salience) of external stimuli that drive behavior (Menon & Uddin, 2010; Seeley et al., 2007). The SN also initiates switching between the opposing DMN and CEN (Goulden et al., 2014; Sridharan, Levitin, & Menon, 2008), mirroring the subcortical component of the limbic-cortical dysregulation model. Regarding depression specifically, Menon (2011) integrates literature demonstrating increased functional connectivity between the SN and DMN, which he theorizes leads to impaired allocation of cognitive resources.

A number of independent research groups have supported the application of the triple network model to depression. In their recent review, Mulders et al. (2015) found

major depression is consistently associated with increased connectivity within the DMN as well as increased connectivity between the SN and DMN and decreased connectivity between the DMN and the CEN. Similarly, Wang and colleagues (2016) recently theorized that aberrant interactions between the DMN, CEN, and SN may contribute to the development of a cognitive vulnerability in those with major depression based on their review of the resting-state fMRI literature in this population. These findings, along with a growing body of empirical research (e.g. de Kwaasteniet et al., 2015; Manoliu et al., 2014; Zheng et al., 2015), support the conceptualization of aberrant connectivity within the triple network model as mechanisms involved in depression. The present study draws primarily on the triple network model, as the model is grounded specifically in the resting-state fMRI literature. It also draws upon aspects of Mayberg's limbic-cortical dysregulation model based on to its contribution to the depression literature and development of the triple network model.

Resting-State fMRI and Functional Connectivity

The present study examined blood-oxygen-level dependent (BOLD) data acquired via functional magnetic resonance imaging (fMRI) while participants were at "rest," i.e. not engaged in any particular task. "Resting-state" fMRI is a methodology that arose as a way of evaluating "intrinsic" brain activity that is not time-locked to specific stimuli or tasks (Raichle & Gusnard, 2005). The goal of this method is to examine patterns in spontaneous low-frequency (< 0.1 Hz) fluctuations of the BOLD signal that are observed when the brain is at rest (Biswal, Yetkin, Haughton, & Hyde, 1995; Lee, Smyser, & Shimony, 2013). This method has advantages over task-based fMRI, such as exploring networks of brain activation in a stimulus-free manner (Wang, Hermens, Hickie, &

Lagopoulos, 2012; Margulies et al., 2010). Early proponents of this method referred to the resting state as a "baseline" of brain activity (Gusnard & Raichle, 2001), but this view has been controversial in the field (Morcom & Fletcher, 2007). Although the fundamental nature of the resting brain is still debated, resting-state fMRI is now widely accepted as a valid method of investigating networks of functional connectivity. As such, it is a promising tool to investigate neural mechanisms of depression and its correlates.

Functional connectivity is the primary dependent variable in resting-state fMRI. Functional connectivity is defined as "the temporal dependence of neuronal activity patterns of anatomically separated brain regions" (van den Heuvel & Hulshoff Pol, 2010). That is, brain regions are said to have functional connectivity if their pattern of activation is related in either the time (correlation) or the frequency (coherence) domain (Margulies et al., 2010). Groups of brain regions with functional connectivity represent networks of brain activation. These networks are thought to communicate and work together towards a common perceptual, behavioral, cognitive, or emotional function, which can be adaptive or maladaptive (van den Heuvel & Hulshoff Pol, 2010). Thus, it is conceivable that aberrant functional connectivity may underlie the cognitive biases and maladaptive behavioral patterns associated with depression.

Biswal et al. (1995) were the first to demonstrate functional connectivity using resting-state fMRI. They measured correlations in spontaneous low frequency fluctuations between spatially distinct areas of the brain at rest that were known to couple during motor task activation. They subsequently demonstrated these significant correlations were not due solely to changes in blood flow, supporting the idea that functional connectivity is influenced by a neuronal mechanism (Biswal, Van Kylen, &

Hyde, 1997). These seminal findings gave rise to the study of functional connectivity in resting-state fMRI, which has grown immensely and is now considered a field in its own right.

There are a number of validated approaches to derive neural networks in resting-state data. The most popular method is seed-based functional connectivity. Here, researchers select an a priori region-of-interest (ROI), or "seed," and examine the temporal relationships between voxels within the ROI and all other voxels in the brain (Lee et al., 2013). This method is advantageous because it is hypothesis-driven and the analysis and interpretation of results is relatively straightforward (Margulies et al., 2010). Seed-selection introduces bias (Wang et al., 2012), however, and analysis is limited to specific areas of the brain, which may preclude serendipitous findings.

An alternative approach is independent component analysis (ICA). ICA is a mathematical technique that decomposes BOLD signals throughout the brain into spatially or temporally distinct, statistically independent networks (Beckmann, DeLuca, Devlin, & Smith, 2005; Lee et al., 2013). Some advantages of ICA over other methods are that it does not require a priori assumptions about the location of networks and that networks can be widely distributed without a single predetermined focal point. ICA can identify independent noise components, such as motion and physiological artifacts (Margulies et al., 2010), which is critical to valid network assessment. In addition, ICA requires minimal preprocessing (Margulies et al., 2010).

Drawbacks of the ICA method include needing a priori selection of the number of components to be derived and a posteriori distinction between valid and noise components, both of which can be subjective and can influence results (Margulies et al.,

2010). Despite these limitations, ICA remains one of the most widely used methods of deriving resting-state neural networks due to its data-driven, exploratory nature. It is a highly reliable method that has provided valuable information to the field of functional connectivity (Smith et al., 2009) as well as to a better understanding of neural mechanisms in psychopathology research (Du et al., 2015; Fox & Greicius, 2010). Furthermore, depression studies utilizing ICA have produced more consistent findings than studies utilizing seed-based methods (Mulders et al., 2015). For these reasons, the present study will employ ICA to derive neural networks and study functional connectivity.

Functional Networks Implicated in Depression

The triple network model of psychopathology (Menon, 2011) implicates the default mode network (DMN), the central executive network (CEN), and the salience network (SN) in the etiology and maintenance of psychological disorders. The model posits that psychopathology arises out of aberrant connectivity within and between these three neural networks. This model has been applied successfully to the study of various forms of psychopathology, including substance use disorders (Sutherland, McHugh, Pariyadath, & Stein, 2012), attention deficit hyperactivity disorder (Castellanos & Proal, 2012), schizophrenia (Manoliu et al., 2013), and depression (Mulders et al., 2015; Wang et al., 2012). The function and anatomy of each network is described below as well as each network's hypothesized role in the etiology and maintenance of depression.

The DMN is the most widely studied network in the resting-state literature. This network is involved in several cognitive processes, including self-referential thought, theory of mind, memory, and emotion regulation (Andrews-Hanna, Smallwood, &

Spreng, 2014; Buckner, Andrew-Hanna, & Schacter, 2008). The DMN is characterized by a number of regions throughout the brain, including the medial prefrontal cortex, lateral frontal cortex, medial parietal cortex, medial temporal lobe, lateral parietal cortex, lateral temporal cortex, cerebellum, and striatum (Andrews-Hanna et al., 2014; Buckner et al., 2008; Raichle et al., 2001). The medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and the inferior parietal lobule (IPL) are considered to be the core nodes of the DMN, as these areas are most commonly identified across imaging modalities (Buckner et al., 2008; Menon, 2011; Mulders et al., 2015). The DMN is described as a task-negative network due to its increased activation during rest and decreased activation during task initiation and maintenance (Fox et al., 2005). Sub-networks within the DMN appear to possess distinct functions (Andrews-Hanna, Reidler, & Sepulcre, 2010; Andrews-Hanna et al., 2014). The midline core regions (MPFC and PCC) are involved in self-referential emotion processing, and a medial temporal lobe sub-network is involved in episodic memory retrieval and future-oriented self-referential thought (Andrews-Hanna et al., 2010).

Similarly to the larger resting-state literature, resting-state studies of depression have focused largely on the DMN. A growing number of studies have found increased connectivity in anterior regions of the DMN in patients compared to controls (Brakowski et al., 2017; Mulders et al., 2015); this aberration is considered to be a potential mechanism of depression (Schneider & Prvulovic, 2013). Increased connectivity in the anterior DMN may also play a role in rumination (Zhu et al., 2012). Studies have found aberrant connectivity in posterior regions of the DMN as well (Mulders et al., 2015), but these findings are less consistent than those of the anterior DMN. Interestingly, studies of

mild or remitted depression (e.g. Pannekoek et al., 2014; Sexton et al., 2012; Veer et al., 2010; Zhu et al., 2012) have been less likely than those of moderate to severe depression (e.g. Greicius et al., 2007; Guo et al., 2014; Li et al., 2013; Manoliu et al., 2014) to demonstrate significant differences in DMN connectivity between patients and controls. Collectively, the literature suggests depression is associated with increased connectivity in the DMN (particularly the anterior DMN) and depression severity may moderate this relationship.

The CEN is implicated in executive functions, such as attention, working memory, problem-solving, decision making, and conflict resolution (Rogers et al., 2004; Sheline, Price, Yan, & Mintun, 2010). It is comprised of the dorsolateral prefrontal cortex (dlPFC), dorsomedial prefrontal cortex (dmPFC), orbitofrontal cortex (OFC), and parietal cortices (Habas et al., 2009; Seeley et al., 2007). These core nodes of the CEN also are coupled with the caudate nucleus and thalamus, but they lack connectivity with limbic structures (Seeley, 2007). Contrary to the DMN, the CEN is considered a task-positive network because CEN activity increases during goal-directed behavior and decreases at rest (Fox et al., 2005). The DMN and CEN are often conceptualized as opposing networks (Hamilton et al., 2011; Seeley et al., 2007).

The SN is involved in filtering relevant information from the environment and determining the motivating value of external stimuli. The SN also is thought to drive behavior regarding these salient stimuli (Menon, 2011; Seeley et al., 2007). The SN has been implicated in "switching" between DMN and CEN activation (Goulden et al., 2014; Menon & Uddin, 2010; Sridharan, Levitin, & Menon, 2008). The SN is comprised of core nodes in the dorsal anterior cingulate cortex (dACC) and the anterior insula (Seeley

et al., 2007). It also is coupled with subcortical regions, such as the amygdala, ventral pallidum, thalamus, hypothalamus, periaqueductal gray, and ventral tegmental area, which are involved in emotion and reward processing.

To our knowledge, only three previous studies have employed ICA to examine networks resembling the CEN or SN in depression. Manoliu et al. (2014) found individuals with major depression, compared to controls, showed decreased connectivity of the anterior insula within the SN, decreased connectivity between the DMN and CEN, and increased connectivity between the SN and DMN. Decreased connectivity of the anterior insula correlated with depression severity as measured by both the Beck Depression Inventory (BDI) and the Hamilton Depression Rating Scale (HAM-D). The depressed group also exhibited aberrant connectivity in the posterior CEN, which included both increased and decreased connectivity compared to controls, but these results did not survive correction for multiple comparisons. Veer et al. (2010) found reduced connectivity of the left frontal pole in a task-positive network, but this network differed from the typical CEN. No group differences in SN connectivity were observed. Sexton et al. (2012) examined functional connectivity within and between the DMN, an "executive control network," and an "affective network." The latter two networks overlapped with the CEN and SN, respectively, but did not encompass all regions typically associated with the CEN and SN. Again, no group differences in connectivity were observed. In general, the CEN and SN have not been adequately studied in depression. These networks may, however, be especially important in further understanding depression given support for their involvement in cognitive and emotional processes (Menon, 2015; Rogers et al., 2004; Seeley et al., 2007; Sheline et al., 2010).

Overall, the most consistent finding in the depression literature is increased connectivity within anterior DMN regions in individuals with depression compared to healthy controls. A growing body of research suggests this neural aberration is associated with depression diagnosis (Schneider & Prvulovic, 2013), pharmacological treatment response (Li et al., 2013), and ruminative response styles (Zhu et al., 2012). Although the precise relationship between DMN connectivity and behavioral outcomes is still unknown, it has been speculated that increased connectivity in the anterior DMN is related to maladaptive internal attention in depression (Guo et al., 2014). Furthermore, depression severity may moderate the relationship between abnormal DMN connectivity and depression diagnosis. Findings on CEN and SN connectivity in depression are limited thus far. The importance of continuing to examine how these networks contribute to the etiology and maintenance of depression is suggested by their roles in cognitive and emotional processes.

Present Study Hypotheses

There is a solid scientific premise for neural mechanism research in depression based on differences in functional connectivity between patients and controls, a relationship between functional connectivity and depression severity, and the results of treatment response studies. The present study added to this literature by addressing the following research question: How is functional connectivity in the resting brain associated to depression severity and/or transdiagnostic features of depression in young adults? We addressed this question by examining three resting-state neural networks, the DMN, the CEN, and the SN, in a sample of young adults with a range of depressive severity, rumination, and emotion dysregulation.

The approach involved a combination of hypothesis testing and exploratory analyses. Two a priori hypotheses were proposed. Hypothesis 1: Depression severity will exhibit significant positive correlation to functional connectivity within the DMN. This hypothesis was based on studies showing increased DMN connectivity in depressed individuals (e.g. Greicius et al., 2007; Guo et al., 2014; Li et al., 2013; Manoliu et al., 2014) and an association between aberrant DMN connectivity and depression severity (Mulders et al., 2015). Hypothesis 2: ROI pairs within the DMN that demonstrate significant correlation to depression severity also will correlate to self-reported rumination. This hypothesis was based on previous studies supporting this relationship (Hamilton et al., 2011; Zhu et al., 2012).

Because few studies thus far have employed ICA to examine the CEN and SN in depression, exploratory analyses of these networks and their relationship to the DMN is warranted. In addition, the relationship between resting-state functional connectivity and emotion regulation strategies in depression has not been examined to our knowledge. Thus, we proposed no a priori hypotheses regarding the association between functional connectivity and self-reported difficulties with emotion regulation.

Method

Parent Studies

The present study is part of a larger investigation being conducted at the Rutgers University Exercise Physiology Lab. The overall study aims to examine the effectiveness of an eight-week aerobic exercise intervention at improving physiological and psychological outcomes in depressed individuals. As part of the larger study, participants engaged in an extensive pre-intervention assessment battery over two sessions, including

baseline measures of cognitive, psychosocial, and physiological functioning. Methodologies employed at the baseline assessment sessions included self-report, behavioral tasks, cue reactivity, electroencephalogram (EEG), electrocardiogram (ECG), impedance cardiography (ICG), and calorimetry. Those who agreed and were eligible also participated in an add-on study to conduct simultaneous functional magnetic resonance imaging (fMRI) and physiology (ECG, blood pressure, respiration) assessment sessions pre- and post- the aerobic exercise intervention. This study was conducted at the Rutgers University Brain Imaging Center (RUBIC). The present study focuses on self-report and resting-state fMRI data from the baseline, pre-treatment test sessions.

Participants

Participants in the larger parent study were men and women between the ages of 18 and 35 years recruited on Rutgers campus via fliers and recruitment tables advertising eight weeks of "low to moderate intensity aerobic exercise." Individuals were recruited from the general university population as well as the university Psychological Services Clinic in order to reach a greater number of depressed individuals. Exclusion criteria for the larger study included history of one or more of the following: bipolar or psychotic disorders, self-injurious or suicidal behavior, neurological disorders, and head injuries resulting in a loss of consciousness. Additional exclusion criteria for the fMRI study included left-handedness and standard MRI contraindications (i.e. permanent metal in the body, pregnancy, and claustrophobia). These were assessed via self-report with the exception of pregnancy, which was assessed via urine dipstick. Psychotropic medication, such as antidepressant medication, was not exclusionary in this study.

A total of 238 participants have completed at least one baseline session in the larger study as of September 1, 2017. Because the fMRI component began approximately two years after the original study start date, only 152 of these participants had the opportunity to enroll in the present study, if eligible. Of these, 74 consented to and completed the baseline fMRI session.

Self-Report Measures

Participants completed a battery of self-report questionnaires during baseline assessment of the larger study. These included measures of basic demographic data, exercise habits, medication, alcohol use, depression and anxiety severity, rumination, distress tolerance, emotion regulation, mindfulness, grit, and mood state. The present study examined data from the following three questionnaires.

The Beck Depression Inventory-II (BDI-II) is a widely used and empirically validated measure of depression severity (Beck, Steer, & Brown, 1996). Participants responded to 21 items corresponding to symptoms of depression, earning 0 – 3 points per item based on the symptom severity. A score from 0 – 13 indicates minimal depression, 14 – 19 indicates mild depression, 20 – 28 indicates moderate depression, and 29 – 63 indicates severe depression.

The Ruminative Response Scale (RRS) is a 22-item subscale of the empirically validated Response Styles Questionnaire (Nolen-Hoeksema & Davis, 1999). The RRS measures rumination: the tendency to focus cognitively on symptoms of distress and their possible causes and consequences (Nolen-Hoeksema et al., 2008). Participants indicated on a scale of 1 (almost never) to 4 (almost always) how often they engage in ruminative behaviors when feeling down, sad, or depressed. The RRS yields a total score as well as

three subscales: Depression, Brooding, and Reflection (Gonzalez, Nolen-Hoeksema, & Treynor, 2003). Larger RRS scores indicate more frequent rumination.

The Difficulties in Emotion Regulation Scale (DERS) is an empirically validated measure of emotion dysregulation comprised of 36 statements (Gratz & Roemer, 2004). Participants rated how often each statement applies them on a Likert scale ranging from 1 (almost never) to 5 (almost always). The DERS yields a total score as well as six subscales. Subscales measure Non-Acceptance of Emotional Responses, Difficulties Engaging in Goal-Directed Behavior, Difficulties with Impulse Control, Lack of Emotional Awareness, Limited Access to Emotion Regulation Strategies, and Lack of Emotional Clarity. Larger values on the total score and all subscales indicate greater difficulty with emotion regulation.

Procedures

The baseline fMRI session included approximately one and a half hours of pre-scan assessment, task training, and preparation. Immediately following informed consent, participants completed additional self-report questionnaires related to perceived stress, alcohol use, and illicit substance use as part of the larger study. Height, weight, temperature, and blood pressure were assessed. Females were screened for pregnancy using a standard urine dipstick. Next, a number of sensors were attached to participants' bodies for physiological data collection during the scan as part of the larger study. These included three ECG electrodes and leads, an abdominal respiration belt, and a continuous blood pressure cuff. Then, a research assistant trained participants on the behavioral tasks they would perform during the scan. Participants then lay on the scanner bed and their

heads were positioned beneath the coil using foam cushions to minimize head movement during scanning.

The scan itself lasted approximately 45 minutes, which included a standard localizer, scout, high-resolution anatomical scan, and field map, as well as seven functional runs. Each functional run corresponded to a behavioral task. First, participants were asked to "visually focus" on a white fixation cross overlaid on a black background in a six-minute resting-state task, the data from which are the focus of this study. Second, they performed a breath-holding task to measure inherent hemodynamic response functions. Next, they performed three increasingly difficult levels of a cognitive task lasting five minutes each. Then, they performed a paced breathing task for five minutes. Last, they perform a second six-minute resting-state task identical to the first.

Neuroimaging Parameters and Data Preprocessing

Imaging data were collected using a 3T Siemens Trio scanner and a Siemens 12-channel head coil. High-resolution anatomical images were acquired using a T_1-weighted MPRAGE protocol with the following scan parameters: repetition time (TR) = 1900 ms, echo time (TE) = 2.51 ms, matrix = 256 × 256 voxels, field-of-view (FOV) = 256 mm, voxel size = 1 × 1 × 1 mm. One hundred seventy-six 1-mm sagittal slices (.5 mm gap) were obtained. Functional blood-oxygen-level dependent (BOLD) data were acquired using a single-shot gradient echo-planar imaging (EPI) sequence with the following scan parameters: TR = 2000 ms, TE = 25 ms, flip angle = 90°, matrix = 64 × 64 voxels, FOV = 192 mm, voxel size = 3 × 3 × 3 mm. Thirty-five contiguous 3-mm sagittal slices (1 mm gap) were acquired.

Resting-state data were preprocessed using FMRIB Software Library (FSL) version 5.0.5 (Jenkinson, Beckmann, Behrens, Woolrich & Smith, 2012; Smith et al., 2004) and Analysis of Functional Neuroimages (AFNI) version 16.02.07 (Cox, 1996). First, non-brain tissue was removed from all anatomical (T_1) and functional (BOLD) images using FSL's Brain Extraction Tool (BET; Smith, 2002) by estimating each image's center-of-gravity and manually adjusting BET parameters as necessary until an optimal result was obtained. The first five volumes were discarded to ensure steady-state magnetization throughout the time series. Two participants were excluded at this stage due to an incomplete structural image and wrap-around artifact in the functional image.

Remaining data (n = 72) were motion-corrected using FSL's MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), and the output was reviewed to identify participants with excessive motion during the resting-state scan. Excessive motion was defined conservatively as maximum displacement greater than 1.5 mm or any pattern in the motion parameters time series that could conceivably affect registration, e.g. steep drift or sudden spikes. Thirteen participants were excluded for excessive motion during the resting-state functional run and were not included in further preprocessing and analyses.

Remaining data (n = 59) were registered to standard space with a two-step process using FMRIB's Non-Linear Image Registration Tool (FNIRT; Jenkinson & Smith, 2001). The data were registered to the T_1-weighted anatomical image using 6 degrees of freedom and then registered to MNI-152 standard space using 12 degrees of freedom. All data were visually inspected for gross errors in registration. Next, registered images were segmented into gray matter, white matter (WM), and cerebral spinal fluid (CSF) using

FSL's FAST (Zhang, Brady, & Smith, 2001). Probability maps of CSF and WM were derived and time-series data for these signals were extracted from each participant. Then, 24 motion parameters were calculated for each participant using AFNI commands based on output from MCFLIRT. These 26 nuisance parameters (WM, CSF, 24 motion) were used as covariates in linear regression models in FSL's FEAT to decrease the effects of signals-of-no-interest. Finally, data were smoothed with a 6 mm full-width at half-maximum Gaussian kernel, and temporal filtering between .01 and .1 Hz was performed.

Independent Component Analysis and Functional Connectivity Calculation

Resting-state neural networks were derived using the Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC) software tool implemented in FSL (Beckmann & Smith, 2004). Group-level (n = 59) probabilistic independent component analysis (ICA) decomposed voxel-level BOLD signals into spatially distinct, statistically independent components, or "networks." The model-order was set to 40 components. MELODIC output data, (i.e. average network maps) were visually inspected to identify the DMN, CEN, and SN based on established neuroanatomical maps (e.g. Menon, 2011; Mulders et al., 2015).

Next, the 'cluster' command in FSL was used to segment each network map into anatomical clusters and extract coordinates for local maxima. Clusters were thresholded at t = 3 (CEN) or t = 4 (DMN and SN). The Harvard-Oxford cortical and sub-cortical atlases implemented in FSL were used to confirm cluster anatomy. ROI's from each network were selected based on established "core" anatomy of the DMN, CEN, and SN (Buckner et al., 2008; Habas et al., 2009; Menon, 2011; Raichle et al., 2001; Seeley et al., 2007). In order to reduce multiple comparisons, ROI's that are not cited as core regions

of each network (e.g. cerebellum) were not included in connectivity analyses. A series of 'fslmaths' commands were used to generate ROI masks by creating a 6 mm binarised sphere around the voxel with maximum intensity within each cluster. These masks were then used with the 'fslmeants' command to extract mean BOLD time series data from each participant for each ROI.

In order to examine within- and between-network connectivity, Pearson correlations between all possible ROI pairs were calculated in MATLAB. This process resulted in $(n^2 - n)/2$ functional connectivity outcome variables, where n is the number of ROI's. Pearson correlation coefficients underwent Fisher Z-score transformation to satisfy assumptions of parametric statistical analyses. Last, the absolute values of the Fisher Z-scores were calculated, as the goal of the current study was to examine connectivity per se rather than to differentiate between positive correlations and negative correlations, termed "anticorrelations" in the resting-state literature, among brain regions. Thus, throughout the remainder of this manuscript the term "functional connectivity value" refers to the absolute value of the Fisher Z-transformed Pearson correlation between the time series of a pair of ROI's.

Statistical Analyses

Fifty-nine participants were included in statistical analyses. First, functional connectivity values between all ROI pairs were correlated to BDI-II scores. P-values were adjusted using false discovery rate in MATLAB to control for multiple comparisons. Then, BDI-II was regressed on the functional connectivity values of the ROI pairs that exhibited significant correlations to BDI-II in a single general linear model. Next, separate models controlling for gender, age, and antidepressant medication

status were analyzed. In order to reduce multiple comparisons, only ROI pairs that were significantly correlated to BDI-II scores were additionally correlated to RRS and DERS total scores and subscales. All statistical analyses were conducted in SAS 9.4 using PROC CORR and PROC GLM procedures. Results were considered statistically significant at $p < 0.05$.

Results

Demographic Characteristics

Participants' ages ranged from 18 – 28 years. The mean age of the sample was 20.66 (± 2.04) years. Participants were approximately 75% (n = 44) female and 25% (n = 15) male. Approximately 40.5% (n = 24) of participants identified as Asian, 34% (n = 20) identified as White, 13.5% (n = 8) identified as Black/African American, and 12% (n = 7) identified as either of mixed or Hispanic/Latino racial background. Hispanic/Latino ethnicity was assessed independently of race. About 17% (n = 10) of participants identified as Hispanic/Latino and 83% (n = 49) of participants did not identify as Hispanic/Latino. The racial and ethnic characteristics of the sample are representative of the university and greater New Brunswick populations. These results are summarized in Table 1 (Appendix A).

Medication

Nineteen participants (32.2%) endorsed current medication use. Eleven participants (18.6%) endorsed taking a single medication, 7 participants (11.9%) endorsed taking two medications, and one participant (1.7%) endorsed taking three medications. Surprisingly, only 6 participants (10.2%) reported current antidepressant therapy. These included Lexapro (n = 3), Zoloft (n = 2), Wellbutrin (n = 2), and

mirtazapine (n = 1). Other psychotropic medications included Adderall (n = 1), Ativan (n = 1), Lamictal (n = 1), and Strattera (n = 1). Non-psychotropic medications endorsed included Albuterol (n = 1), Allegra (n = 1), Claritin (n = 1), minocycline (n = 1), pantoprazole (n = 1), Percocet (n = 1), Zyrtec (n = 1), and various forms of contraceptives (n = 9).

Self-Report Measures: Depression, Rumination, and Emotion Dysregulation

Univariate statistics for all self-report measures are summarized in Table 2 (Appendix B). BDI-II scores ranged from 0 to 59 across the sample. The sample range covered over 93% of the total possible range of BDI-II scores (0 – 63). Approximately 25.5% (n = 15) of participants fell in the "minimal" depression range, 24% (n = 14) fell in the "mild" range, 37% (n = 22) fell in the "moderate" range, and 13.5% (n = 8) fell in the "severe" range, according to the BDI-II manual (Beck et al., 1996). The mean BDI-II score was 20.49 (±10.67) and the scores were normally distributed.

RRS total scores ranged from 27 to 80, spanning over 80% of the total possible range (22 – 88). The mean RRS total score was 53.15 (±13.01). Depression subscale (RRS_D) scores ranged from 14 – 46 (possible range is 12 – 48) and the mean score was 30.15 (±8.02). Brooding subscale (RRS_B) scores ranged from 6 – 18 (possible range is 5 – 20) and the mean score was 12.06 (±3.12) Reflection subscale scores spanned the total possible range from 5 – 20 and the mean score was 10.94 (±3.81). The total score and subscales were all normally distributed across the sample.

DERS total scores ranged from 53 to 146, spanning approximately 65% of the total possible range (36 – 180). The mean total score was 89.88 (±23.76). Scores for 5 out of the 6 subscales covered over 80% of the total possible range of scores. The Non-

Acceptance of Emotional Responses subscale (DERS_N) scores ranged from 6 – 26 (possible range is 6 – 30), and the mean score was 14.55 (±5.88). The Difficulties Engaging in Goal Directed Behavior subscale (DERS_G) scores ranged from 5 – 24 (possible range is 5 – 25), and the mean score was 15.13 (±4.29). The Impulse Control Difficulties subscale (DERS_I) scores ranged from 6 – 29 (possible range is 6 – 30), and the mean DERS_I score was 12.41 (±5.61). Scores of the Lack of Emotional Awareness subscale (DERS_A) ranged from 7 – 30 (possible range is 6 – 30). The mean DERS_A score was 15.89 (±5.56). The Lack of Emotional Clarity subscale (DERS_C) scores ranged from 6 – 24 (possible range is 5 – 25), and the mean score was 12.25 (±4.42). The Limited Access to Emotion Regulation Strategies subscale (DERS_S) scores covered only 38% of the total possible range (8 – 40) with a minimum score of 8 and a maximum score of 24. The mean DERS_S score was 19.64 (±7.09). The total score and all subscales were normally distributed across the sample.

Neural Networks and ROI's

Independent component analysis successfully identified the DMN, CEN, and SN. Each network was represented in a single component. The DMN was comprised of four core ROI's: medial prefrontal cortex, posterior cingulate cortex, and bilateral (i.e. right and left) inferior parietal lobule. The CEN and SN were each comprised of five core ROI's. The CEN included bilateral dorsolateral prefrontal cortex, paracingulate gyrus, and bilateral posterior parietal cortex. The SN included anterior cingulate gyrus, bilateral insula, and bilateral middle frontal gyrus. These 14 ROI's resulted in 91 possible ROI pairs that were included in functional connectivity analyses. Network and ROI data are displayed in Figure 1 (Appendix D) and are summarized in Table 3 (Appendix C).

Functional Connectivity and Depression Severity

BDI-II was significantly correlated ($p < 0.05$) to functional connectivity between two ROI pairs: right dorsolateral prefrontal cortex to paracingulate gyrus and left dorsolateral prefrontal cortex to left inferior parietal lobule.

The right dorsolateral prefrontal cortex (RDLPFC) and paracingulate gyrus (PCG) are core nodes within the CEN. The average connectivity between these regions was $Z = 0.37$. There was a significant positive correlation between RDLPFC-PCG connectivity values and BDI-II scores ($r = 0.31$, $p < 0.05$). Higher depression severity was associated with greater connectivity between the RDLPFC and PCG (see Figure 2 in Appendix E).

The left dorsolateral prefrontal cortex (LDLPFC) is a core node of the CEN and the left inferior parietal lobule (LIPL) is a core node of the DMN. The average connectivity between these regions was $Z = 0.28$. There was a significant negative correlation between LDLPFC-PCG connectivity and BDI-II scores ($r = -0.26$, $p < 0.05$). Thus, higher depression severity was associated with less connectivity between the LDLPFC and LIPL (see Figure 3 in Appendix F)

The significant correlations between RDLPFC-PCG connectivity and LDLPFC-PCG connectivity with BDI-II were no longer significant after controlling for multiple comparisons using false discovery rate. The variables were carried forward in additional exploratory analyses given the limited amount of research on the role of CEN connectivity in the depression literature.

RDLPFC-PCG and LDLPFC-LIPL connectivity values were not significantly correlated with each other ($r = -0.22$, $p > 0.05$). Therefore, we included both variables as predictors of BDI-II in a single general linear model. The omnibus test was significant

($F(2, 56) = 4.33,\ p < .05$), but of the two predictors only RDLPFC-PCG was significant ($t(56) = 2.06,\ p < .05$). The model accounted for 13.4% of the variance in BDI-II scores ($R^2 = 0.134$). This pattern of results remained consistent when controlling for age, sex, and antidepressant medication status in separate models.

Functional Connectivity, Rumination, and Emotion Dysregulation

To reduce multiple comparisons, only the RDLPFC-PCG and LDLPFC-LIPL pairs were additionally correlated to RRS and DERS total scores and subscales. RDLPFC-PCG connectivity values were positively correlated to the RRS Reflection subscale ($r = 0.31$, $p < 0.05$), the DERS Non-Acceptance of Emotional Response subscale ($r = 0.29$, $p < 0.05$), and the DERS Impulse Control Difficulties subscale ($r = 0.28$, $p < 0.05$). RDLPFC-PCG connectivity values were negatively correlated to the DERS Difficulty Engaging in Goal Directed Behavior subscale ($r = -0.28$, $p < 0.05$).

Discussion

DMN, Depression, and Rumination

Two a priori hypotheses were proposed: first, that depression severity would exhibit significant positive correlation to functional connectivity within the DMN, and second, that ROI pairs within the DMN that demonstrate significant correlation to depression severity also would correlate to self-reported rumination. These hypotheses were based on previous ICA studies that found increased DMN connectivity is associated with depression diagnosis (e.g. Greicius et al., 2007; Guo et al., 2014; Li et al., 2013; Manoliu et al., 2014) and rumination (Hamilton et al., 2011; Zhu et al., 2012). No significant correlations between within-network DMN functional connectivity values and

BDI-II or RRS scores were observed in the present study. Thus, the a priori hypotheses were not supported.

Several factors may have accounted for the inability of the present study to replicate previous findings implicating the DMN in depression and rumination. First, the present study examined depression as a continuous measure whereas the majority of previous studies have compared individuals diagnosed with major depression to non-depressed controls (Brakowski et al., 2017; Mulders et al., 2015). Of the ICA studies that have tested the relationship between depression severity and resting-state connectivity (e.g. Coutinho et al., 2016; Guo et al., 2014; Li et al., 2013; Maoliu et al., 2014, Sexton et al., 2012; Veer et al., 2010), most tested this relationship only in participants who meet diagnostic criteria for a depressive disorder (Brakowski et al., 2017). Interestingly, although many studies have demonstrated differences in DMN connectivity between individuals diagnosed with depression and controls (Mulders et al., 2015) as well as associations between resting-state connectivity and depression severity (Brakowski et al., 2017), only one study has demonstrated a significant correlation between DMN connectivity and depression severity (Coutinho et al., 2016). It is possible that aberrant DMN connectivity may differentiate individuals with moderate to severe depression from non-depressed controls, yet not vary with depression severity on a granular level across the spectrum of severity.

Second, the present study operationalized functional connectivity using a different method from those of previous studies in this area. We employed a ROI-based approach to test connectivity between core nodes of the DMN, CEN, and SN both within and between the three networks. Functional connectivity was operationalized as the temporal

correlation between the average activation time series of two brain regions. Many previous studies in this area have utilized a network-based approach in which connectivity is operationalized as z-scores that represent the relative connectivity of each voxel within a network to the average connectivity of the whole network (e.g. Greicius et al., 2007; Manoliu et al., 2014). These two methods, both of which are valid approaches, each yield distinct outcomes and possible interpretations. The ROI method yields information about the connectivity between distinct brain regions both within and between networks, and the network method yields information about the connectivity of voxels within a specific network relative to the connectivity of the network as a whole. For example, Zhu et al. (2012) found a positive correlation between anterior DMN connectivity and rumination, but this analysis was precluded in the present study; connectivity was tested between pairs of ROI's and the DMN includes only one anterior ROI (i.e. medial prefrontal cortex).

Third, the present study examined young adults, the majority of whom were between the ages of 18 and 25 years. Most previous studies in this area examined adults who were on average at least 10 year older than our sample with greater variability in age across participants (e.g. Greicus et al., 2007; Li et al., 2013; Sexton et al., 2012; Manoliu et al., 2014; Veer et al., 2010). Because the brain and resting-state networks are still developing throughout young adulthood (Dosenbach et al., 2010), it is possible young adults may exhibit unique associations between depression severity and functional connectivity compared to older adults.

Functional Connectivity, Depression Severity, Rumination, and Emotion Dysregulation

The present study found connectivity of both the left and right DLPFC were related to depression severity. Although these findings did not survive correction for multiple comparisons, they are noteworthy given the extensive literature supporting the role of the DLPFC in depression (Chang et al., 2011; Grajny et al., 2016; Hamilton et al., 2012; Koenigs & Grafman, 2009). Bilateral DLPFC are core nodes of the CEN, and their functions are similar to those of the larger network, including executive processes such as working memory (Brunoni & Vanderhasselt, 2014), attention control (Kane & Engle, 2002), planning (Kaller, Rahm, Spreer, Weiller, & Unterrainer, 2010), and problem solving/reasoning (Kroger et al., 2002). The latter two functions are affected by depression (Fossati, Ergis, & Allilaire, 2002), and executive function has been shown to improve with successful treatment/remission of depression (Biringer et al., 2005; Moser et al., 2002). Moreover, the DLPFC is an effective target of transcranial magnetic stimulation treatment for depression (Baeken et al., 2014; Fox, Buckner, White, Greicius, & Pascual-Leone, 2012; Lefaucheur et al., 2014) and DLPFC connectivity has been shown to predict electroconvulsive treatment response (Van Waarde et al., 2015). The present findings, if replicated, would add to this growing body of literature by supporting DLPFC connectivity as a potentially useful predictor of individual differences in depression severity.

We found a positive correlation between depression severity and functional connectivity between the right DLPFC and paracingulate gyrus (PCG). This ROI pair represents within-network connectivity of the anterior CEN. As described above, the DLPFC is involved in a number of executive functions. The PCG is less studied but has been shown to be involved in theory of mind, which is defined as the ability to explain or

predict others' thoughts, feelings, or behavior based on the perception of their mental state (Gallagher & Frith, 2003). We speculate that hyperconnectivity between the right DLPFC and PCG may underlie deficits in executive functioning associated with social cognition that have been demonstrated in depression (Uekermann et al., 2008; Wolkenstein, Schönenberg, Schirm, & Hautzinger, 2011). Interestingly, RDLPFC-PCG connectivity was additionally positively correlated to reflective rumination, non-acceptance of emotional responses, and impulse control difficulties. Each of these behavioral patterns can be conceptualized as either an over- or under-utilization of an executive function; reflective rumination and non-acceptance of emotion can be thought of as extreme forms of mentalization, and impulsivity can be thought of as a deficit in inhibition. Overall, results of the present study are tentatively suggestive of increased connectivity within the anterior CEN, specifically between the right DLPFC and PCG, as a mechanism of depression, reflective rumination, non-acceptance of emotion, and impulsivity. More research is needed to replicate and increase confidence in these relations.

The result potentially implicating functional connectivity within the anterior CEN in depression is novel in the ICA literature. The only previous ICA study that examined the role of the CEN in depression found individuals with major depressive disorder, compared to controls, exhibited a distinct pattern of increased and decreased connectivity in the posterior CEN (Manoliu et al., 2014). Seed-based connectivity studies have had mixed findings, with some showing increased (Sheline et al., 2010; Zhou et al., 2010) and others showing decreased (Liston et al., 2014; Alexopoulos et al., 2012) CEN connectivity is associated with depression diagnosis. These inconsistencies in findings

may be due to differing methodologies between studies (Brakowski et al., 2017). More research using multiple methods to probe connectivity is needed to clarify the potential role of the anterior and posterior CEN in depression.

The present study also found depression severity was negatively correlated to connectivity between the left dorsolateral prefrontal cortex (LDLPFC) and the left inferior parietal lobule (LIPL). LDLPFC-LIPL connectivity was also negatively correlated to difficulties engaging in goal directed behavior. This ROI pair represents connectivity between the CEN and DMN. LDLPFC-LIPL connectivity was a less robust predictor of depression compared to RDLPFC-PCG connectivity in the present study, as the former was not a significant predictor of depression severity when both variables were included in a single general linear model. Nevertheless, this finding is in accord with existing literature. At least two previous studies have reported that decreased CEN-DMN connectivity is associated with depression (de Kwaasteniet et al., 2015; Manoliu et al., 2014). We note the present findings are most similar to those of de Kwaasteniet and colleagues (2015), who found individuals with treatment resistant depression, compared to both non-treatment resistant patients and healthy controls, had greatly reduced connectivity between the DLPFC and angular gyrus, which is a subcompnent of the IPL. It is possible DLPFC-IPL connectivity is a mechanism involved in treatment-resistant depression specifically, but the present study was not designed to differentiate between treatment responders and non-responders. This study adds to the literature by suggesting that reduced LDLPFC-LIPL connectivity may be a predictor of individual differences in depression severity as well as difficulties engaging in goal directed behavior.

Alternative Mechanisms

It is possible that alternative biological mechanisms may influence both depression as well as the observed differences in resting-state functional connectivity. For example, evidence suggests certain cardiovascular mechanisms, such as heart rate variability (HRV) and the baroreflex mechanism, may play a role in the link between depression and heart disease (Grippo & Johnson, 2002). Depressed individuals often exhibit decreased HRV compared to their non-depressed counter parts (Kemp et al., 2010; Koenig, Kemp, Beauchaine, Thayer, & Kaess, 2016), and some evidence suggests depressed individuals may also have attenuated baroreflex sensitivity (Broadley, Frenneaux, Moskvina, Jones, & Korszun, 2005). HRV has also been shown to affect resting-state functional connectivity in the brain. In a novel study, Chang and colleagues (2013) employed simultaneous cardiac and fMRI assessment to demonstrate connectivity of the anterior cingulate cortex and amygdala to regions such as the DLPFC, brainstem, and thalamus is affected by HRV oscillations. Thus, HRV and/or other cardiovascular processes may mediate the observed relationships between depression and functional connectivity in the brain.

Strengths and Limitations

The present study had several strengths. First, we examined resting-state functional connectivity as it relates to depression as a continuous construct. Although many studies have tested correlations between depression severity and functional connectivity, the vast majority have been limited in that they only tested this relationship in individuals who met DSM criteria for a depressive disorder. These studies have treated non-depressed "controls" as a categorically distinct group from individuals who meet criteria for a depressive disorder despite weak evidence for reliability of symptom-based

classification of depression (Regier et al., 2013). This study treated depression, rumination, and emotion dysregulation as continuous measures across the full sample of participants. The normal, unimodal distributions of depression severity, rumination, and emotion dysregulation in the present sample supported this approach, which allowed us to examine potential neural mechanisms associated with these constructs without a priori assumptions about the nature of the relationships.

To our knowledge, only two previous studies have examined the relationship between functional connectivity and depression severity as a continuous construct (Coutinho et al., 2016; Philippi, Motzkin, Pujana, & Koenigs et al., 2015). Both studies utilized distinct methods from each other and from the present study, precluding a direct comparison of results across studies. However, we note both previous studies examined depression severity only in the minimal to mild range. Thus, this is the first study to our knowledge to examine the association between functional connectivity and depression severity across the full range.

A second strength of the present study was the study of multiple behavioral constructs associated with depression in addition to depression severity. Rumination and emotion dysregulation are not diagnostic symptoms of depression, but these constructs are associated strongly to depression (Berking, Wirtz, Svaldi, & Hofmann, 2014; Nolen-Hoeksema, 2000) and may be informative to the understanding of distinct presentations of depression. The present study found two potential neural mechanisms associated with depression are each additionally associated with distinct patterns of rumination and emotion dysregulation. Anterior connectivity within the CEN between the right dosrolateral prefrontal cortex and paracingulate gyrus was associated with reflective

rumination, non-acceptance of emotional responses, and impulse control difficulties. Connectivity between the left dorsolateral prefrontal cortex (anterior CEN) and left inferior parietal lobule (posterior DMN) was associated with difficulty engaging in goal directed behavior. These findings suggest that specific behavioral patterns associated with depression may have distinct underlying neural mechanisms. If replicated, these findings could support these mechanisms as treatment targets for specific clinical presentations of depression.

Despite the heuristic value of the present findings to a growing literature on mechanisms of individual differences in depression and related constructs for the reasons described above, the present study is not without limitations. First, the observed correlations between resting-state functional connectivity and depression severity did not survive multiple comparison correction, and thus it is possible the findings are spurious. Second, the sample size, although larger than many previous studies in this area, is relatively small in an absolute sense and may have lacked power to detect some associations. Third, we restricted our analyses to three a priori neural networks. Although there is strong scientific premise to hypothesize the DMN, CEN, and SN are implicated in depression (Kaiser et al., 2015; Mulders et al., 2015; Wang, Öngür, Auerbach, & Yao, 2016) focusing on these networks precluded our ability to replicate findings implicating other neural networks in depression (e.g. Veer et al., 2010). Fourth, by taking the absolute values of connectivity scores, the present study was unable to differentiate between correlations and anticorrelations between brain areas. This distinction and its implication for the nature of neural mechanisms is complex and outside the scope of this study.

However, this is an important area of future research, and many functional connectivity studies in depression do not address it.

Summary and Future Directions

The present study sought to examine resting-state functional connectivity within and between the default mode network, central executive network, and the salience network across individuals who had a wide range of depression severity with the goal of identifying neural mechanisms associated with depression severity and related constructs. Findings suggest connectivity between the right dorsolateral prefrontal cortex and paracingulate gyrus (CEN within-network connectivity) and connectivity between the left dorsolateral prefrontal cortex and left inferior parietal lobule (CEN-DMN between-network connectivity) may be predictors of individual differences in depression severity. General linear modeling controlling for age, sex, and antidepressant status suggest the former predictor may be more robust. These results are generally supported by existing literature. These findings should be interpreted with caution, however, given that they did not pass FDR correction for multiple comparisons. Interestingly, each predictor was associated with a distinct pattern of transdiagnostic behavioral constructs. CEN within-network connectivity was associated with reflective rumination, non-acceptance of emotional responses, and impulse control difficulties, and CEN-DMN between network connectivity was associated with difficulties engaging in goal directed behavior. If replicated, these results could add knowledge about how resting-state functional connectivity varies with depression severity and related transdiagnostic constructs and could inform new targets for treatment of specific presentations of depression.

Future directions of this research will include analytic approaches that reduce the number of multiple comparisons. For example, network homogeneity analysis (Uddin et al., 2008) that yields a single functional connectivity score for each network of interest rather than for each voxel or ROI within the networks is an alternative approach that reduces multiple comparisons substantially. In addition, examining how the DMN, CEN, and SN interact at the network level could complement the ROI-level relations observed in the present study. If the present findings are replicated, additional research could examine if functional connectivity between the reported brain areas mediates the relationships between depression, rumination, and emotion dysregulation variables. Potential mediation by cardiovascular processes can also be explored, as this study employed simultaneous fMRI, electrocardiogram, blood pressure, and respiration assessment. Lastly, research is needed to explore potential differences between correlations and anticorrelations between brain areas as distinct mechanisms underlying depression and related constructs.

Appendix A

Table 1

Sample Demographics

Characteristic	n	Percent
Gender		
Females	44	74.58%
Males	15	25.42%
Race		
Asian	24	40.68%
White	20	33.90%
Black	8	13.56%
Other	7	11.86%
Ethnicity		
Hispanic	10	16.95%
Non-Hispanic	49	83.05%
	Range	Mean (SD)
Age (in years)	18 - 28	20.66 (2.04)

Notes: Gender, race, ethnicity, and age characteristics of the sample after exclusions for excessive motion. Total n = 59.

Appendix B

Table 2

Self-Report Measures

Scale	Description	n	Range	Mean (SD)
BDI-II	Depression Severity	59	0 – 59	20.49 (10.67)
RRS	Rumination Total	54	27 – 80	53.15 (13.01)
RRS_D	Depression	54	14 – 46	30.15 (8.02)
RRS_B	Brooding	54	6 – 18	12.06 (3.12)
RRS_R	Reflection	54	5 – 20	10.94 (3.81)
DERS	Difficulties in Emotional Regulation Total	56	53 – 146	89.88 (23.76)
DERS_N	Non-Acceptance of Emotional Response	56	6 – 26	14.55 (5.88)
DERS_G	Difficulties Engaging in Goal Directed Behavior	56	5 – 24	15.13 (4.29)
DERS_I	Impulse Control Difficulties	56	6 – 29	12.41 (5.61)
DERS_A	Lack of Emotional Awareness	56	7 – 30	15.89 (5.56)
DERS_S	Limited Access to Emotion Regulation Strategies	56	8 – 24	19.64 (7.09)
DERS_C	Lack of Emotional Clarity	56	6 – 24	12.25 (4.42)

Notes: Univariate statistics of self-report measures. All variables were normally distributed. RRS data for n = 5 participants were missing, and DERS data for n = 3 participants were missing.

Appendix C

Table 3

Resting-State Network Anatomy and Coordinates

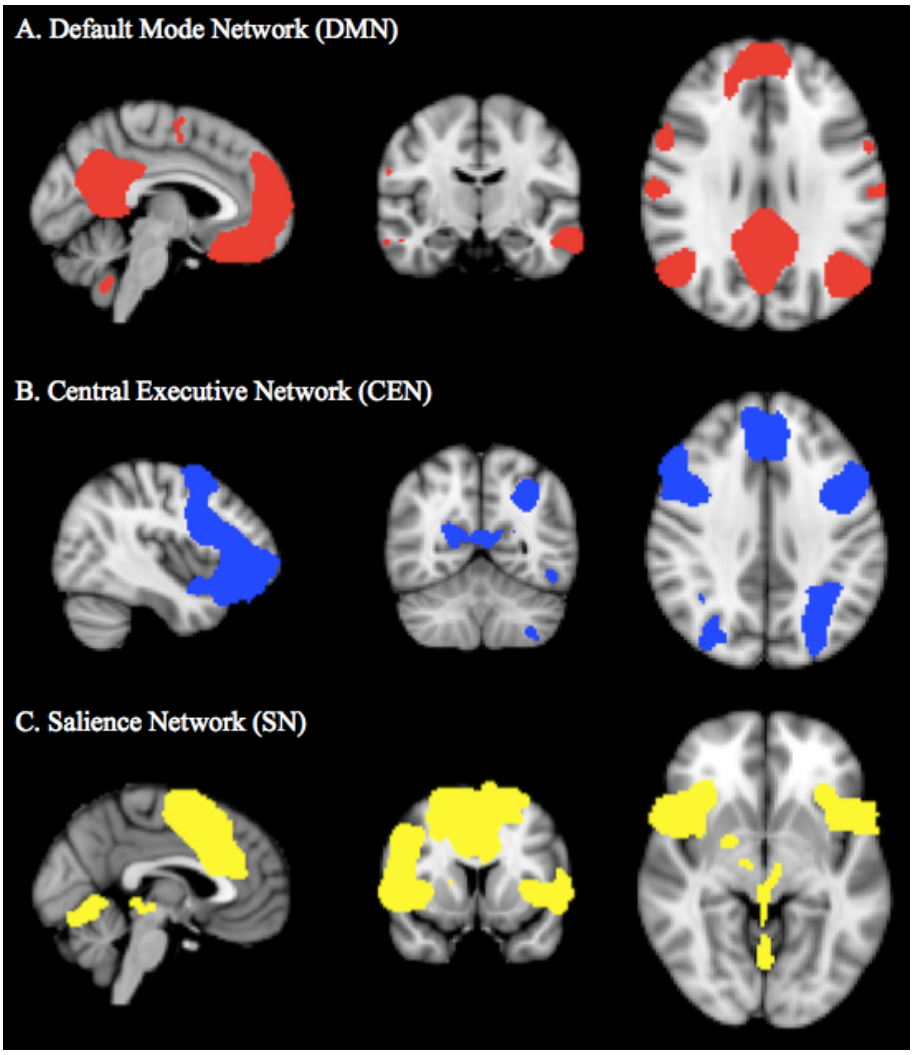
Network/ROI	Cluster Size	x	y	z
Default Mode Network (DMN)				
Medial Prefrontal Cortex	4690	0	44	-18
Posterior Cingulate Cortex	3037	2	-56	26
Left Inferior Parietal Lobule	925	-46	-68	30
Right Inferior Parietal Lobule	326	52	-64	32
Central Executive Network (CEN)				
Left Dorsolateral Prefrontal Cortex	7551	-46	26	16
Right Dorsolateral Prefrontal Cortex	6762	52	26	20
Paracingulate Gyrus	1531	4	24	46
Left Posterior Parietal Cortex	1097	-32	-58	40
Right Posterior Parietal Cortex	177	34	-72	34
Salience Network (SN)				
Anterior Cingulate Gyrus	8504	2	16	38
Right Insula	1208	38	16	2
Left Insula	676	-38	12	0
Right Middle Frontal Gyrus	539	32	44	18
Left Middle Frontal Gyrus	145	-30	50	16

Notes: Cluster size is reported in number of voxels. Coordinates are reported in MNI standard space.

Appendix D

Figure 1

Resting-State Networks: The Triple Network Model



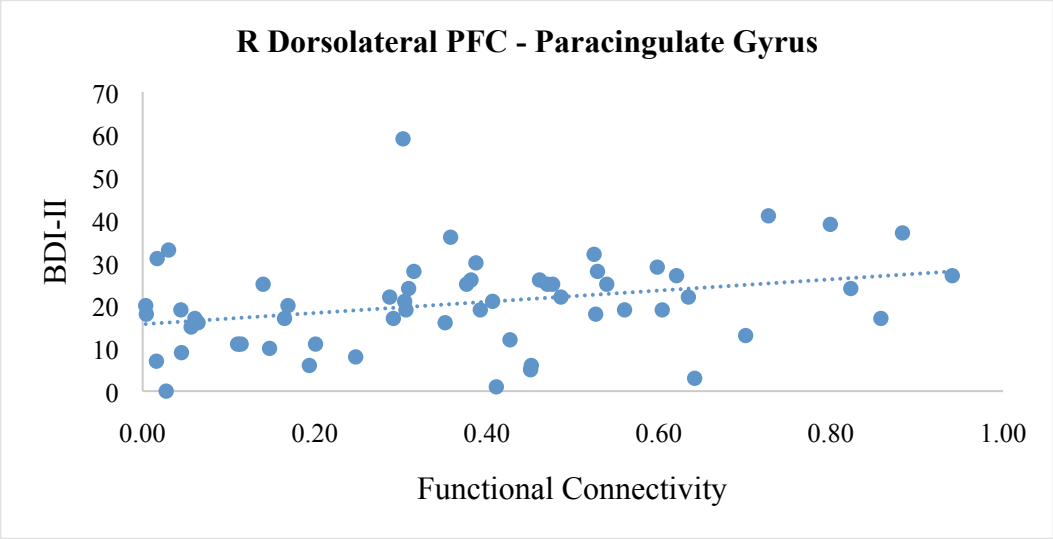
Notes: Thresholded images of the DMN, CEN, and SN in sagittal, coronal, and axial views. Each network is shown at a distinct set of MNI coordinates reported by Menon (2011) to facilitate direct visual comparison of the networks between studies. A. DMN is pictured at x = 42, y = -58, z = 36. Core regions include medial prefrontal cortex,

posterior cingulate cortex, and bilateral inferior parietal lobule; B. CEN is pictured at x = -2, y = 10, z = -6. Core regions include bilateral dorsolateral prefrontal cortex, paracingulate gyrus, and bilateral posterior parietal cortex; C. SN is pictured at x = -4, y = -12, z = 28. Core regions include anterior cingulate gyrus, bilateral insula, and bilateral middle frontal gyrus

Appendix E

Figure 2

Correlation Between Depression Severity and RDLPFC-PCG Connectivity Values

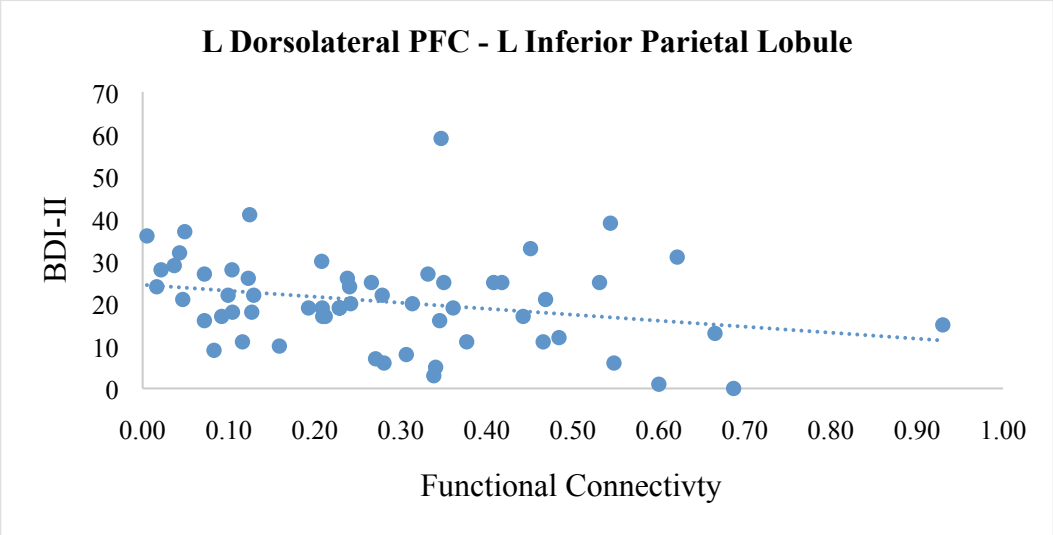


Notes: Positive correlation between BDI-II scores and RDLPFC-PCG connectivity values ($r = 0.31$; $p < 0.05$). This relationship was no longer significant after false discovery rate correction for multiple comparisons.

Appendix F

Figure 3

Correlation Between Depression Severity and LDLPFC-LIPL Connectivity Values



Notes: Negative correlation between BDI-II scores and LDLPFC-LIPL connectivity values (r = -0.26; $p < 0.05$). This relationship was no longer significant after false discovery rate correction for multiple comparisons.

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