THE RELATIONSHIP BETWEEN THE DEFAULT MODE RESTING STATE NEURAL NETWORK, RESPIRATORY SINUS ARRHYTHMIA, AND SELF-FOCUSED COGNITION: AN EMPIRICAL ANALYSIS

By

Victoria Bruno Egizio

B.S., Psychology, Dominican University, 2006

M.S., Psychology, University of Pittsburgh, 2008

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This dissertation was presented

by

Victoria Bruno Egizio

It was defended on

May 27, 2011

and approved by

Stephen Manuck, PhD, Distinguished University Professor of Health Psychology and Behavioral Medicine, Department of Psychology

Anna Marsland, PhD, RN, Associate Professor, Department of Psychology

Peter Gianaros, PhD, Associate Professor, Department of Psychology

Kirk Erickson, PhD, Assistant Professor, Department of Psychology

Dissertation Director: J. Richard Jennings, PhD, Professor, Departments of Psychiatry and Psychology

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Functional activity within the default mode resting state neural network (RSNN) and the resting respiratory sinus arrhythmia (RSA) may represent an integrated neural and peripheral cardiovascular index of the baseline, resting state in humans. Research also indicates that the integrated physiological baseline potentially formed by the default mode RSNN and resting RSA may be associated with self-focused cognition. We hypothesize that measures of default mode RSNN (namely functional connectivity strength), resting RSA, and self-focused cognition are, indeed, correlated and aim to demonstrate these relationships. Measures of default mode RSNN functional connectivity strength were derived using functional magnetic resonance imaging, measures of resting RSA were obtained via electrocardiogram, and self-focused cognition was assessed using survey methods. Although our results were largely unsupportive of our hypothesis, we present several possibly methodological confounds that may have impacted our findings, and we describe directions for future research.

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1.0 INTRODUCTION

Functional activity within the default mode resting state neural network (RSNN) and the resting respiratory sinus arrhythmia (RSA) may represent an integrated neural and peripheral cardiovascular index of the baseline, resting, tonic state in humans. The default mode RSNN is a set of brain regions that are more active during resting neuroimaging protocols than they are while participants complete experimental tasks. RSA is commonly defined as the rhythmic fluctuation in heart rate at the respiratory frequency. Notably, both the default mode RSNN and RSA are primarily associated with resting, minimally-aroused, waking bodily states (i.e. the baseline state), and the activity of both is typically down-regulated when environmental demands (e.g. the completion of laboratory tasks) are made upon an individual. This joint association suggests that the coordinated activity of the default mode RSNN and resting RSA may form an integrated psychophysiological baseline.

The potential mechanistic pathway linking the activity of the default mode RSNN and resting RSA is one of neural co-activation. Specifically, many of the brain regions that comprise the default mode RSNN are also each separately associated with the generation of RSA. This common neural basis between the default mode RSNN and resting RSA may form a mechanistic pathway coordinating their activity. Research also indicates that the integrated physiological baseline potentially formed by the default mode RSNN and resting RSA may serve various functional purposes, perhaps relevant to psychological functioning, going beyond simple inactivity. An emerging body of research suggests that the default mode RSNN and resting RSA

are each associated with self-focused, or self-reflective, cognition. Thus, brain regional co-activation may commonly underlie and coordinate activity within the default mode RSNN, RSA levels, and self-focused cognition.

In order to set the stage for future research examining the relationship between the default mode RSNN and resting RSA, initial research needs to empirically demonstrate that measures of default mode RSNN, namely functional connectivity strength, and resting RSA are, indeed, correlated. As such, the primary goal of the current study is to establish that functional connectivity strength within the default mode RSNN varies in association with RSA levels. It is hypothesized that this will be the case. To probe the possible psychological implications of this association, the current study also aims to assess 1) whether functional connectivity strength within the default mode RSNN varies in association with one's level of self-focused cognition and 2) whether activity within the default mode RSNN commonly covaries with RSA and self-focused cognition. This second set of analyses regarding psychological function is largely exploratory, given the limited prior research in this area. The current research proposal will take the following form. First, definitions describing the criteria used to define the default mode RSNN and resting RSA, two rather complex constructs, will be presented. Second, the common neural substrates potentially linking the default mode RSNN and resting RSA will be discussed. Third, the potential functional purposes of an integrated default mode RSNN and RSA will be discussed, with a particular focus on self-focused cognition, as it has garnered the most empirical support. And, finally, the specific aims guiding the proposed research will be presented.

1.1 DEFINITIONS

1.1.1 Default mode RSNN

The definition of the default mode RSNN includes four criteria. The first criterion is that the default mode RSNN is a set of brain regions that are more active during resting neuroimaging protocols than they are while participants complete experimental tasks. Resting neuroimaging protocols require that conscious participants lie in a scanner (with their eyes open, closed, or viewing a fixation point) and passively think, letting their minds wander without focusing on anything in particular (Auer, 2008). Participants must be awake and non-anesthetized during the resting neuroimaging protocol as research suggests that functional connectivity among brain regions implicated in the default mode RSNN is attenuated during sleep and medical sedation (Greicius, et al., 2008; Horovitz, et al., 2009; Horovitz, et al., 2008). The second criterion is that the brain regions implicated in the default mode RSNN exhibit a uniform oxygen extraction fraction (OEF) during resting neuroimaging protocols. The OEF is a metabolic ratio representing the balance between oxygen delivery to brain regions (i.e. blood flow) and oxygen consumption or extraction (Raichle & Gusnard, 2002; Raichle & Snyder, 2007). A uniform OEF suggests that brain regions are in a metabolic state inconsistent with task-evoked neural activation and, perhaps, more indicative of on-going, task-independent neural activity (Raichle, 2003; Raichle & Gusnard, 2002, 2005). The OEF is the gold-standard for verifying that brain regions are in a resting state and can only be obtained using positron emission tomography (PET). Since PET is an imaging method high in cost and participant burden, most studies of the default mode RSNN have used functional magnetic resonance imaging (fMRI) instead, consequently failing to satisfy this criterion. Many investigators have waived this criterion for such pragmatic reasons. For the purposes of the current investigation, it will be considered a criterion that is optimal, but less

necessary, to meet. The third criterion is that the default mode RSNN include the following brain regions: the pACC (Brodmann Areas (BAs) 24, 25, 32), VPMFC (BAs 10, 11), and the PCC (BAs 23, 31). Based on our review of the literature, these brain regions are those most reliably associated with the default mode RSNN. The fourth criterion is that the component brain regions of the default mode RSNN exhibit inter-correlated activity or functional connectivity. Among the most common analytic methods for generating such functional connectivity are the seed region analysis approach and independent component analysis. Briefly, seed region analyses involve extracting time series data from a seed region, or a particular voxel(s) that corresponds to a brain region, of interest (Buxton, 2007). Correlation maps correlating the activity of the seed region with activity in other voxels throughout the brain, sometimes chosen a priori, can be generated. Seed region activity can also be entered as the independent variable in regression models predicting activity in other voxels throughout the brain (Margulies, et al., 2007; Roy, et al., 2009). Independent component analysis (ICA) is a statistical method used to separate a multivariate signal into its additive sub-components (McKeown, et al., 1998; McKeown & Sejnowski, 1998). By maximizing the statistical independence of the signal sub-components, ICA ultimately identifies the independent components. ICA has been described as an extension of factor analysis (McKeown, et al., 1998). Many ICA algorithms have been published and are in common use (e.g. infomax and FastICA) (McKeown & Sejnowski, 1998). In terms of resting neuroimaging protocols, an ICA algorithm is typically applied to data representing the time-courses of all brain voxels. The algorithm isolates independent components, or sets of voxels that each have time-courses independent of each other. For example, perhaps activity in voxels corresponding to the amygdala, VMPFC, and insula shares a similar time-course, forming one component, while activity in voxels corresponding to the hypothalamus and pACC shares a

separate time-course, forming another component. Each component is interpreted as representing a neural network (Birn, Diamond, Smith, & Bandettini, 2006). Research indicates that measures of functional connectivity within the default mode RSNN are rather robust and show test-retest reliability (Damoiseaux, et al., 2006; Van Dijk, et al., 2009).

Despite the utility of the definition provided above, it is important to acknowledge the inherent difficulty of studying the functional purpose of the default mode RSNN, a *resting* neural state that one might assume has limited, if any, observable functionality. This point is worth noting at the outset because one of the aims of the current study is to assess the functional correlates of the default mode RSNN. While researchers suggest that learning more about the functional purpose of the default mode RSNN may help us to understand neuronal dynamics and evoked neural responses, questions remain about the best manner in which to behaviorally study resting neural states since rest is, by definition, the absence of activity (Friston, 2009; Morcom & Fletcher, 2007; Raichle & Snyder, 2007). Researchers have fallen into two camps on this issue. One camp asserts that resting neural states are not amenable to controlled experimental study and that the type of cognition occurring at rest is intractable (Morcom & Fletcher, 2007). Because any attempted assessment of resting activity disrupts it, resting neural states are not assessable and should not be studied in their own right (Morcom & Fletcher, 2007). Another camp, conversely, advocates the study of resting neural states. They suggest that identifying controllable experimental manipulations that affect activity in brain regions implicated in RSNNs helps researchers to infer what types of cognitive processes those brain regions may support at rest (Morcom & Fletcher, 2007; Raichle & Snyder, 2007). Admittedly, this method is somewhat circular and relies on the assumption that consistency exists between anatomical brain structures and their functions regardless of mental state, an assumption that is not always valid (Poldrack, Halchenko, & Hanson, 2009). While results obtained using this method should be interpreted cautiously, it appears to be the most viable option for studying the potential

functional purposes of the default mode RSNN, given current neuroimaging techniques. The research presented in subsequent sections should be considered in light of this interpretative caveat. That said, the definition of the default mode RSNN was presented above in order to establish a standard within this research area. The fact that *three* criteria should be met in order to appropriately study the default mode RSNN helps to ensure more reliable, repeatable results.

1.1.2 Resting RSA

As previously stated, RSA is the rhythmic fluctuation in heart rate at the respiratory frequency. It arises primarily from the regulation of efferent vagus nerve activity by the central respiratory drive, a brainstem respiratory pattern generator, in a process known as "respiratory-gating" (Berntson, et al., 1997; Berntson, Cacioppo, & Quigley, 1993; Eckberg, 2003; Houtveen, Rietveld, & de Geus, 2002). Respiratory gating of vagal efferents results in inhibition of their activity during inspiration and dis-inhibition of their activity during expiration. Thus, vagal efferents' release of acetylcholine at the sino-atrial node of the heart during inspiration is suppressed, allowing heart rate to increase; the opposite happens during expiration. This mechanism contributes to the generation of RSA, a phenomenon that likely supports optimal pulmonary gas exchange by matching perfusion of blood to ventilation (Yasuma & Hayano, 2004).

Resting levels of RSA should be assessed either in a laboratory setting (with participants seated) or, more optimally, during a resting neuroimaging protocol such that measures of RSA and default mode RSNN activity are concurrent. In either setting, conscious participants should be instructed to passively think, letting their minds wander without focusing on anything in particular. A variety of RSA quantification techniques have been developed and their guidelines have been presented by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology Task Force (1996) and the *Psychophysiology* Committee Report on RSA (1997). These quantitative indices of RSA are commonly used in both experimental and correlational studies of cardiac vagal activity in humans.

All quantitative RSA indices are derived from continuous electrocardiogram (ECG) recordings. The two most prominent categories of quantification techniques are time-domain methods and frequency-domain methods. While only frequency-domain methods will be employed in the current research protocol, both methods will be described here to provide context.

Time-domain methods are simpler to perform and can assess heart rate at any point in time or in intervals between successive, so-called “normal” QRS complexes ("Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996). These reciprocals of heart rate are used in the quantification of various time-domain indices of RSA such as the number of interval differences of successive normal-to-normal (NN) intervals greater than 50 milliseconds (NN50), the proportion derived by dividing NN50 by the total number of NN intervals (PNN50), the mean of successive differences in NN intervals (MSD), the mean square successive difference (MSSD), and the square root of the mean of squared successive differences between NN intervals (RMSSD) (J. J. Allen, Chambers, & Towers, 2007; Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996). Other time-domain methods of RSA quantification include the peak-to-valley/peak-to-trough statistic, a breath-by-breath index of heart rate fluctuations that reflects the difference between the longest and the shortest heart rates within a given respiratory cycle, and the Porges’ adaptive polynomial filter method (J. J. Allen, et al., 2007; Berntson, et al., 1997; Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996). All time-domain indices measure short-term variations in heart rate that are of a high, respiratory-linked frequency; the RSA values that these quantification techniques produce are all highly correlated

(J. J. Allen, et al., 2007; Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996).

The other category of RSA quantification techniques is frequency-domain methods; these are the methods that will be employed in the proposed research. Spectral methods decompose the total variation of electrocardiogram-recorded data into frequency components; spectral power for particular frequency bands is quantified by deriving the area under the spectral density function within the particular frequency range (Berntson, et al., 1997). The most common spectral analysis methods are fast Fourier transform (a non-parametric method that utilizes an algorithm on an a priori basis to estimate the best fit of a sine wave to ECG-derived data) and autoregressive modeling (a parametric method that determines model fit using the ECG-derived data alone) ("Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996). The frequency bands most commonly studied include the very low frequency (0.003-0.04 Hz), the low frequency (0.04-0.15 Hz), and the high frequency (0.15-0.40 Hz) ("Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996). The high frequency band is at the respiratory frequency and is considered to reflect RSA; the power spectral components corresponding to this band are often referred to as indexing high-frequency heart rate variability (HF-HRV) (Berntson, et al., 1997). Overall, there are several quantitative indices of RSA. Not only are RSA values produced by the various time-domain indices inter-correlated, time-domain-derived RSA values are typically highly correlated with HF-HRV (J. J. Allen, et al., 2007; Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996).

Both the Task Force and the *Psychophysiology* Committee have presented general considerations that should guide proper ECG recording and processing prior to the quantification of RSA using either time or frequency-domain methods. Regarding ECG recording, heart rate variability often increases with the length of the recording. Thus, recording periods should not be unnecessarily prolonged. At least 1 minute of continuous ECG recording is needed for accurate quantification of HF-HRV, specifically. Finally, it is also recommended that the ECG be sampled at 500-1000 Hz. Regarding ECG processing, the data should be assessed for artifacts prior to RSA quantification. Specific attention should be paid to the presence of ectopic beats, arrhythmias, missing data, and noise; methods for addressing these variables are detailed in Berntson and colleagues (1997).

The psychophysiological research community has primarily become interested in the quantitative measures of RSA described above as indices of cardiac vagal activity. Indeed, studies employing vagal (muscarinic receptor) and/or sympathetic (beta-adrenergic) pharmacological blockades have shown that the autonomic contributions to both time and frequency-domain-derived indices of RSA are predominantly vagal in nature (Berntson, et al., 1997; Berntson, et al., 1993; Denver, Reed, & Porges, 2007; Grossman, Karemaker, & Wieling, 1991; Grossman & Kollai, 1993; Grossman, Stemmler, & Meinhardt, 1990; Grossman & Taylor, 2007; Martinmaki, Rusko, Kooistra, Kettunen, & Saalasti, 2006; Medigue, et al., 2001; Penttila, et al., 2001; Pyetan, Toledo, Zoran, & Akselrod, 2003). These studies also show that complete vagal blockades typically reduce quantitative measures of RSA by upwards of 90%, often completely eliminating them; the effects of blockade share a dose-related function with RSA. As such, the quantification of RSA using these time and frequency-domain methods appears to be a valid means of analyzing cardiac vagal activity. HF-HRV, in particular, has become the RSA measure of choice for many researchers and has stronger predictive validity with a wider range of psychological and physiological variables than do time-domain measures of RSA (J. J. Allen, et al., 2007; Denver, et al., 2007).

2.0 MECHANISTIC PATHWAY LINKING THE DEFAULT MODE RSNN AND RESTING RSA

2.1 COMMON NEURAL BASIS SHARED BETWEEN THE DEFAULT MODE RSNN AND RESTING RSA

There is a significant amount of literature detailing the brain regions implicated in each the default mode RSNN and in resting RSA. The following section details this literature and also examines which brain regions, in particular, are implicated in both the default mode RSNN and resting RSA. These overlapping brain regions likely support co-activated, potentially coordinated, activity of the default mode RSNN and RSA, helping them to form an integrated psychophysiological baseline.

2.1.1 Brain regions implicated in the default mode RSNN

Based on our review of the literature, there are several brain regions consistently associated with the default mode RSNN across studies: the bilateral hypothalamus, pACC, VMPFC, insula, cerebellum, PCC, precuneus, retrosplenial cortex, the temporoparietal junction, and the brainstem (containing the nucleus of the tractus solitarius (NTS); current neuroimaging spatial resolution precludes the isolation of such small structures as the NTS proper. As such, changes in brainstem activity are likely imprecise indicators of NTS activity). (Birn, et al., 2006; R. L. Bluhm, et al., 2007; R. L. Bluhm, et al., 2008a; D'Argembeau, et al., 2005; Damoiseaux, et al., 2006; Esposito, et al., 2008; Fransson, 2005, 2006; Fransson & Marrelec, 2008; Greicius, Krasnow, Reiss, & Menon, 2003b; Greicius, Supekar, Menon, & Dougherty, 2009; Harrison, Pujol, et al., 2008b; Harrison,

Pujol, Ortiz, et al., 2008; Harrison, Yucel, Pujol, & Pantelis, 2007; Kennedy & Courchesne, 2008; Long, et al., 2008; Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007; Mazoyer, et al., 2001; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Thomason, et al., 2008; Tian, et al., 2008; van Buuren, et al., 2009; van den Heuvel, Mandl, & Hulshoff Pol, 2008; Waites, Stanislavsky, Abbott, & Jackson, 2005; C. Yan, et al., 2009; Zhao, et al., 2007; Zhong, et al., 2009; Zhou, et al., 2009). These brain regions are implicated in the default mode RSNN regardless of 1) the type of resting state protocol (eyes-closed, eyes-open, eyes-open/fixation) used and 2) the functional connectivity analytic technique used. Moreover, several studies report that the functional connectivity among brain regions forming the default mode RSNN is, in general, moderately reliable ($r = 0.69$) when examined within subjects (Damoiseaux, et al., 2006; Honey, et al., 2009; Meindl, et al., 2009; Shehzad, et al., 2009; Van Dijk, et al., 2010). The studies cited in this section all defined the default mode RSNN in keeping with the guidelines presented previously. Finally, as a *brief* primer, the purported physiological and psychological functions of the brain regions implicated in the default mode RSNN are listed in Table 1 (Barbas, Saha, Rempel-Clower, & Ghashghaei, 2003; Bush, Luu, & Posner, 2000; Cavanna, 2007; Cavanna & Trimble, 2006; Dalgleish, 2004; Damasio, 1996; Damoiseaux, et al., 2006; Decety & Lamm, 2007; Devinsky, Morrell, & Vogt, 1995; Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Guyton & Hall, 2005; Miller & Cohen, 2001; Phillips, Drevets, Rauch, & Lane, 2003a, 2003b; Pothuizen, Aggleton, & Vann, 2008; Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007; Svoboda, McKinnon, & Levine, 2006; Vogt & Laureys, 2005; Vogt, Vogt, & Laureys, 2006).

Table 1 Functions of Key Brain Regions

Default Mode Resting State Neural Network Brain Region	*Functions*
Brainstem (medulla oblongata, pons, and midbrain)	Basic, life-sustaining functions (autonomic control, motor behavior, respiration, alertness, consciousness, and the sleep-wake cycle); relays information between visceral and higher-order brain regions *Key Reference: Guyton & Hall, 2005*
Hypothalamus	Autonomic control, hormonal control, hunger, thirst, body temperature, fatigue, and the sleep-wake cycle *Key References: Dalgleish, 2004; Guyton & Hall, 2005*
Perigenual Anterior Cingulate Cortex	Processes affective and motivational information and affects autonomic and endocrine function *Key References: Bush, Luu, & Posner, 2000; Dalgleish, 2004; Devinsky, Morrell, & Vogt, 1995; Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Miller & Cohen, 2001; Phillips, Drevets, Rauch, & Lane, 2003; Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007*

Table 1 (continued)

Default Mode Resting State Neural Network Brain Region	*Functions*
Ventro-medial Prefrontal Cortex	Integrates bodily feedback with emotional processing, decision-making, and memory; controls cognitive and behavioral inhibition and disinhibition; involved in autonomic function *Key References: Barbas, 2000 & 2007; Dalgleish, 2004; Damasio, 1996; Miller & Cohen, 2001*
Insula	Generates affective states in response to emotional stimuli; involved in interoception of bodily states, empathy, and bodily self-awareness *Key References: Guyton & Hall, 2005; Phillips, Drevets, Rauch, & Lane, 2003*
Cerebellum	Autonomic regulation, autobiographical memory, and, more primarily, motor control *Key References: Guyton & Hall, 2005; Svoboda, KcKinnon, & Levine, 2006*
PCC	Autobiographical memory, emotional processing, consciousness, and self-reflection *Key References: Svoboda, KcKinnon, & Levine, 2006; Vogt & Laureys, 2005; Vogt, Vogt, & Laureys, 2006*

Table 1 (continued)

Default Mode Resting State Neural Network Brain Region	*Functions*
Precuneus	Consciousness, autobiographical memory, and visuo-spatial imagery and memory, episodic memory retrieval, and self-referential processing *Key References: Cavanna, 2007; Cavanna & Trimble, 2006; Svoboda, KcKinnon, & Levine, 2006; Pothuizen, Aggleton, & Vann 2008; Vogt, Vogt, & Laureys, 2006; Vogt & Laureys, 2005*
Retrosplenial Cortex	Consciousness, autobiographical memory, and visuo-spatial imagery and memory *Key References: Cavanna, 2007; Cavanna & Trimble, 2006; Svoboda, KcKinnon, & Levine, 2006; Pothuizen, Aggleton, & Vann 2008; Vogt, Vogt, & Laureys, 2006; Vogt & Laureys, 2005*
Temporoparietal Junction	Generates self-other distinctions, empathy, and motivation *Key References: Decety & Lamm, 2007*

2.1.2 Brain regions implicated in resting RSA

To determine which brain regions are implicated in RSA, we first examined neuroanatomical and neurophysiological animal studies. Based on this literature, it appears that the nucleus of the tractus solitarius (NTS), parabrachial nucleus of the pons, various hypothalamic nuclei, periaqueductal gray, central nucleus of the amygdala, the insula, pACC, VMPFC, and the cerebellum are regions of interest (Baklavadzhyan, et al., 2000; Bannister & Mathias, 1992; Benarroch, 1997; Cechetto, 1994; Dampney, 1994; Devinsky, et al., 1995; Groenewegen & Uylings, 2000; Loewy & McKellar, 1980; Loewy & Spyer, 1990; Neafsey, 1990; Nisimaru, 2004; Ongur & Price, 2000; Oppenheimer, Gelb, Girvin, & Hachinski, 1992; Resstel & Correa, 2006; Ter Horst & Postema, 1997; Van Eden & Buijs, 2000; Verberne & Owens, 1998; Vogt & Gabriel, 1993; Waites, et al., 2005). These brain regions each have direct and/or indirect connections with preganglionic vagal efferents and all appear to influence cardiovascular function when stimulated or lesioned. Although these brain regions likely influence cardiovascular function through vagal pathways, sympathetic pathways cannot be completely ruled out since each brain region also shares connections with sympathetic neurons. Generally, the literature is such that directional relationships between activity in these brain regions and increases or decreases in cardiac activity remain unclear (Loewy & Spyer, 1990). Acknowledging the limitations of the current literature, these brain regions remain the most likely set of candidate regions involved in generating RSA.

Referencing human neuroimaging studies, it appears that RSA (quantified as HF-HRV) may be positively associated with left insula, left amygdala-hippocampal complex, right cerebellum, bilateral pACC, and bilateral VMPFC activity. A total of eight studies have examined RSA in neuroimaging protocols involving community samples of adult participants. Of these studies, six assessed changes in RSA associated with effortful cognitive tasks (e.g. the Stroop task, memory tasks, and serial subtraction tasks) while two studies examined changes in RSA that were

associated with emotion induction tasks. No empirical research examining the relationship between resting RSA and brain functional activity assessed by neuroimaging has been conducted, to our knowledge. Thus, the proposed research will rely on inferences drawn from this task-related work. To begin with the studies of RSA in the context of effortful cognitive tasks, some studies have compared RSA and neural activity each assessed during resting baseline or control conditions to RSA and neural activity each assessed during effortful cognitive task conditions (Gianaros, Van Der Veen, & Jennings, 2004; Shapiro, et al., 2000). Of such studies, Shapiro and colleagues did not report significant associations between RSA and neural activity in a small sample of men. However, Gianaros and colleagues found that increases in RSA from control to effortful task conditions were positively associated with right cerebellum activity while decreases in RSA were positively associated with left insula, left amygdala-hippocampal complex, and right VMPFC activity. These results held in both hypertensive versus normotensive and male versus female sub-sets of a large participant sample.

Complementing the above findings are others from studies that examined the *correlation* between levels of RSA and neural activity *during* effortful cognitive tasks. While one study did not find associations between levels of RSA and neural activity within the set of brain regions previously shown to be involved in RSA in animals (Neumann, Lawrence, Jennings, Ferrell, & Manuck, 2005), other studies reported positive associations between RSA and activity in the right cerebellum (Critchley, et al., 2003) and the left pACC (Critchley, et al., 2003; Matthews, Paulus, Simmons, Nelesen, & Dimsdale, 2004), right pACC, and bilateral VMPFC (Ahs, Sollers, Furmark, Fredrikson, & Thayer, 2009). In sum, comparing across all studies that examined the association between RSA and neural activity in the context of effortful cognitive tasks, it appears that positive associations exist between RSA and activity in the left insula, left amygdala-hippocampal complex, right cerebellum, bilateral pACC, and bilateral VMPFC. There are many methodological differences between these studies (e.g. whether RSA and neural activity were assessed concurrently, variations in the type of neuroimaging methods-such as the use of

positron emission tomography as versus functional magnetic resonance imaging-or experimental protocols used). It is possible that inconsistencies in results between studies arose from these many methodological differences, although no specific patterns were evident.

In addition to the studies that examined the association between RSA and neural activity in the context of effortful cognitive tasks, two studies examined changes in these variables associated with emotion induction tasks. The first of these studies included a sample of participants who lost a first degree relative in the past year and examined RSA and neural activity in response to grief-eliciting photos and words (O'Connor, Gundel, McRae, & Lane, 2007). The authors reported no associations between levels of RSA and neural activity within the set of brain regions previously shown to be involved in RSA in animals. The second study utilized a paradigm in which participants were shown neutral, happy, sad, and disgusting films. Participants were also asked to recall personal experiences of the same valences (Lane, et al., 2008). RSA and neural activity were assessed throughout the protocol. With neutral, happy, sad, and disgusting stimuli, there were positive associations between RSA and left pACC activity. With happy stimuli, there were positive associations between RSA and left insula and bilateral VMPFC activity. It is possible that these studies produced different results because of differences in the specific types of neuroimaging and other experimental methods employed.

Overall, RSA levels appear to be positively associated with left insula, left amygdala-hippocampal complex, right cerebellum, bilateral pACC, and bilateral VMPFC activity during human neuroimaging protocols. This result seems to hold in community samples of participants and there is some indication that RSA may be associated with similar patterns of neural activity in both males and females. Although the current study is most concerned with *resting* RSA levels, the studies cited above primarily examined task-related RSA levels. While this is not an optimal literature base, it is important to reiterate that there are no published studies (of which we are aware) that assess brain activation in association with resting RSA.

Comparing across the animal and human literatures, it appears that the amygdala, pACC, VMPFC, insula, and cerebellum may all be implicated in RSA. Although only the animal literature implicated the NTS and hypothalamus with RSA, both of these brain regions are quite small and are located subcortically, making them difficult to visualize during human neuroimaging protocols. It is likely that both of these neural regions support RSA in humans, as well.

2.1.3 Brain regions commonly implicated in both the default mode RSNN and resting RSA

From the above literature, it seems that the bilateral VMPFC, pACC, cerebellum, insula, NTS, and hypothalamus are commonly implicated in both the default mode RSNN and resting RSA. Thus, it appears that there is potentially a shared neural basis between the default mode RSNN and resting RSA which, ultimately, may contribute to their coactive, potentially coordinated, functionality (see Figure 1). Given that these shared neural regions are implicated in various psychological processes, as detailed in Table 1, it is likely that the relationship between the default mode RSNN and resting RSA has psychological implications. Finally, the author notes that this "co-activation" hypothesis is in keeping with Porges' popular and influential polyvagal theory.

Specifically, the theory poses that various distributed, un-specified cortical brain regions simultaneously regulate both social/emotional processing and RSA, forming a so-called social engagement system (Porges, 2007). This social engagement system reportedly serves as a neural and peripheral physiological circuit that underlies maladaptive and adaptive social and emotional processing (Porges, 2007). Similarly, the mechanistic pathway linking the default mode RSNN and RSA proposed in this section suggests that the activity of specific brain regions concurrently supports both activity within the default mode RSNN and RSA, forming an integrated physiological baseline with potential psychological relevance, specifically to self-focused cognition (described in greater detail in the "The Potential Functional Purpose of the Integrated

Baseline Formed by the Default Mode RSNN and Resting RSA" section). Thus, this type of purported co-activation pathway is not unfamiliar within the field of cardiovascular psychophysiology.

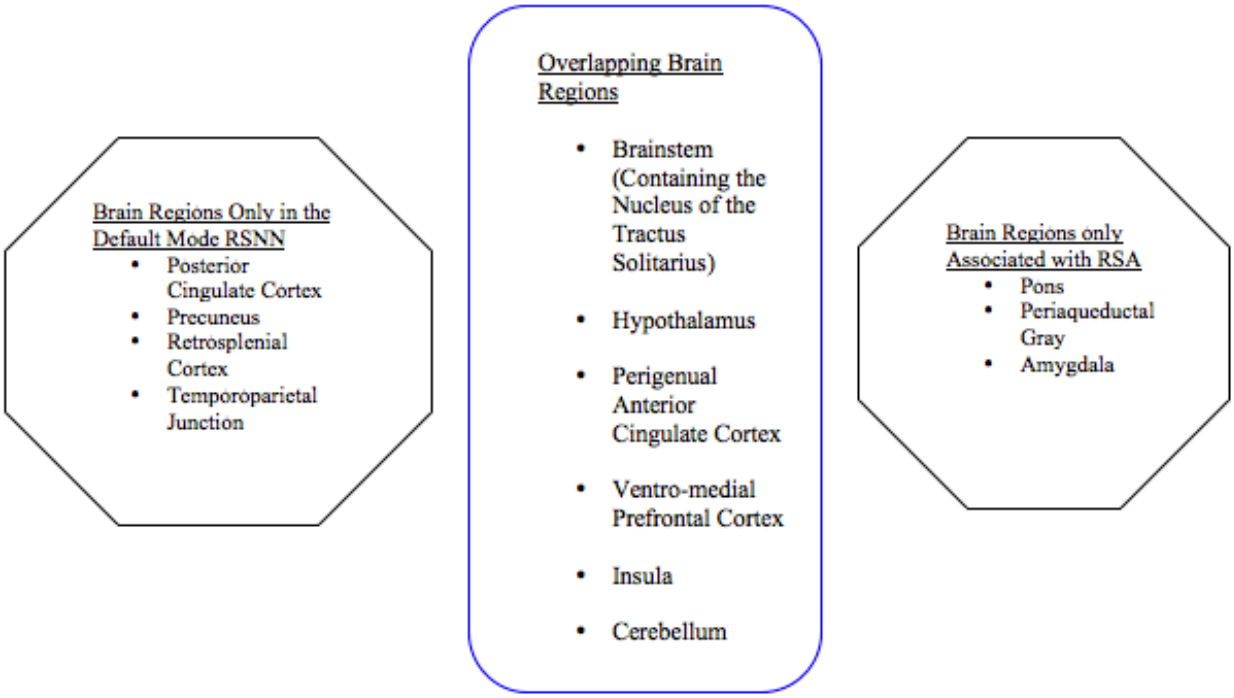

Figure 1 The Default Mode RSNN and Resting RSA Share a Common Neural Basis

3.0 POTENTIAL FUNCTIONAL PURPOSES OF THE ASSOCIATION BETWEEN THE DEFAULT MODE RSNN AND RESTING RSA

Now that the definitions of and possible mechanisms underlying the association between the default mode RSNN and resting RSA have been discussed, the potential functional purposes of the association will be described. Research suggests that the physiological baseline potentially formed by the default mode RSNN and resting RSA may serve various functional purposes. Given the hypothesis that the default mode RSNN and resting RSA are joined by common neural substrates, it follows that these neural regions also foster a connection between the default mode RSNN and RSA and other brain-mediated physiological or psychological processes. The preponderance of research supports the assertion that the physiological baseline is most likely implicated in self-focused cognition. Other physiologically reasonable, but more speculative and less empirical work suggests that the integrated baseline may be associated with other basic physiological processes such as homeostatic bodily regulation or psychological processes such as an individual's general, non-specific monitoring of/attending to the external environment.

3.1 SELF-FOCUSED COGNITION

Researchers have suggested that the default mode RSNN and RSA both appear to be implicated in self-focused cognition. Specifically, regarding the default mode RSNN, Harrison and colleagues (Harrison, Pujol, et al., 2008a) used ICA to identify one component each from a resting condition and a self-reflective moral dilemma condition that were significantly correlated

with a template component representing the default mode RSNN developed based on prior deactivation analysis research. This technique allowed for the identification of components highly similar to the default mode RSNN from those two conditions. When calculating the percentage of common voxels across the default mode RSNN-representative components generated for the two conditions, the authors reported a high degree of concordance (97%). This result indicates that a significant portion of the brain regions forming the default mode RSNN-representative component during the resting state also vary concurrently to form a similar component during performance of a self-reflective task. Notably, the pACC, VMPFC, and cerebellum, structures also implicated in resting RSA, corresponded to these overlapping voxels. This study met all of the definitional criteria for the default mode described previously except that the authors used fMRI, preventing them from obtaining the OEF values for brain regions of interest. While this result demonstrates that the anatomical features of default mode RSNN can be detected rather consistently at rest and during a self-reflective task, an interesting finding, it does not suggest what exact functional purpose(s) the RSNN-representative component serves during those conditions. Judging the functional purpose of the components is also complicated by the fact that a large percentage of voxels (42%) included within each condition's default mode RSNN-representative components was not commonly shared between conditions. The authors nevertheless contend that the 97% voxel overlap suggests that the default mode RSNN plays a role in self-focused cognition. This conclusion is rather inferential because it relies on the assumption that the overlapping voxels share the same functional purpose, supporting self-directed internal mentation, in *both* conditions. While there is relatively direct evidence that these voxels support self-focused cognition during the task, there is no evidence that they serve the same functional purpose during the resting condition.

Another study also attempted to assess the relationship between the default mode RSNN and self-focused cognition. First, D'Argembeau and colleagues (D'Argembeau, et al., 2005) subtracted PET-obtained neuroimaging data in the following manner. Data from a condition in

which participants reflected on others' personality traits was subtracted from data obtained during a condition in which participants reflected on their own personality traits in order to isolate neural activity selectively associated with self-reflection. Also, data from a condition in which participants reflected on a social issue (e.g. the right to vote) was subtracted from a resting condition. This subtraction was intended to create a deactivation map isolating which brain regions were more active at rest and included in the default mode RSNN. Conjunction analysis on the resultant self-reflection and resting data showed that the pACC and VMPFC were commonly active during those conditions. This study met all of the definitional criteria for the default mode described previously except that, while the authors used PET, they did not report the OEF values for brain regions of interest during the resting condition. Also, the image subtraction and conjunction methods used in this study do not assess correlated so much as co-active regional brain activity; this does not satisfy the default mode RSNN definitional criteria. Although this study's result suggests that the pACC and VMPFC may be regions of the default mode RSNN that particularly support self-focused cognition, it cannot be definitively concluded that these brain regions also support self-focused cognition during the resting condition. Moreover, the pACC and VMPFC are just two of several brain regions implicated in the default mode RSNN; thus, it is unclear that the functional purpose of the default mode RSNN, as a whole, would be supporting self-focused cognition. Overall, despite their limitations, these two studies tentatively suggest that the default mode RSNN, particularly the pACC and VMPFC regions, may be involved in self-focused cognition.

RSA has also been associated with self-focused cognition. Increases in RSA above pre-training levels have been reported in participants who have undergone training in autogenic relaxation, progressive muscle relaxation, and mindfulness body scan meditation (Ditto, Eclache, & Goldman, 2006; Sakakibara, Takeuchi, & Hayano, 1994; Tang, et al., 2009). Specifically, these RSA increases have been found *during* the practice of relaxation while participants are in the laboratory, a time when participants are instructed to focus on their own bodily sensations, a

type of self-focused cognition. While these studies assessed RSA in accordance with the definition provided previously, they were marked by other limitations. None of the authors explicitly asked participants to verify that they focused on self-referential thoughts during the practice of relaxation. This makes it difficult to discern whether the changes in RSA indeed accompany self-focused cognition or whether they are associated with other variables. Also, the studies conducted by Ditto and colleagues and Tang and colleagues required participants to practice relaxation on their own in between laboratory sessions. It is possible that this additional relaxation practice had a cumulative influence on tonic RSA, confounding the measures of RSA obtained during the laboratory relaxation. However, the facts that 1) the association between increased RSA and relaxation practice holds across studies and 2) Sakakibara and colleagues only had participants practice relaxation in the laboratory, not between sessions, are compelling. These findings may support an association between RSA levels and self-focused cognition, in so far as the relaxation protocols sufficiently elicited self-referential thoughts.

Other research also suggests that RSA may be associated with self-focused cognition. Wilhelm and colleagues (Wilhelm, Kochar, Roth, & Gross, 2001) found that participants' RSA increased above baseline levels during an experimental protocol in which their wrists were touched by an experimenter. Concomitant with this increase in RSA, participants also reported increases in feelings of self-consciousness and embarrassment, feelings indicative of self-referential thought. However, the fact that these feelings were reported in the context of a social interaction makes it difficult to parse out how much participants' cognitions were oriented towards themselves as versus the experimenter. RSA was assessed appropriately in this study, according to the definition provided previously. To the extent that this study adequately measured self-focused cognition, it may also support an association between it and RSA level. Overall, it seems possible that self-focused cognition may be associated with levels of RSA, much as it is with default mode RSNN activity (or at least that of the pACC and VMPFC regions). It should be noted that the types of tasks used to elicit self-referential thoughts in the

default mode RSNN studies were somewhat different from the tasks included in the RSA studies, potentially making it difficult to compare results across studies. This research, although encouraging, is rather preliminary and more work simultaneously examining default mode RSNN activity and RSA using face-valid self-referential tasks is needed to validate this hypothesis.

3.2 BODILY HOMEOSTASIS

The second, somewhat less empirically-supported functional purpose potentially shared by the default mode RSNN and RSA is that they may be involved in maintaining bodily homeostasis. To begin, Raichle and colleagues (Raichle, 2003; Raichle & Gusnard, 2002, 2005) conducted initial default mode RSNN research that was focused on so-called "task-related deactivations" observed in neuroimaging data. Such deactivations occur when researchers subtract task-related imaging data from resting state imaging data; this produces a map of brain region that are more "active" during rest. Over time, this map of brain regions has come to be known as the default mode RSNN and other methodologies (such as the functional connectivity described in previous sections), in addition to the examination of task-related deactivations, have become popular ways of assessing the default mode RSNN. That said, Raichle and colleagues were specifically interested in determining what type of neural activity the task-related deactivations represented. They reasoned that deactivations could have two possible origins. Deactivations could result when particular brain regions show transient increases in neural activity that are greater in the resting state than in the task-engaged state (Raichle, et al., 2001). This might suggest that certain functional processes requiring increased neural activity occur during the resting state. Alternatively, deactivations could result when particular brain regions reduce their level of on-going baseline activity to adjust to task demands (Raichle, et al., 2001). Central to this distinction in transient versus on-going baseline brain activity is the oxygen extraction fraction (OEF), a

metabolic ratio representing the balance between oxygen delivery to brain regions (i.e. blood flow) and oxygen consumption or extraction (Raichle & Gusnard, 2002; Raichle & Snyder, 2007). This quantitative measure can only be provided by PET (see the Default Mode Defined section of this manuscript for more information). Defining transient brain activity, PET studies indicate that when brain metabolic activity transiently increases, the rate of oxygen delivery/blood flow increases while the rate of oxygen consumption decreases, resulting in an increased OEF (Raichle & Snyder, 2007). Defining task-independent, on-going, baseline brain activity, such activity is characterized by the matching of oxygen delivery and consumption, resulting in a uniform OEF. Thus, if the subset of brain regions previously shown to deactivate during task-engaged protocols exhibit OEF levels above the mean OEF calculated across the brain during a resting neuroimaging protocol, this would support the hypothesis that the deactivations result from transient increases in brain activity. If the subset of brain regions instead exhibited OEF levels that were uniform and comparable to the mean OEF calculated across the brain, this would support the hypothesis that the deactivations result from reductions in on-going baseline neural activity.

Within the context of these hypotheses, Raichle and colleagues (Raichle, et al., 2001) empirically examined the OEF levels of the subset of brain regions previously shown to deactivate in response to task-engaged protocols during a resting neuroimaging protocol. They found that the brain regions each had uniform OEFs, comparable to the mean, while participants rested with their eyes open, eyes closed, or during visual fixation. Thus, based on Raichle and colleagues' hypotheses, the subset of brain regions consistently shown to deactivate during various task-engaged protocols likely 'deactivates' as a function of reducing its level of on-going baseline activity in response to task demands. This finding lead Raichle and colleagues to coin the term "default mode RSNN" to describe the subset of brain regions selectively more active during resting state rather than task-engaged protocols; these brain regions are effectively most active in a *default* neural state, a neural baseline.

While this study did not *empirically* assess the possible functional purposes of the default mode RSNN, Raichle and others have speculated that the default mode RSNN, functioning as a neural baseline, may support various neural and peripheral bodily homeostatic processes such as neuronal repair, cellular metabolism, and body temperature maintenance (Fukunaga, et al., 2008; Gusnard, Raichle, & Raichle, 2001; Raichle, et al., 2001). While this supposition appears probable, numerous functions fall under the umbrella of bodily homeostasis, making it difficult to test this rather general hypothesis. Empirical research tracking changes in default mode RSNN activity as a function of challenges to physiological homeostasis such as baroreceptor stimulation or temperature changes may help to more narrowly define the types of homeostatic processing supported by the default mode RSNN. Overall, it seems fair to conclude that the default mode RSNN represents baseline neural activity in the absence of arousal. It is possible that this baseline neural activity supports homeostatic bodily processes such as those described above, but this conclusion is speculative, quite general and non-specific, and lacks empirical support.

Similar to the default mode RSNN, resting levels of RSA have also been associated with the absence of arousal and homeostatic bodily processes. When comparing resting baseline RSA with RSA levels during laboratory protocols designed to challenge and arouse participants, both humans and non-human primates showed reliable task-related decreases in RSA (M. T. Allen, Boquet, & Shelley, 1991; Bowers, Crockett, & Bowden, 1998). This suggests that periods of rest and minimal arousal may be selectively associated with higher levels of RSA, much as they are associated with higher levels of default mode RSNN activity. Incremental increases in RSA are also reported during the 3-minute recovery period following completion of challenging laboratory tasks (de Geus, van Doornen, de Visser, & Orlebeke, 1990; Spalding, Jeffers, Porges, & Hatfield, 2000). This may indicate that RSA plays a role in restoring cardiovascular homeostasis following its perturbation. Furthermore, RSA decreases from resting baseline levels during periods of energy expenditure such as physical exercise (Houtveen, et al., 2002). The RSA decrease has been shown to result, in part, from decreased vagal outflow (Houtveen, et al.,

2002). Conversely, RSA increases above baseline levels while participants practice standardized relaxation protocols in the laboratory (Ditto, et al., 2006; Sakakibara, et al., 1994; Tang, et al., 2009). This research indicates that RSA may be selectively associated with physiological states marked by energy conservation. Finally, RSA levels after one eats a meal are higher than RSA levels prior to food ingestion, suggesting that RSA supports states of energy production (Uijtdehaage, Stern, & Koch, 1992).

Overall, the default mode RSNN and resting RSA appear to commonly characterize bodily states of rest and limited arousal. They both may be involved in a physiological baseline state that is down-regulated to meet environmental demands. It is possible that this baseline state supports homeostatic bodily processing, but research testing the joint responses of the default mode RSNN and RSA in response to homeostatic perturbations must be conducted to provide empirical support for this speculation.

Finally, on a related note, the default mode RSNN and the resting RSA may each be affected by visceral afferent signals, coordinating their involvement in homeostatic bodily processing. Although this manuscript has and will continue to focus on the theory that common neural activation underlies the association between the default mode RSNN, RSA, and their joint functionality (a rather "top-down model"), it is possible that some "bottom-up" influences like visceral afferent signals play a role in their union. As depicted in Figure 2, the vagus nerve, a nerve that is 80% afferent, conveys sensory information (e.g. regarding organ distension and pressure changes) to various subcortical and cortical brain regions via connections with the NTS (Adam, 1998; Guyton & Hall, 2005). The vagus nerve, as well as the glossopharyngeal nerve, is also embedded with baroreceptors (mechanoreceptors involved in sensing changes in blood pressure and heart rate); thus, these nerves also convey to various subcortical and cortical brain regions, via the NTS, information regarding autonomic activity (Guyton & Hall, 2005). As such, visceral afferent signals important to maintaining bodily homeostasis (e.g, basal functioning of

internal organs and blood pressure maintenance) may ultimately influence processing within the default mode RSNN. Since the NTS also shares connections with the efferent vagus nerve, these visceral afferent signals may also ultimately influence RSA levels (as is the case with baroreceptor signaling (Guyton & Hall, 2005)). As such, visceral afferent signals conveying information relevant to homeostasis may jointly influence activity within the default mode RSNN and RSA. Researchers speculated that visceral afferent signals might affect subsequent physiological function and cognition (e.g., memory and emotion processing) via such neurally-mediated pathways (Adam, 1998; Dworkin, 2007; Dworkin, et al., 1994; Lacey & Lacey, 1970, 1974, 1978, 1979). Although this visceral afferent model is interesting, it lacks solid empirical support, making it difficult to draw strong conclusions as to how visceral afferent signals may impact functionality of the default mode RSNN and resting RSA.

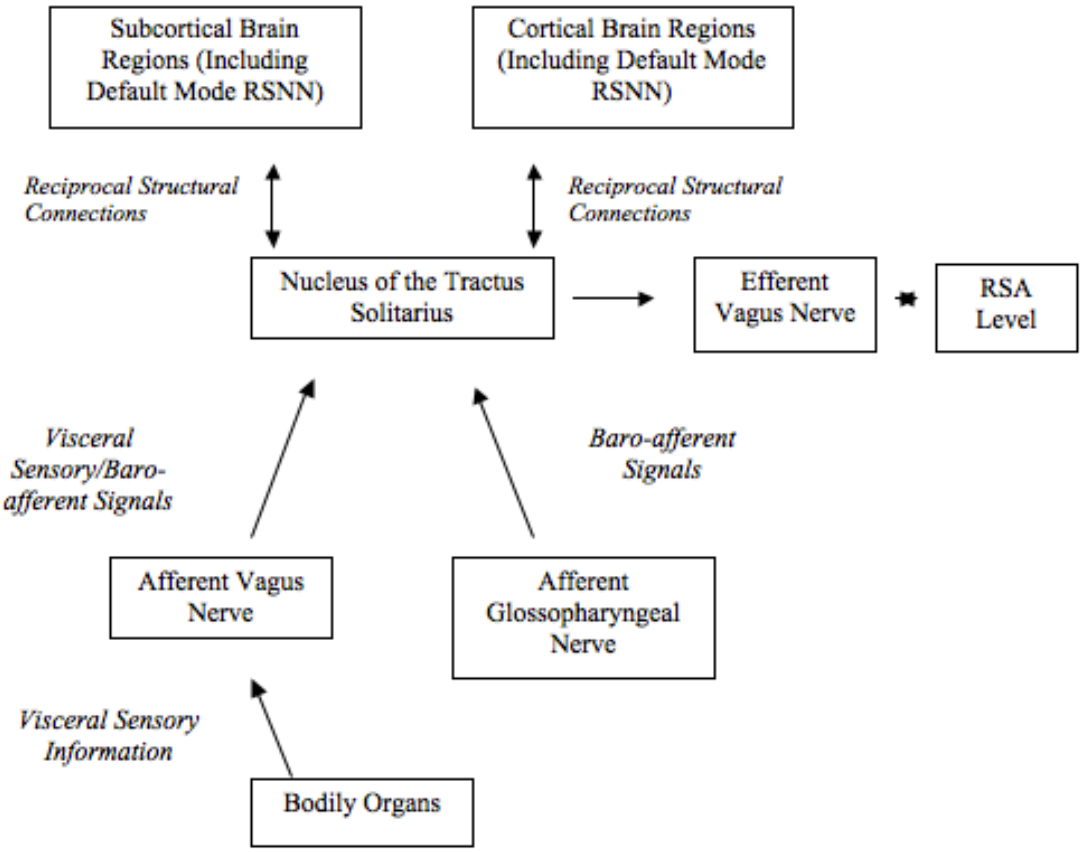

Figure 2 Visceral Afferent Connections Between the Default Mode RSNN and Resting RSA

3.3 MONITORING THE EXTERNAL ENVIRONMENT

Finally, researchers have also speculated that the default mode RSNN may be involved in supporting a non-specific, broad attentional focus on the external environment, passively monitoring for unexpected or salient events (Buckner, Andrews-Hanna, & Schacter, 2008; Raichle & Snyder, 2007). This hypothesis has been suggested because, while task-engaged protocols requiring focused, sustained attention are associated with less default mode RSNN activity, passive protocols in which attention is less focused are associated with more default mode activity. It has been proposed that the brain may revert to passively monitoring the environment at such times when focal attention is not required (Buckner, et al., 2008). Raichle and colleagues (Raichle, et al., 2001) have posited that the default mode RSNN may monitor the external environment in this way because it is evolutionarily advantageous. Having a subset of brain regions automatically and continuously scanning the environment for threats to personal well-being, a function only down-regulated when focal attention is necessary, promotes survival.

The proposal that the default mode RSNN is involved in broadly, passively monitoring the external environment is based on research suggesting that brain regions implicated in the default mode RSNN are also active during diffuse attention tasks. Vogt and colleagues' (Vogt, Finch, & Olson, 1992) review of the functions of the cingulate cortex found that the PCC contains neurons that monitor eye movements and respond to sensory stimuli. This review also reported that single cell recording studies conducted in primates show that PCC neurons do not respond to focal sensory stimuli as much as they do to large stimulus arrays. Research also demonstrates that the pACC and PCC are both more active during target-detection task conditions in which stimuli appear randomly in multiple locations than they are during conditions in which focal stimuli are presented (Buckner, et al., 2008; Hahn, Ross, & Stein, 2007). This work may imply that the PCC

and pACC, reliable regions of the default mode RSNN, are involved in regulating attention towards diffuse and unpredictable stimuli. Buckner, Raichle, and Hahn and colleagues' (Buckner, et al., 2008; Hahn, et al., 2007; Raichle, et al., 2001) have taken this conclusion a step farther by speculating that 1) the PCC and pACC may support this type of attention during resting neuroimaging protocols and 2) the entire default mode RSNN may support such attention by virtue of including the PCC and pACC regions. This is a rather inferential interpretation of the research. Firstly, the studies cited by Vogt and colleagues and that conducted by Hahn and colleagues all examined PCC and pACC activity in response to experimental tasks. It is presumptive to suggest that these brain regions support the same functional purpose in both task-engaged and resting conditions. Also, these results only apply to two component regions of the default mode RSNN and are not necessarily representative of default mode RSNN activity as a whole. While the contention that the default mode RSNN may be implicated in passively monitoring the external environment is intriguing, there is only circumstantial data (for the most part, not meeting the default mode RSNN definitional criteria set out at the beginning of this proposal) minimally supporting it.

Although research linking the default mode RSNN to broad, passive monitoring of the external environment is limited, it is interesting to note that changes in RSA may also support a similar functional purpose. Research indicates that lower levels of RSA may be associated with active, focal attention while higher levels of RSA may accompany passive, diffuse attention. Specifically, Porges (Porges, 1992) postulated that sustained decrements in RSA indicate a down-regulation of homeostasis in service of assembling the metabolic factors necessary to meet ergotropic demands. Porges suggested that allocating sustained attention to stimuli may be such an ergotropic demand. Supporting this theory, research has shown that levels of RSA during

lengthy continuous performance tests (considered to be the gold standard in sustained attention measurement) are, in fact, lower than baseline resting levels of RSA (Duschek, Muckenthaler, Werner, & del Paso, 2009; Suess, Porges, & Plude, 1994). While these results seem to indicate that sustained, focused attention may be associated with decreased RSA, it is impossible to know for certain whether this effect is selectively elicited by the attentional components of the tasks or some other feature of them (e.g. level of cognitive demand). That said, these results suggest that decreases in RSA may accompany sustained focal attention in much the same way decreases in default mode RSNN activity do. While Porges' theory does not explicitly propose this, it might be possible that resting baseline levels of RSA support a less focal, less sustained type of attention such as general and passive monitoring of the external environment. It is therefore feasible that, like activity of the default mode RSNN, resting levels of RSA support passive, ongoing monitoring of the external environment until they are down-regulated to facilitate sustained, focal attention. This supposition remains quite speculative, pending empirical research.

3.4 SUMMARY

In sum, it appears that the integrated baseline potentially formed by the default mode RSNN and RSA may serve a functional purpose in maintaining bodily homeostasis, monitoring the external environment, and self-focused cognition. Specifically, there is some preliminary *empirical* evidence to suggest that the default mode RSNN and resting RSA may both be involved in self-focused cognition. Less empirical and more speculative work indicates that the default mode RSNN and resting RSA may be related in supporting either intrinsic, baseline neural activity maintaining bodily homeostasis or monitoring of the external environment. Thus, the

preponderance of the limited, but available, evidence suggests that the integrated physiological baseline potentially formed by the default mode RSNN and resting RSA might be involved in self-focused cognition.

4.0 AIMS OF THE CURRENT RESEARCH

Based on the literature just reviewed, the current study aims to empirically examine the association between the default mode RSNN and resting RSA. As such, the primary goal of the current study is to establish that functional connectivity strength within the default mode RSNN varies in association with RSA levels. It is hypothesized that the two variables will be associated. The secondary, more exploratory goal of this research is to ascertain whether the association between the default mode RSNN and resting RSA is, in fact, related to self-focused cognition. To probe the possible psychological implications of this association, the current study also aims to assess 1) whether functional connectivity strength within the default mode RSNN varies in association with one's level of self-focused cognition and 2) whether activity within the default mode RSNN commonly covaries with RSA and self-focused cognition.

5.0 RESEARCH DESIGN AND METHODS

5.1 OVERVIEW

This research included a subset of 117 male and female participants from the University of Pittsburgh Adult Health and Behavior-Phase II (AHAB-II) project. AHAB-II is a data registry containing the psychological and biological data of participants residing in Southwestern Pennsylvania. The current research focused particularly on neuroimaging, RSA, psychological self-report, and demographic data collected from April 2008-May 2009. Specifically, this subset of participants completed self-report and demographic data collection. They also underwent a baseline RSA and respiration monitoring protocol in a laboratory.

5.2 PARTICIPANTS

Participants were individuals residing in the Pittsburgh area who were recruited via neighborhood mailings. They were between 30-55 years of age and 82% were Caucasian. Inclusion criteria included that participants be employed at least 25 hours/week (but not regularly working night shifts) and be proficient in English speaking and reading for the past 10 years. Exclusion criteria included 1), history of atherosclerotic disease or treatment, 2) reported history of schizophrenia or bipolar disorder, 3) chronic hepatitis, 4) renal failure, 5) neurological disorder, 6) lung disease requiring drug treatment, 7) stage 2 hypertension, 8) alcohol consumption exceeding 35 beverages per week, 9) pregnancy and lactation (in females), and 10)

the use of cardiovascular, psychotropic, glucocorticoid, lipid-lowering, insulin, or weight-loss medications. Due to the neuroimaging protocol, participants were excluded if they were claustrophobic, had metal objects permanently placed in or on their body, had tattooed eyeliner, and if their body habitus was such that they could not fit into the scanner.

5.3 ASSESSMENT OF RSA

In the laboratory, participants underwent an electrocardiogram (ECG) during a resting baseline period lasting five minutes. Three silver-silver chloride electrodes were used; they were placed on both wrists and the left ankle (ground). During this period, participants were instructed to stay still and calm without falling asleep. The ECG signal was digitized (12 bit), sampled (at 1000Hz), and stored for offline processing using Mindware acquisition software (Mindware, version 2.16; Mindware Technologies Ltd., Columbus, OH). Prior to HF-HRV calculation, R wave markers in the ECG signal were assessed for artifacts by visual inspection and by an automatic artifact detection algorithm available in a customized software package (Mindware Heart Rate Scoring Module, version 2.16; Mindware Technologies Ltd., Columbus, OH). Following manual corrections of suspected artifacts, minute-by-minute estimates of heart rate and HF-HRV were established as directed by current guidelines and demonstrated by Gianaros and colleagues (Gianaros, et al., 2005). First, for each minute of the baseline, a 60-second time series of interbeat intervals (the time in milliseconds between sequential ECG R spikes) was created using an interpolation algorithm with a 250-ms sampling time. The time series was linearly detrended, mean-centered, and tapered using a Hamming window. Spectral power values were determined (in ms^2/Hz) with fast Fourier transformations, and the power values in the 0.15- to 0.40-Hz spectral bandwidth were integrated (ms^2). Prior to statistical analyses, a natural log

(ln) transformation was applied to the spectral power values, correcting for distributional violations. Resulting minute-by-minute estimates of HF-HRV were averaged for the baseline period.

Research indicates that measures of RSA, like those described above, may also need to be examined for the possibly confounding effects of respiration. Specifically, increases in respiratory frequency can lead to a progressive decline in RSA values because the respiratory frequency may outpace the frequency of vagal output (Hirsch; Berntson 1993). To help control for such an effect, as the *Psychophysiology* Committee Report on RSA suggests, the RSA data was assessed for outlying values and such outliers were removed (Berntson, et al., 1997). Also per the Report's recommendations, participants' respiratory frequencies recorded during data collection (respiration recording procedure described below) were examined to ensure that all participants have respiratory rates inside of the HF band of spectral power utilized in this study.

5.4 ASSESSMENT OF RESPIRATION

During the laboratory data collection, participants' respiration rates were also assessed during the five-minute resting baseline using an abdominal respiration belt (Grass Instrument Co; Quincy, MA). The respiratory signal was stored for offline processing using Mindware acquisition software (Mindware, version 2.16; Mindware Technologies Ltd., Columbus, OH). The respiratory frequency (Hz) was derived from this data. Note that, while a trial each of paced breathing and a trial of un-paced breathing was conducted in the laboratory, this research we focused on the un-paced breathing trial (and the ECG collected during that trial). This decision was made because the act of pacing respiration may disturb the "rest" that is the subject of the current research.

5.5 BRAIN IMAGING

Participants abstained from caffeine, tobacco, and exercise for three hours prior to scanning. They also abstained from alcohol and taking non-essential medications for 12 hours prior to scanning. Participants were scanned with a Siemens Trio 3T scanner. They were instructed to lie still and not fall asleep during the five minute and six second scanning session. An automated shim procedure was applied to reduce magnetic field inhomogeneities. T2 structural images were acquired for visualization and normalization of functional imaging data. Blood oxygen-level dependent (BOLD) functional images were obtained using a gradient-echo echo-planar imaging (EPI) sequence covering 34 axial-oblique slices (3 mm thick, 0 m gap) oriented to the AC-PC line, including the majority of the cerebellum (TR/TE=2000/25 msec, FOV=24 cm, matrix=64 x 64). Scanning parameters were selected to maximize the BOLD signal's quality. Prior to the collection of BOLD functional MRI (fMRI) data for each participant, a reference EPI scan was obtained and visually inspected for artifacts and for good signal across the whole brain.

BOLD fMRI data was pre-processed in the following manner. First, Statistical Parametric Mapping software (SPM; http://www.fil.ion.ucl.ac.uk/spm) was used to realign each participant's scans to the first volume in their series, to correct for head motion. Then, images were spatially normalized into a standard stereotaxic space (the Montreal Neurological Institute template) with a 12 parameter affine model. Finally, images were smoothed to minimize noise and differences in gyral anatomy using a Gaussian filter (6 mm full-width at half-maximum).

5.6 ASSESSMENT OF SELF-FOCUSED COGNITION

Self-focused cognition was operationalized as the openness to feeling facet of the NEO Personality Inventory-Revised (NEO PI-R). The NEO PI-R is a 240-item self-report measure of the five primary personality dimensions traditionally described in the personality literature and

commonly identified in factor-analytic studies of personality (Costa & McCrae, 1992). The five primary dimensions include neuroticism, conscientiousness, agreeableness, extraversion, and openness to experience (a construct described as "intellectual curiosity and independence of judgment", openness to feeling is a facet of openness to experience). In a hierarchical design, each of these primary dimensions is associated with a set of six facets, scales that are related to the primary dimension (Costa & McCrae, 1992). Thus, for each participant, five primary dimension scores and 30 facet scores can be derived. Several studies have shown that internal consistency for the primary dimensions and facets is high (alpha coefficients generally range from 0.58 to 0.95, those for openness to feeling range from 0.66 to 0.69) (Costa & McCrae, 1992). Studies have also shown that the short and long-term test-retest reliability for the primary dimensions and facets is high (test-retest coefficients ranging from 0.66-0.91, 0.54 for openness to feeling) (Carter, et al., 2001; Costa & McCrae, 1992). Finally, research suggests that the primary dimension and facets have strong convergent validity; openness to feeling correlates highly (r=0.64-0.73) with various alternate measures of similar constructs (e.g. the self-acceptance scale of the Revised California Personality Inventory) (Costa & McCrae, 1992).

The openness to feeling facet of the NEO PI-R was chosen as the construct of interest because its items most closely captures the essence of those used in prior studies of self-focused cognition and the default mode RSNN or resting RSA. Specifically, past studies of self-focused cognition and the default mode RSNN or resting RSA have used various tasks and self-report measures to probe self-focused cognition. Some researchers had participants reflect on what they would do when faced with moral dilemmas, other researchers asked participants to reflect on their own personality traits (D'Argembeau, et al., 2005; Harrison, Pujol, et al., 2008a). Research has also operationalized self-focused cognition in the form of contemplating one's own bodily state during relaxation training and as a product of self-report measures asking about feelings of embarrassment and self-consciousness (Ditto, et al., 2006; Sakakibara, et al., 1994; Tang, et al., 2009; Wilhelm, et al., 2001). Each of the methods of assessing self-focused cognition ultimately

requires participants to reflect on their own inner world of emotions, decision-making, and bodily awareness. The openness to feeling facet of the NEO PI-R is a trait-like measure indicating the degree to which participants typically consider this inner world. It assesses how self-reflective and self-aware participants generally are on a daily basis by asking participants to rate their response to such statements as, "I seldom pay much attention to my feelings at the moment" and "how I feel about things is important to me" (Costa & McCrae, 1992). The majority of past research required participants to reflect on affective and mood characteristics, to some extent. Thus, openness to feeling may be a relevant, general assessment of an individual's sensitivity to affect and mood. Openness to feeling may function nicely as an "umbrella" construct, overarching the types of assessments used in past studies of self-focused cognition, making it a rather advantageous measure for use in the current study.

5.7 STATISTICAL PLAN

5.7.1 Isolation of the default mode RSNN

fMRI data was analyzed using the SPM software. The data went through many steps of analysis before the final group-level default mode RSNN was generated. The general approach used involved generating a seed region of interest (the PCC) and then assessing that seed's functional connectivity. This approach was chosen because many fMRI studies have successfully isolated the default mode RSNN using it; it appears to be a reliable and valid method (R. L. Bluhm, et al., 2007; Kennedy & Courchesne, 2008)((Birn, et al., 2006; R. L. Bluhm, et al., 2008b; Fransson, 2005, 2006; Greicius, et al., 2009; Monk, et al., 2009; C. Yan, et al., 2009; Zhou, et al., 2009). The first step was referred to as the "Level 1a." In this step, data was analyzed on a within subjects basis. Specifically, participants' realignment parameters (indices of participant head motion) will be entered as regressors into a general linear model (GLM) analysis in order to

capture whole-brain, voxel-wise functional connectivity maps of covariance with the realignment parameters. Each participant's PCC seed time series was isolated from the output of this Level 1a analysis; the next step described produced the PCC seed region of interest for each participant. This PCC seed region was centered at the Montreal Neurological Institute (MNI) coordinates 0 -60 12, coordinates based on prior research (R. L. Bluhm, et al., 2007; R. L. Bluhm, et al., 2008b; Fransson, 2005, 2006). Additionally, a seed region of interest taken from the fourth ventricle (centered at the MNI coordinates -4 -50 -32) was isolated for each participant in the same manner; these coordinates are comparable to those used in prior research (H. Yan, et al., 2009). In another within-subjects analysis referred to as step "Level 1b", participants' PCC seed, fourth ventricle seed, realignment parameters, and outlying head motion values each were entered as regressors into a general linear model (GLM) analysis. This analysis captured whole-brain, voxel-wise functional connectivity maps of covariance with the PCC seed region while controlling for the effects of the other regressors. In a final analysis, "Level 2", each participant's Level 1b output was entered into a one sample t-test; this produced a between subjects, group level result capturing the whole-brain, voxel wise functional connectivity map of covariance with the PCC seed region, the default mode RSNN. The Level 2 result was thresholded at $p<0.0001$, cluster size 25, based on prior research (R. Bluhm, et al., 2009; Greicius, et al., 2003b).

Cardiac and respiratory artifacts are common in resting state fMRI data because resting neuronal activity occurs at rather low frequencies within the neuroimaging signal. These frequencies are comparable to those at which cardiac and respiratory rhythms are observed, making it difficult to parse out the specific effects of neuronal activity. Also, participants are more likely to move during resting state protocols given the fact that study participants are often asked to lie still, unengaged, for several minutes. See the following articles for further discussion of these issues (Auer, 2008; Birn, Murphy, & Bandettini, 2008; Chang, et al., 2009; Murphy, Birn, Handwerker, Jones, & Bandettini, 2009; Weissenbacher, et al., 2009). Given the possibility of such confounds affecting the data used in the current investigation, the realignment parameters

and outlying head motion values were included as covariates in the above analyses. The fourth ventricle seed time series was also included as a covariate because it reflects signal changes that are likely due to cardiac pulsation and head motion rather than signal changes attributable to neuronal activity (Weissenbacher, et al., 2009). Similar correction procedures have been employed by various researchers and are becoming standard within the field of resting state neuroimaging (Auer, 2008; Cole, Smith, & Beckmann, 2010; Fox, Zhang, Snyder, & Raichle, 2009; Murphy, et al., 2009; Van Dijk, et al., 2009; C. Yan, et al., 2009).

5.7.2 Analytic approach I

This approach was based on our knowledge, outlined in the Introduction, that only certain brain regions are commonly associated with both the default mode RSNN and resting RSA. Thus, instead of broadly assessing the entire default mode RSNN and unnecessarily increasing type I error rate, Approach II focused on parsing out which component regions of the default mode RSNN are most associated with the default mode RSNN and openness to feeling. In addition to this goal, based on the literature presented in the Introduction, it seemed that the default mode RSNN brain regions most relevant to RSA were the pACC and VMPFC. The analyses proposed in this section helped to determine whether RSA is particularly associated with the pACC and VMPFC or with other component brain regions of the network as well. For example, if RSA covaried strongly with the pACC and VMPFC activity, but not with that of other component brain regions, perhaps the conclusion could be drawn that the RSA was not really associated with the default mode RSNN so much as it was with pACC and VMPFC functional connectivity, forming its own, newly-defined psychophysiological network. Likewise, this analytic approach helped to determine 1) the extent to which openness to feeling covaried with default mode RSNN activity as versus that of another network and 2) whether resultant neural network activity

commonly varied with both RSA and openness to feeling levels. This more parsimonious approach began by using the Level 2 default mode RSNN as generated in the "Isolation of the Default Mode RSNN" section. Functional connectivity coefficients (also called eigenvariates, or patterns of spatio-temporal correlation between the PCC seed and the pACC (bilateral Brodmann Areas (BAs) 24 (MNI coordinates 0 -6 44), 25 (MNI coordinates 0 12 -4), 32 (MNI coordinates 0 20 36)) and VPMFC (bilateral BAs 10 (MNI coordinates 0 60 22), 11 (MNI coordinates 0 32 -14)), were extracted. The specific MNI coordinates were based on prior research and represent the center of mass of each BA; the pACC and VMPFC are midline brain structures and research shows that both the left and right portions of each structure are implicated in the default mode RSNN, so isolating the center of mass for each BA corresponding to these structures provided an optimal representation of their activity (this same rationale applied to the retrosplenial cortex BAs 29 and 30 described below) (Birn, et al., 2006; R. L. Bluhm, et al., 2007; R. L. Bluhm, et al., 2008b; Fransson, 2005, 2006; Greicius, Krasnow, Reiss, & Menon, 2003a; Kennedy & Courchesne, 2008; Margulies, et al., 2007; Monk, et al., 2009; C. Yan, et al., 2009; Zhou, et al., 2009). These regions were chosen because, after carefully reviewing the literature cited in the "Brain Regions Implicated in the Default Mode RSNN" section, it appeared that the bilateral VMPFC and pACC are the brain regions related to RSA that are most consistently associated with the default mode. Since the pACC and VMPFC are commonly associated with both the default mode RSNN and RSA, we hypothesized that their functional connectivity coefficients represent the functional connectivity within the default mode RSNN that is most associated with RSA (i.e. accounts for a high percentage (>50%) of the variance in the regression models). Functional connectivity coefficients between the PCC seed and the retrosplenial cortex (bilateral BAs 29 (MNI coordinates 0 -52 8) and 30 (MNI coordinates 0 -68

10)), and the temporoparietal junction (posterior Sylvian fissure, MNI coordinates 50 -45 39 and -50 -45 39) were also extracted (Decety & Lamm, 2007). Since the retrosplenial cortex and the temporoparietal junction were not commonly associated in the literature with both the default mode RSNN and RSA, we hypothesized that these functional connectivity coefficients represent the functional connectivity within the default mode RSNN that is less associated with RSA (i.e. accounts for a high percentage (<50%) of the variance in the regression models). These values were imported into Statistica software (Statistica, Version 8, Statsoft, Tulsa, OK) for analysis. In order to assess the overall functional connectivity between the PCC and the pACC, the mean of the functional connectivity coefficients corresponding to BAs 24, 25, and 32 was calculated. Likewise, in order to assess the overall functional connectivity between the PCC and the VMPFC, the mean of the functional connectivity coefficients corresponding to BAs 10 and 11 was calculated. The same process was undertaken in order to assess the overall functional connectivity between the PCC and retrosplenial cortex and the PCC and temporoparietal junction, respectively. Not only did these mean values provide *overall, comprehensive* indices of functional connectivity in the brain regions of interest, but the use of such aggregate measures lended increased reliability to the results. In order to test the first aim of the proposed research (establish whether functional connectivity strength within the default mode RSNN varies in association with RSA levels), two-step hierarchical regression analyses were conducted testing whether RSA levels predict each mean functional connectivity coefficient (four regression analyses total). At step one, relevant covariates were entered into the model (see Covariates section below). At step two, RSA values were entered into the model. We expected that the regressions involving the pACC and VMPFC functional connectivity coefficients would be most significant. In order to test the second aim of the proposed research (determine whether

functional connectivity strength within the default mode RSNN varies in association with one's level of self-focused cognition), additional two-step hierarchical regression analyses were conducted testing whether openness to feeling levels predict each mean functional connectivity coefficient (four regression analyses total). At step one, relevant covariates were entered into the model (see Covariates section below). At step two, openness to feeling values were entered into the model. We expected that regressions involving each functional connectivity coefficient would be significant. See Table 2 for *some* possible results produced by these analyses and their interpretations. Note that this is not an exhaustive list of all possible outcomes. Finally, exploratory, follow-up analyses were undertaken to assess regression models containing the functional connectivity coefficients for particular BAs, alone.

Table 2 Possible Interpretations of Results

Result	*Possible Interpretation*
Resting RSA is only associated with PCC/pACC & PCC/VMPFC (not PCC/retrosplenial cortex or PCC/temporoparietal junction)	Perhaps the PCC/pACC & PCC/VMPFC form their own network associated with resting RSA, the default mode RSNN is not actually involved. A new psychophysiological network is found, or this might just indicate that a subset of the default mode RSNN is dedicated to involvement with resting RSA.
Resting RSA is primarily associated (>50% variance) with PCC/pACC & PCC/VMPFC and less associated (<50% variance) with PCC/retrosplenial cortex & PCC/temporoparietal junction	Perhaps the default mode RSNN is associated with resting RSA, but the majority of the covariance is driven by PCC, pACC, & VMPFC connectivity.
Resting RSA is not associated with any functional connectivity coefficients	Functional connectivity within these brain regions may not underlie resting RSA levels and other resting neural networks/functional connectivity coefficients may need to be explored.
All of the above can also be applied to openness to feeling	
Openness to feeling is only associated with PCC/retrosplenial cortex & PCC/temporoparietal junction while resting RSA is associated with PCC/pACC & PCC/VMPFC	Perhaps the default mode RSNN is not commonly associated with openness to feeling & resting RSA. Maybe 2 separate sub-networks exist? Maybe the various component regions of the default mode RSNN subserve different psychophysiological functions simultaneously or dynamically. Maybe these are actually 2 newly-defined psychophysiological networks separate from the default mode RSNN.

In order to test the third aim of the proposed research (examine whether activity within the default mode RSNN commonly covaries with RSA and self-focused cognition), we intended to use a formal meditational analysis approach. This formal mediation would have allow us to determine whether activity within the default mode RSNN acts as a mediator (acts to commonly facilitate) resting RSA and openness to feeling.

The test of mediation that we intended to use followed traditionally-accepted methods (Baron & Kenny, 1986; Cohen, Cohen, West, & Aiken, 2003). Three regression equations each controlling for relevant covariates (see Covariates section below) would have been used. The first equation would have tested if resting RSA significantly predicts default mode RSNN activity (specifically, the mean functional connectivity coefficients associated with the pACC and VMPC); this same analysis was already described in the previous paragraph. The second equation would have tested whether resting RSA significantly predicts openness to feeling. The final equation would have tested whether resting RSA and the mean functional connectivity coefficients associated with the pACC and VMPFC entered into the regression simultaneously predicts openness to feeling. The following criteria would have been used to indicate mediation: 1) the first and second equations were significant 2) the functional connectivity coefficients significantly predicted the dependent variable in the third equation 3) the direct relationship between the resting RSA and openness to feeling in the third equation was less than in the second, demonstrating partial mediation and 4) resting RSA had no effect on openness to feeling when the mean functional connectivity coefficients were controlled in the third equation,

indicating full mediation. We intended to use Sobel's significance test to examine the relationship of the independent variable on the dependent variable through the functional connectivity coefficients (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002; MacKinnon, Warsi, & Dwyer, 1995). Note that we planned to conduct this process twice, once with the pACC mean functional connectivity coefficient acting as the mediator and a second time with the VMPFC mean functional connectivity coefficient acting as the mediator. See Table 3 for *some* possible results produced by these analyses and their interpretations. Note that this is not an exhaustive list of all possible outcomes.

Table 3 Possible Interpretations of Results

Result	*Possible Interpretation*
Mediation is not found but Analytic Approach I found spatial overlap	Perhaps another meditational pathway links the default mode RSNN, resting RSA, & openness to feeling. Maybe resting RSA is the mediator?
Partial, not full, mediation is detected	Perhaps third variables need to be considered. Other psychological or physiological variables?

5.7.3 Analytic approach II

This approach first addressed whether functional connectivity strength within the default mode RSNN varied in association with RSA levels. This was done within SPM as a variation on the Level 2 analysis described above; instead of entering each participant's Level 1b output into a one sample t-test, the data was entered into a multiple regression. This regression model covaried for participants' mean RSA levels (as well as all covariates detailed in the next section). The resulting group level map depicted how PCC seed functional connectivity (the default mode

RSNN) varied as a function of participants' RSA levels; the positive association between these variables was of particular interest. Significant areas of activation were reported. The same type of multiple regression analysis was conducted substituting participants' mean openness to feeling values for RSA; the resulting group level map depicted how PCC seed functional connectivity (the default mode RSNN) varied as a function of participants' openness to feeling values. The Level 2 result was thresholded at $p<0.0001$, cluster size 25, based on prior research (R. Bluhm, et al., 2009; Greicius, et al., 2003b).

Finally, to determine whether activity within the default mode RSNN commonly covaries with RSA and self-focused cognition, we intended to use MRIcron software (http://www.cabiatl.com/mricro/). This software would have helped to assess the degree of spatial overlap between the activation maps resulting from each of the multiple regressions described above. Common areas of activation would have been reported. Through this series of analyses, Analytic Approach I sufficiently addressed the aims of the proposed research: 1) establish whether functional connectivity strength within the default mode RSNN varies in association with RSA levels, 2) determine whether functional connectivity strength within the default mode RSNN varies in association with one's level of self-focused cognition, and 3) examine whether activity within the default mode RSNN commonly covaries with RSA and self-focused cognition. See Table 4 for *some* possible results produced by these analyses and their interpretations. Note that this is not an exhaustive list of all possible outcomes. However, Analytic Approach II is rather descriptive and data driven; recent research suggests that this type of analytic approach may increase investigators' type I error rate (Vul, Harris, Winkielman, & Pashler, 2009). As such, the results from Analytic Approach II were compared for convergence with those of Analytic Approach I, a narrower, hypothesis-driven approach.

Table 4 Possible Interpretations of Results

Result	*Possible Interpretation*
Resting RSA is not significantly associated with the whole default mode RSNN, just some regions	Perhaps another network other than the default mode RSNN is implicated. This may mean that the brain regions associated with resting RSA actually form their own separate, newly-defined psychophysiological network. Or, it may indicate that a subset of the default mode RSNN is particularly associated with resting RSA, that its function is resting RSA regulation.
The above can also apply to openness to feeling	
There is no spatial overlap	There is no covariance shared between the changes in default mode RSNN functional connectivity associated with each resting RSA and openness to feeling. Perhaps other proposed analyses will detect other neural networks (or subsets of the default mode RSNN) that separately are associated with resting RSA and openness to feeling.
There is only spatial overlap among particular brain regions	Perhaps the *whole* default mode RSNN is not underlying the neural association between resting RSA and openness to feeling. Is this a separate network? Further examination of the brain regions implicated might help in determining why they are so isolated and how they commonly subserve resting RSA and openness to feeling. This might lead to the definition of a new psychophysiological network.
There is spatial overlap among all brain regions traditionally included in the default mode RSNN	Default mode RSNN activity does covary with both resting RSA and openness to feeling indicating that resting neural activity/processing serves the functional purpose of co-regulating and possibly coordinating resting RSA and openness to feeling levels.

5.7.4 Covariates

For Analytic Approaches I and II, the following covariates were included: gender, age, body mass index (BMI; weight in kg/height in meters^2), smoking status (current, former, never), the number of alcoholic beverages consumed per week, IQ, and depression. Most of these covariates are commonly used in studies assessing separately RSA and brain activity (Egizio, et al., 2008; Gianaros, et al., 2009). More specifically, research suggests that females may have greater RSA levels than males (Snieder, van Doornen, Boomsma, & Thayer, 2007). Also, although most research indicates that default mode RSNN connectivity strength is comparable in males and females, some work suggests that there may be gender differences of small effect size in PCC and precuneus connectivity (R. L. Bluhm, et al., 2008b). Regarding age, muscarinic receptor sensitivity decreases with age, leading to lower levels of RSA (Jennings & Yovetich, 1991). Age is also related to differences in PCC and precuneus connectivity strength (R. L. Bluhm, et al., 2008b). Body habitus, assessed via BMI, and smoking also share known inverse associations with RSA (Masi, Hawkley, Rickett, & Cacioppo, 2007). Nicotine use has been associated with changes in default mode RSNN regional prefrontal activity, as well (Cole, Beckmann, et al., 2010). High levels of alcohol consumption have been associated with low RSA levels and changes in brain structure morphology and function (Schulte, Warzel, Strasburger, & Sabel, 2001; Sullivan & Pfefferbaum, 2005). IQ and general cognitive ability, assessed in this study via the Wechsler Abbreviated Scale of Intelligence (please see Homack and Reynolds (Homack & Reynolds, 2007) for information about this measure's psychometric properties), have been associated with the NEO PI-R primary dimension openness to experience and with the openness to feeling facet (Wainwright, Wright, Luciano, Geffen, & Martin, 2008). That said, IQ does not appear to be associated with RSA or default mode activity. Finally, depression has been related

to 1) low levels of resting RSA in several studies, 2) variations in default mode RSNN connectivity strength, and 3) levels of the NEO PI-R primary dimension openness to experience and the openness to feeling facet (R. Bluhm, et al., 2009; Broyd, et al., 2008; Carney & Freedland, 2009; Carney, Freedland, & Veith, 2005; Costa, Bagby, Herbst, & McCrae, 2005; Greicius, et al., 2007b; Heisel, et al., 2006; Kemp, et al., 2010; Sheline, Price, Yan, & Mintun, 2010). Given that depression is related to all variables of interest, depressive symptoms were examined as a covariate as well as serve as an independent variable in Analytic Approaches I and II (note that Approach II analyses examined both positive and negative associations between depressive symptoms and default mode functional connectivity strength since studies suggest that functional connectivity strength may be positively or negatively associated with depression (R. Bluhm, et al., 2009; Broyd, et al., 2008; Greicius, et al., 2007a; Sheline, et al., 2010)); this plan allowed for thorough exploration of depressive symptoms' potential relationships with the variables of interest. The Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depressive symptoms in this study; please see Radloff for information on the measure's psychometric properties (Radloff, 1977).

6.0 RESULTS

6.1 DATA PROCESSING AND REDUCTION

6.1.1 Overview

To accommodate missing or poor-quality data points while still optimally using available data, three databases were derived from the data provided by the original sample of 117 participants. Specifically, one database, referred to as the Primary Database, included only participants who had complete data for all variables of interest (82 participants). The second database, referred to as the Optimal RSA Database, included only participants who had complete 1) imaging, 2) RSA, and 3) CES-D data, regardless of the quality of their openness to feeling data (84 participants). The third database, referred to as the Optimal Openness to Feeling Database, included only participants who had complete 1) imaging, 2) openness to feeling, and 3) CES-D data, regardless of the quality of their RSA data (103 participants). Analytic Approach I was conducted using all three databases while Analytic Approach II, contingent upon all participants having complete data, was only conducted using the Primary Database. Please see Table 5 for participants' demographics, within each database. There were no significant differences between any variables.

Table 5 Participant Demographics

Primary Database (n=82)

Characteristic	Mean	SD
Age (years)	41.20	7.68
Number of alcoholic beverages consumed/week (square root)	1.44	1.30
Body mass index (ln kg/ meter^2)	3.26	0.19
Basal HF-HRV (ln ms^2)	5.70	1.89
Intelligence Quotient	114.45	11.94
Openness to Feeling	21.13	3.84
CES-D (square root)	2.46	1.40

Optimal RSA Database (n=84)

Characteristic	Mean	SD
Age (years)	41.37	7.67
Number of alcoholic beverages consumed/week (square root)	1.41	1.30
Body mass index (ln kg/ meter^2)	3.26	0.19
Basal HF-HRV (ln ms^2)	5.71	1.90
Intelligence Quotient	114.10	12.19
Openness to Feeling	21.13	3.84
CES-D (square root)	2.42	1.41

Table 5 (continued)

Optimal Openness to Feeling Database (n=103)

Characteristic	Mean	SD
Age (years)	40.99	7.71
Number of alcoholic beverages consumed/week (square root)	1.37	1.26
Body mass index (ln kg/ meter^2)	3.24	0.18
Basal HF-HRV (ln ms^2)	5.73	1.90
Intelligence Quotient	115.65	12.15
Openness to Feeling	21.20	4.20
CES-D (square root)	2.43	1.37

Note. High-frequency heart rate variability (HF-HRV), Center for Epidemiologic Studies Depression Scale (CES-D), and respiratory sinus arrhythmia (RSA). Primary Database included 35 males and 54% of participants reported no lifetime history of tobacco use. The Optimal RSA Database included 35 males and 54% of participants reported no lifetime history of tobacco use. The Optimal Openness to Feeling Database included 41 males and 60% of participants reported no lifetime history of tobacco use.

6.1.2 RSA

ECG recordings were assessed for artifacts, HF-HRV was calculated and natural log transformed, HF-HRV values were assessed for outliers, and HF-HRV values were checked to ensure that they fell within participants' respiratory band as proposed in the "Assessment of RSA" section. Ten participants lacked usable ECG recordings, two participants had outlying HF-HRV values (when the Shapiro-Wilk test was applied to the data and a QQ plot and histogram were analyzed), and 12 participants' HF-HRV values fell outside of their respiratory band. Participants were excluded from analyses as described in the "Overview" section.

6.1.3 Brain imaging

Brain images were preprocessed as described in the previous "Brain Imaging" section. However, one participant lacked complete imaging data (this individual did not have 150 scans taken) and nine participants showed evidence of signal dropout in relevant cortical and subcortical areas. Participants were excluded from analyses as described in the "Overview" section. Also, for Analytic Approach I, the distributions of the eigenvariates corresponding to BAs 24, 25, 32, 10, 11, 29, and 30 as well as the bilateral temporoparietal cortex were assessed. As their distributions were not normal (when the Shapiro-Wilk test was applied to the data and a QQ plot and histogram were analyzed), each variable was transformed using 'natural log + 1', to preserve negative values.

For the Primary Database, two participants had outlying BA 25 values, two participants had outlying BA 32 values, two participants had outlying mean BA 10 and 11 values, two participants had outlying BA 10 values, one participant had an outlying BA 11 value, two participants had outlying mean temporoparietal cortex values, one participant had an outlying right temporoparietal cortex value, and one participant had an outlying left temporoparietal cortex value. These participants were excluded from analyses.

For the Optimal RSA Database, two participants had outlying BA 25 values, two participants had outlying BA 32 values, one participant had an outlying mean BA 10 and 11 value, one participant had an outlying BA 10 value, one participant had an outlying BA 11 value, one participant had an outlying mean temporoparietal cortex value, one participant had an outlying right temporoparietal cortex value, and one participant had an outlying left temporoparietal cortex value.

For the Optimal Openness to Feeling Database, four participants had outlying BA 25 values, one participant had an outlying BA 32 value, one participant had an outlying mean BA 10 and 11 value, one participant had an outlying BA 11 value, one participant had an outlying mean temporoparietal cortex value, one participant had an outlying right temporoparietal cortex value, and two participants had outlying left temporoparietal cortex values,

6.1.4 Openness to feeling

Openness to feeling values were normally distributed (when the Shapiro-Wilk test was applied to the data and a QQ plot and histogram were analyzed), with the exception of one participant. This participant, and two others lacking NEO PI-R data, were excluded from analyses as described in the “Overview” section.

6.1.5 Covariates

All covariates' distributions were assessed for normalcy using the Shapiro-Wilk test and assessment of QQ plots and histograms. Age, sex, openness to feeling, and IQ were normally distributed. However, BMI required a natural log transformation and the CES-D and participants' reported alcohol consumption over seven days required square root transformations. Finally, participants' tobacco use status was dichotomized to include either participants who reported no lifetime use of tobacco versus participants who reported current or past use of tobacco.

6.2 ANALYTIC APPROACH I

As proposed, eigenvariates were extracted for BAs and MNI coordinates corresponding to the pACC, VMPFC, retrosplenial cortex, and temporoparietal junction. The eigenvariates were extracted from the Level 2 group level analysis capturing the whole-brain, voxel wise functional connectivity map of covariance with the PCC seed region, the default mode RSNN. This functional connectivity map can be seen in Figure 3; for reference, please see Figure 4 and Table 6 to compare how this study's isolation of the default mode RSNN adequately captured activity in the brain regions of interest, as well as the typical default mode RSNN brain regions described in the Introduction. Overall, the result indicates a valid default mode RSNN characterization.

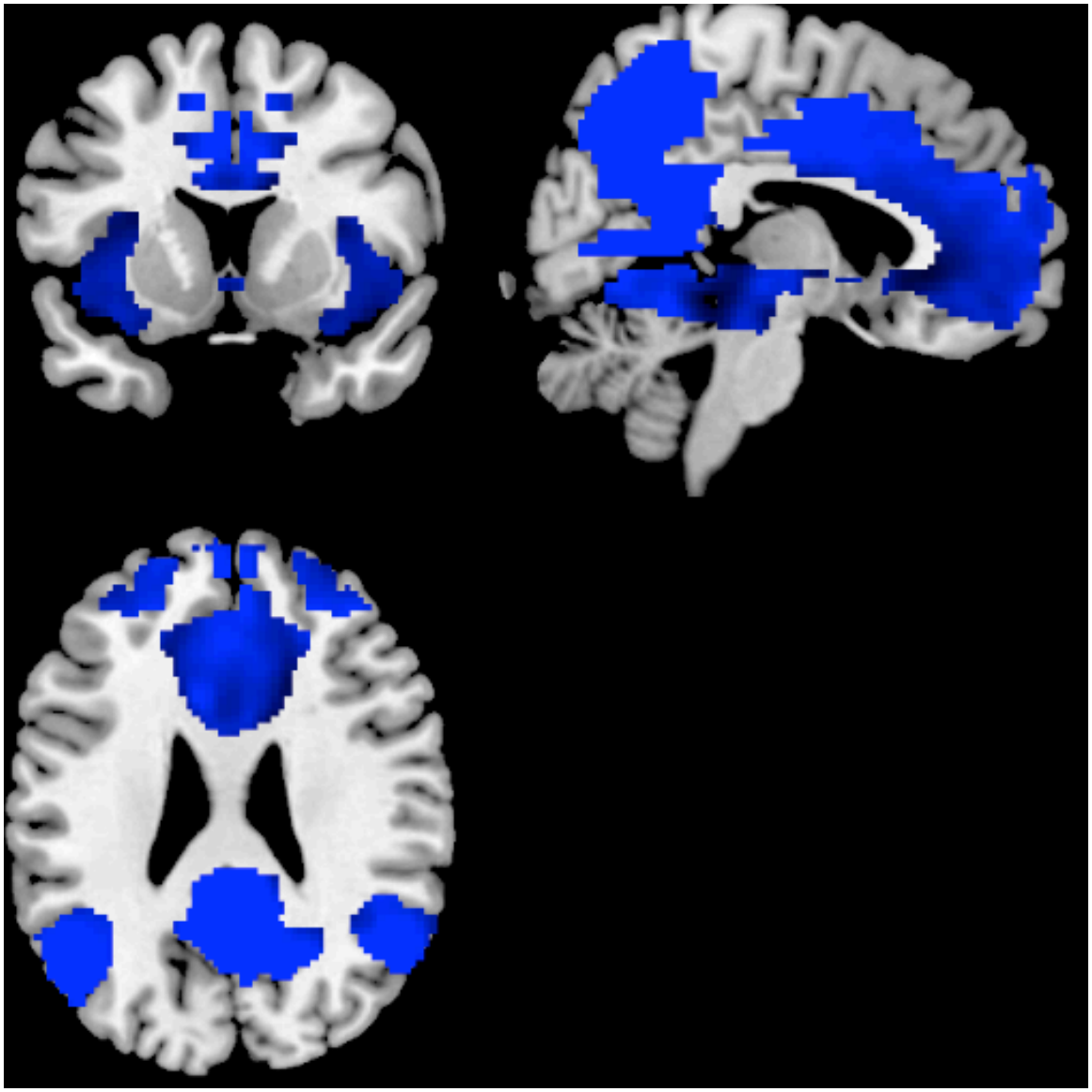

Figure 3 View of the Default Mode RSNN Isolated in This Study

Note. Functional connectivity map depicted here drawn from the Primary database (n=82). For ease of viewing, we examined functional connectivity between the PCC-seed and an ROI Mask including the bilateral hypothalamus, pACC, VMPFC, insula, cerebellum, precuneus, retrosplenial cortex, the temporoparietal junction, and the brainstem created with the Wake Forest PickAtlas ($p<0.005$, cluster size=20).

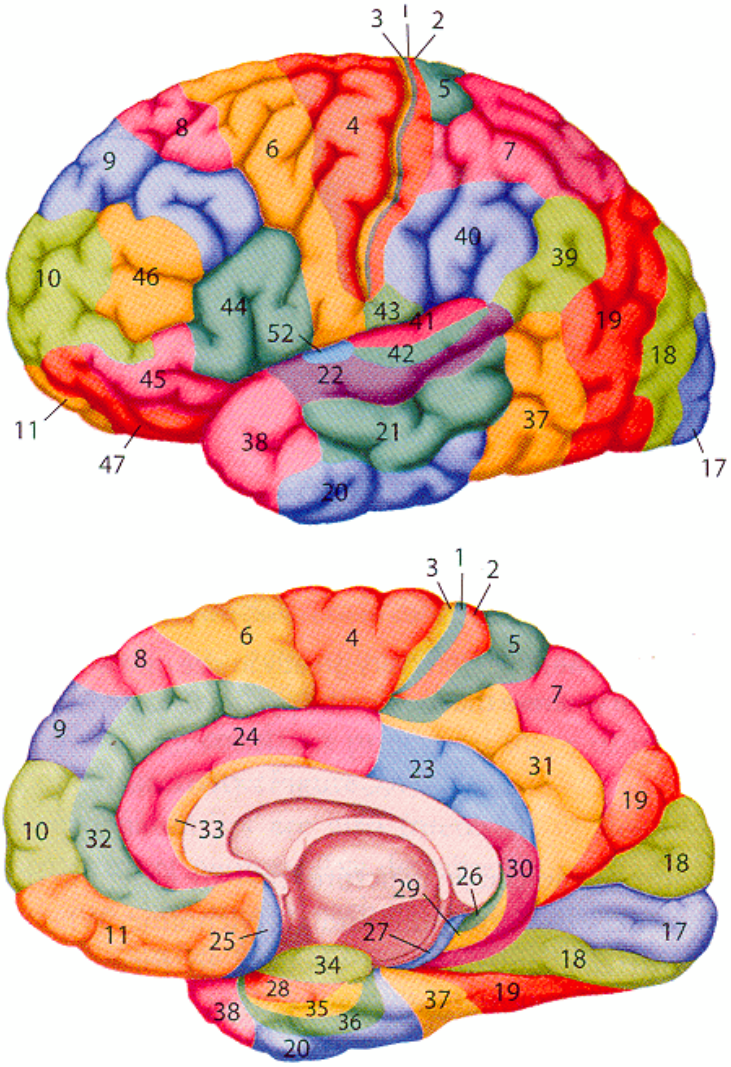

Figure 4 Brodmann Area and Sylvian Fissure References

Note. Image taken from www.mrc-cbu.cam.ac.uk (Medical Research Council, Cognitive and Brain Sciences Unit). Temporoparietal junction located just posterior to BA 41 and ventral to BA 40.

Table 6 Brain Regions Showing Functional Connectivity with the PCC-Seed – The Default Mode RSNN

Brain Region	MNI Coordinates	BA	K_E	t value	p value
Posterior Cingulate Cortex	-2 -58 12	23	1182	72.24	0.000
	-2 -60 28	31	1182	23.79	0.000
Precuneus	6 -50 24		1182	24.43	0.000
Temporal Lobe	-32 -80 30		1500	20.68	0.000
Parietal Lobe/Angular Gyrus	-34 -66 38	39	1500	18.32	0.000
	-44 -68 32		1726	18.06	0.000
	46 -64 32		1726	19.49	0.000
	32 -60 50		1726	17.45	0.000
Temporal Lobe/Angular Gyrus	50 -62 24	39	1726	19.09	0.000
Mid Cingulate	0 0 44		1533	17.45	0.000
Medial Frontal Gyrus	-4 10 50		1533	16.92	0.000
Perigenual Anterior Cingulate Cortex	-4 -20 38	24	1533	16.45	0.000

Note. MNI=Montreal Neurological Institute, BA=Brodmann area

Correlations among key variables, presented in Tables 7-9, showed several significant findings. First, while there was a significant relationship between RSA and openness to feeling in the Primary and Optimal RSA databases (essentially the same correlation including the same participants as the same participants missing openness to feeling data were excluded from both databases), this relationship failed to remain significant ($r=0.03$, $p=0.81$) in the Optimal Openness to Feeling Database. When significant, the correlation was only marginally so ($p=0.042$) and the relationship between variables, though linear, was marked by a lot of scatter; these factors worsened as more participants were added to the sample. The latter database included more participants (103) in this correlation, and thus had more statistical power, than did the other two databases (82). Across databases, significant correlations were found between the mean pACC and 1) mean VMPFC, 2) mean retrosplenial cortex, and 3) mean temporoparietal cortex. There were also consistent significant correlations between the mean VMPFC and mean temporoparietal junction. Within the Optimal Openness to Feeling Database, the database with the most power to detect associations with that variable, a significant correlation between openness to feeling and the CES-D was found. In addition, we examined intercorrelations among the key variables of interest, RSA, openness to feeling, and CES-D values and the covariates (Table 10). We present only the correlations derived from the primary database since results were similar using the other two databases (aside from the aforementioned openness to feeling/CES-D correlation).

Table 7 Primary Database Key Variables Correlations (n=82)

	RSA	Openness to Feeling	CES-D	Mean pACC	Mean VMPFC	Mean RC	Mean TJ
RSA		-0.23*					
Openness to Feeling	-0.23*						
CES-D							
Mean pACC					0.63**	0.37**	0.55**
Mean VMPFC				0.63**			0.40**
Mean RC				0.37**			
Mean TJ				0.55**	0.40**		

Note. Respiratory sinus arrhythmia (RSA), Center for Epidemiologic Studies Depression Scale (CES-D), perigenual anterior cingulate cortex (pACC), ventromedial prefrontal cortex (VMPFC), retrosplenial cortex (RC), and temporoparietal junction (TJ).

*p<0.05; **p<0.01

Table 8 Optimal RSA Database Key Variables Correlations

	RSA	Openness to Feeling	CES-D	Mean pACC	Mean VMPFC	Mean RC	Mean TJ
RSA		-0.23* n=82					
Openness to Feeling	-0.23* n=82						
CES-D							
Mean pACC					0.63** n=84	0.36** n=84	0.55** n=84
Mean VMPFC				0.63** n=84			0.35** n=84
Mean RC				0.36** n=84			
Mean TJ				0.55** n=84	0.35** n=84		

Note. Respiratory sinus arrhythmia (RSA), Center for Epidemiologic Studies Depression Scale (CES-D), perigenual anterior cingulate cortex (pACC), ventromedial prefrontal cortex (VMPFC), retrosplenial cortex (RC), and temporoparietal junction (TJ).

*p<0.05; **p<0.01

Table 9 Optimal Openness to Feeling Database Key Variables Correlations

	RSA	Openness to Feeling	CES-D	Mean pACC	Mean VMPFC	Mean RC	Mean TJ
RSA							
Openness to Feeling			0.21* n=103				
CES-D		0.21* n=103					
Mean pACC					0.59** n=103	0.37** n=103	0.52** n=103
Mean VMPFC				0.60** n=103			0.35** n=103
Mean RC				0.37** n=103			
Mean TJ				0.52** n=103	0.35** n=103		

Note. Respiratory sinus arrhythmia (RSA), Center for Epidemiologic Studies Depression Scale (CES-D), perigenual anterior cingulate cortex (pACC), ventromedial prefrontal cortex (VMPFC), retrosplenial cortex (RC), and temporoparietal junction (TJ).

*p<0.05; **p<0.01

Table 10 Primary Database Correlations Between Independent Variables and Covariates (n=82)

	RSA	Openness to Feeling	CES-D	Age	Sex	IQ	BMI	Alcohol Use	Smoking Status
RSA		-0.23*							
Openness to Feeling	-0.23*						-0.27*	0.27*	
CES-D									
Age	-0.26*				0.27*			0.24*	
Sex				0.27*		-0.24*			
IQ					-0.24*		-0.23*		-0.28*
BMI		-0.27*				-0.23*		-0.32**	
Alcohol Use		0.27*		0.24*			-0.32**		
Smoking Status						-0.28*			

Note. Respiratory sinus arrhythmia (RSA), Center for Epidemiologic Studies Depression Scale (CES-D), intelligence quotient (IQ), and body mass index (BMI). Women are significantly older than men and men have higher IQ scores than women.

*p<0.05; **p<0.01

All hierarchical regression models were subjected to functional form and residual analyses, ensuring that function form was linear, heteroscedasticity was not present, residuals were normally distributed, and outliers (leverage) were not present. Multicollinearity was not present in any regression model. Separate, hierarchical regression models testing whether RSA, openness to feeling, or the CES-D were associated with mean pACC, VMPFC, retrosplenial cortex, or temporoparietal junction functional connectivity coefficients were not significant in any of the three databases (p values ranged from 0.13-0.95).

Proposed mediation models could not be tested. However, separate, exploratory, hierarchical regression models testing whether any of the individual BAs constituting the pACC, VMPFC, and retrosplenial cortex or the isolated right and left portions of the temporoparietal junction showed some significant relationships with the independent variables. In the Primary Database, a significant association between RSA and BA 30 was found (please see Table 11; results reported did not include the CES-D as a covariate because this model was intended to be part of the test of mediation described below. Results including the CES-D as a covariate were comparable). Moreover, a significant relationship between the CES-D and BA 30 was also found (please see Table 12).

Despite these significant regression models, the first steps towards demonstrating mediation, mediation among these variables was ultimately not supported because a hierarchical regression model with RSA as the independent variable and the CES-D as the dependent variable was not significant (p=0.92). Results were comparable in the Optimal RSA Database (please see Tables 13 and 14); the hierarchical regression model with RSA as the independent variable and the CES-D as the dependent variable was also not significant (p=0.90). Finally, while the relationship between RSA and BA 30 or the CES-D was not tested in the Optimal Openness to

Feeling Database (because this database had only as many participants with valid RSA data as did the Primary database, rendering redundant results), the relationship between the CES-D and BA 30 was, notably, not significant in this larger, more powerful dataset ($p=0.098$).

Table 11 Summary of Hierarchical Regression Analysis for RSA and BA 30 (n=82)

Variable	Beta	t	SE	ΔR^2
Step 1				
Sex	-0.27	-2.35	0.03	0.08*
Age	-0.14	-1.21	0.002	
BMI	-0.09	-0.79	0.08	
Tobacco Use	-0.08	-0.75	0.03	
Alcohol Use	0.21	1.82	0.01	
IQ	-0.07	-0.61	0.001	
Step 2				
RSA	-0.23	-2.06	0.06	0.05*

Note. Respiratory sinus arrhythmia (RSA), Brodmann area (BA), body mass index (BMI), and intelligence quotient (IQ).

*$p < 0.05$

Table 12 Summary of Hierarchical Regression Analysis for CES-D and BA 30 (n=82)

Variable	Beta	t	SE	ΔR^2
Step 1				
Sex	-0.24	-2.09	0.03	0.08*
Age	-0.15	-1.32	0.002	
BMI	-0.11	-0.97	0.08	
Tobacco Use	-0.02	-0.19	0.03	
Alcohol Use	0.25	2.19	0.01	
IQ	-0.08	-0.68	0.001	
Step 2				
CES-D	-0.26	-2.36	0.01	0.06*

Note. Respiratory sinus arrhythmia (RSA), Brodmann area (BA), body mass index (BMI), intelligence quotient (IQ), and Center for Epidemiologic Studies Depression Scale (CES-D).

*$p < 0.05$

Table 13 Summary of Hierarchical Regression Analysis for RSA and BA 30 (n=84)

Variable	Beta	t	SE	ΔR^2
Step 1				
Sex	-0.27	-2.36	0.03	0.08*
Age	-0.14	-1.21	0.002	
BMI	-0.09	-0.80	0.08	
Tobacco Use	-0.08	-0.73	0.03	
Alcohol Use	0.21	1.83	0.01	
IQ	-0.07	-0.60	0.001	
Step 2				
RSA	-0.23	-2.14	0.06	0.05*

Note. Respiratory sinus arrhythmia (RSA), Brodmann area (BA), body mass index (BMI), and intelligence quotient (IQ).

*$p < 0.05$

Table 14 Summary of Hierarchical Regression Analysis for CES-D and BA 30 (n=84)

Variable	Beta	t	SE	ΔR^2
Step 1				
Sex	-0.24	-2.09	0.03	0.08*
Age	-0.15	-1.30	0.002	
BMI	-0.09	-0.85	0.08	
Tobacco Use	-0.006	-0.05	0.03	
Alcohol Use	0.25	2.22	0.01	
IQ	-0.06	-0.54	0.001	
Step 2				
CES-D	-0.25	-2.34	0.01	0.06*

Note. Respiratory sinus arrhythmia (RSA), Brodmann area (BA), body mass index (BMI), intelligence quotient (IQ), and Center for Epidemiologic Studies Depression Scale (CES-D).

*$p < 0.05$

6.3 ANALYTIC APPROACH II

While our chosen statistical threshold was $p<0.0001$, cluster size 25, in keeping with some other prior literature, we also examined changes in functional connectivity strength at the more liberal thresholds $p<0.001$ and $p<0.005$, cluster size 20 and $p<0.05$, cluster sizes 100 and 150 (both extent thresholds yielded comparable results) (R. Bluhm, et al., 2008; Mormino, et al., 2011; Roy, et al., 2009). We also corrected for family wise error rate at the lower statistical thresholds. As there is some controversy in the literature regarding statistical threshold choice, results for all analyses will be presented (Van Dijk, et al., 2010; Vul, et al., 2009). To begin, all results from analyses conducted at $p<0.0001$, cluster size 25 and $p<0.001$, cluster size 20 were not significant, as were results from analyses that included correction for family wise error. Also, results from analyses conducted at $p<0.05$, cluster size 150 were quite similar to those conducted at $p<0.005$, cluster size 20. These analyses revealed rather comparable patterns of functional connectivity, results small in effect size, and new patterns of functional connectivity were largely conceptually unrelated to our hypotheses (e.g., some results showed functional connectivity with regions such as the occipital lobe) or were indicative of signal noise (e.g., functional connectivity was observed with the corpus callosum) rather than true neural activity. As such, results from these analyses will not be reported in detail.

That said, we found some evidence that PCC seed functional connectivity varied as a function of participants' RSA levels at the lower thresholds ($p<0.005$, cluster size 20 and $p<0.05$, cluster size 150; see Table 15); however, results were not consistent with our predictions nor the literature regarding RSA's neural correlates. Specifically, the connectivity observed between the PCC seed and corpus callosum is improbable and likely resulted from signal noise and/or errors in coregistration (errors may be due to the fact that our participant sample is about 20 years older

than the participant sample used to generate the MNI template). Likewise, the group level map that depicted how PCC seed functional connectivity varied as a function of participants' openness to feeling levels demonstrated some increased connectivity at $p<0.005$, cluster size 20 and $p<0.05$, cluster size 150 (see Table 16). Results were generally in keeping with our hypotheses, but were limited in scope and of small effect size.

Table 15 Brain Regions Showing Increased PCC Seed Connectivity in Association with Higher RSA

Brain Region	MNI Coordinates	BA	K_E	t value	p value
Corpus Callosum	-6 -34 16		112	4.71	0.00

Note. MNI=Montreal Neurological Institute, BA=Brodmann area. $p<0.005$, cluster size 20.

Table 16 Brain Regions Showing Increased PCC Seed Connectivity in Association with Higher RSA (Other Statistical Cutoff)

Brain Region	MNI Coordinates	BA	K_E	t value	p value
Corpus Callosum	-6 -34 16		438	4.71	0.00
	10 -32 20		438	2.86	0.002
	-18 -48 16		438	2.23	0.011

Note. MNI=Montreal Neurological Institute, BA=Brodmann area. $p<0.05$, cluster size 20.

Finally, the group level map that depicted how PCC seed functional connectivity varied as a function of participants' CES-D scores demonstrated some increased connectivity at $p<0.005$, cluster size 20 and $p<0.05$, cluster size 150 (see Table 17). These results were of small effect size and were mixed with regard to how they fit with prior literature; past studies have not reported associations between depression and functional connectivity in the cerebellum, cerebrum, temporal lobe, or hippocampus (the last two regions observed only at the lowest statistical threshold). However, they have reported increased connectivity with frontal regions and the cingulate cortex (Broyd, et al., 2008; Greicius, et al., 2007a; Sheline, et al., 2010). Lastly, decreased, but not increased, caudate connectivity has been reported (Broyd, et al., 2008; Greicius, et al., 2007a). These results should be interpreted with the caveat that all cited studies of depression and the default mode RSNN were of a case versus control design, including clinically depressed participants. Also, while Bluhm and colleagues (2009) used a PCC seed methodology to isolate the default mode RSNN, Sheline and colleagues (2010) used a precuneus seed and Broyd and colleagues (2008) and Greicius and colleagues (2007) used ICA. These methodological differences may account for disparities between our results and those reported in the literature.

Table 17 Brain Regions Showing Increased PCC Seed Connectivity in Association with Higher Openness to Feeling Levels

Brain Region	MNI Coordinates	BA	K_E	t value	p value
Mid Frontal Gyrus	44 8 46		181	3.79	0.000
	36 6 58		181	3.22	0.001
	36 6 42		181	3.21	0.001
Parietal Lobe	10 -50 38	31	21	3.04	0.002

Note. MNI=Montreal Neurological Institute, BA=Brodmann area. $p<0.05$, cluster size 20.

We also examined negative associations between PCC seed functional connectivity and participants' CES-D scores and found significant associations of rather small effect size at the lower thresholds ($p<0.005$, cluster size 20 and $p<0.05$, cluster size 150; see Table 18). These results were either inconsistent with prior literature (i.e., the precuneus, cuneus, and frontal regions typically are associated with increased, not decreased, connectivity (Broyd, et al., 2008; Greicius, et al., 2007a; Sheline, et al., 2010) or had not been reported in the prior literature (i.e., no prior studies report decreased connectivity associated with the postcentral or precentral gyri and parietal, occipital (only observed at the lowest statistical threshold), or temporal cortices). Again, the lack of consistency between our results and those reported in the literature may be due to significant methodological differences.

Table 18 Brain Regions Showing Increased PCC Seed Connectivity in Association with Higher Openness to Feeling Levels (Other Statistical Cutoff)

Brain Region	MNI Coordinates	BA	K_E	t value	p value
Mid Frontal Gyrus	44 8 46		729	3.79	0.000
	36 6 58		167	3.22	0.001
	36 6 42		193	3.21	0.001
Parietal Lobe	-60 -50 32		193	3.16	0.001
	-54 -48 48		193	2.14	0.018
	62 -50 32		828	2.70	0.004
	8 -54 50	7	358	2.11	0.019
Dorsal Posterior Cingulate	10 -50 38	31	358	3.04	0.002
Insula	56 -44 20	13	828	2.98	0.002
Temporal Lobe	62 -54 20		828	2.70	0.004
	-46 -58 -2		164	2.30	0.012
	-54 -52 -12		164	2.13	0.018
Dorsolateral Prefrontal Cortex	-36 8 40	9	152	2.56	0.006

Table 18 (continued)

Brain Region	MNI Coordinates	BA	K_E	t value	p value
Subgyral Frontal Lobe	-48 -2 40		152	2.34	0.011
	-48 -10 44		152	2.05	0.022
Limbic Lobe	16 -20 38		152	2.47	0.008
	8 -22 34		248	2.21	0.015
Anterior Cingulate Cortex	-2 -24 38	24	248	1.93	0.028
Occipital Lobe	-52 -62 -12	37	164	2.30	0.012

Note. MNI=Montreal Neurological Institute, BA=Brodmann area. $p<0.05$, cluster size 150.

Since there were 1) no significant associations between RSA, Openness to Feeling, CES-D Scores and PCC seed functional connectivity at our stringent threshold and 2) associations between PCC seed functional connectivity and RSA were not conceptually significant at lower thresholds (i.e., connectivity with the corpus callosum was observed) we were unable to assess the spatial overlap between connectivity maps.

6.4 IMPORTANT ANALYTIC CAVEAT

It is important to note that our measures of RSA were limited; inter-rater reliability for a random sampling of 20 participants was $r=0.60$, $p<0.05$. Many data recordings contained artifacts, research assistants who collected the data noted technological difficulties during the ECG recording process, and another piece of equipment (a freezer) in close proximity to the ECG introduced artifacts into recorded signals. These problems were largely resolved half-way through data collection, leaving 34 participants with data ostensibly collected without these confounds. Inter-rater reliability for these participants' RSA values was $r=0.95$, $p<0.05$. All of the Analytic Approach I and II analyses were conducted only using these participants' data. However, no Analytic Approach I regression models were significant (p values ranged from 0.315-0.973). Also, no Analytic Approach II models showed significant functional connectivity at the various thresholds listed in the previous section. Given the smaller sample size, we dropped covariates in various permutations depending on statistical relationships with other variables and on the basis of prior literature, but this did not affect the significance of results.

6.5 SUPPLEMENTARY ANALYSES

To probe our findings, or lack thereof, further, we conducted supplementary analyses assessing the functional connectivity of a brain region highly associated with RSA; based on the literature, we chose BA 25, a brain region on the pACC/VMPFC border (MNI coordinates for the seed are 0 12 -4) (Egizio, 2010; Yu, et al., 2011). As detailed in the "Introduction" the pACC and VMPFC are the two brain regions most consistently associated both with changes in RSA in humans and with preganglionic vagal outputs shown in animal studies (Baklavadzhyan, et al., 2000; Bannister & Mathias, 1992; Benarroch, 1997; Cechetto, 1994; Dampney, 1994; Devinsky, et al., 1995; Groenewegen & Uylings, 2000; Loewy & McKellar, 1980; Loewy & Spyer, 1990; Neafsey, 1990; Nisimaru, 2004; Ongur & Price, 2000; Oppenheimer, et al., 1992; Resstel & Correa, 2006; Ter Horst & Postema, 1997; Van Eden & Buijs, 2000; Verberne & Owens, 1998; Vogt & Gabriel, 1993; Waites, et al., 2005). Thus, we deemed it most logical to investigate functional connectivity associated with the juncture of these two very important brain regions at the subgenual ACC, BA 25. Moreover, research suggests that this particular BA is a primary, hub-like, autonomic region with many structural and functional connections to several other areas of the brain implicated in autonomic processing (Benarroch, 1997; Dampney, 1994; Dampney, et al., 2002; Hurley KM, Herbert H, Moga MM, & CB, 1991; Hurley, Herbert, Moga, & Saper, 1991; Kimmerly, O'Leary, Menon, Gati, & Shoemaker, 2005; Loewy & Spyer, 1990; Margulies, et al., 2007; Resstel & Correa, 2006; Spyer, 1999; Thayer, et al., 2008; Verberne & Owens, 1998). Functional connectivity associated with BA 25 can be seen in Figure 5 and is detailed in Table 19.

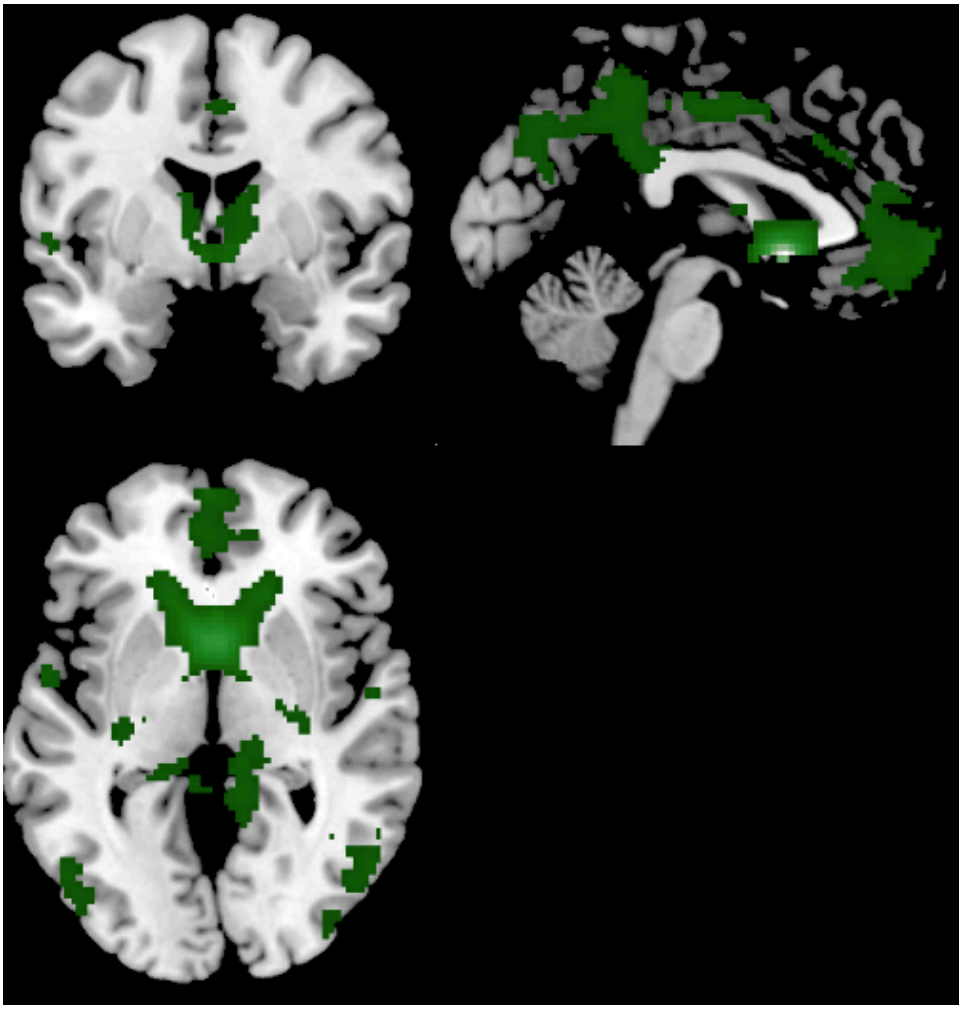

Figure 5 View of the RSA Network Isolated in This Study

Note. Functional connectivity map depicted here drawn from the Primary database (n=82). We examined functional connectivity between the BA25-seed and the whole brain (for ease of viewing the specific brain regions that compose this network, $p<0.0000000000000001$, cluster size=20).

Table 19 Brain Regions Showing Increased PCC Seed Connectivity in Association with Higher CES-D Scores

Brain Region	MNI Coordinates	BA	K_E	t value	p value
Anterior Lobe Cerebellum	0 -44 -10		68	3.92	0.000
Subgyral Frontal Lobe	-20 10 34		72	3.59	0.000
Cingulate Gyrus	-16 20 36		72	2.83	0.003
Cerebrum, sub-lobar, Extra Nuclear, White Matter	30 -44 6		39	3.29	0.001
Caudate Body	16 -14 24		40	3.23	0.001

Note. MNI=Montreal Neurological Institute, BA=Brodmann area, CESD=Center for Epidemiologic Studies Depression Scale. $p<0.005$, cluster size 20.

However, RSA, openness to feeling, and CES-D levels were not significantly associated with changes in the BA 25/RSA RSNN's functional connectivity strength at higher statistical thresholds ($p<0.0001$, cluster size 20 and $p<0.001$, cluster size 20) or when correction for family wise error was applied at lower statistical thresholds. Moreover, RSA levels were not significantly associated with changes in the network's functional connectivity at lower statistical thresholds either ($p<0.005$, cluster size 20 and $p<0.05$, cluster size 150). The group level map that depicted how network functional connectivity varied as a function of participants' openness to feeling levels demonstrated some increased connectivity at $p<0.005$, cluster size 20 and $p<0.05$, cluster size 150 (see Table 20; results from analyses at the lowest statistical threshold were comparable to those presented in this table).

These results are difficult to interpret because we did not predict any particular associations between regions within the RSA RSNN and openness to feeling and there is no literature base to compare our results to. However, they are somewhat similar to those found for the association between default mode RSNN functional connectivity and openness to feeling but are of rather small effect size.

Finally, although the group level map that depicted how BA 25 seed functional connectivity positively varied as a function of participants' CES-D levels was not significant at any statistical threshold, the group level map depicting the variables' negative association showed slightly different results. At $p<0.005$, cluster size 20 and $p<0.05$, cluster size 150, there were some significant results (see Table 21; results from analyses at the lowest statistical threshold were generally similar to those presented in this table).

These results are also difficult to interpret because we did not predict any particular associations between regions within the RSA RSNN and CES-D scores and there is no literature

base to compare our results to. However, they are somewhat similar to those found for the association between default mode RSNN functional connectivity and CES-D scores but are of rather small effect size.

Table 20 Brain Regions Showing Increased PCC Seed Connectivity in Association with Higher CES-D Scores (Other Statistical Cutoff)

Brain Region	MNI Coordinates	BA	K_E	t value	p value
Anterior Lobe Cerebellum	0 -44 -10		418	3.92	0.000
	4 -46 -2		418	2.63	0.005
Subgyral Frontal Lobe	-20 10 34		587	3.59	0.000
	-36 54 -10		301	2.01	0.005
	-22 42 2		301	2.45	0.008
	-26 34 6		301	2.32	0.012
Cingulate Gyrus	-16 20 36		587	2.83	0.003
Frontal Eye Fields	-22 38 48	8	587	2.62	0.005
Temporal Lobe	34 -52 8		215	2.17	0.017
Corpus Callosum	2 0 20		403	3.16	0.001
	10 24 14		301	2.59	0.006
	14 32 6		150	2.20	0.015
Hippocampus	32 -16 -14		403	2.80	0.003
Caudate Body	16 -14 24		403	3.23	0.001

Note. MNI=Montreal Neurological Institute, BA=Brodmann area, CESD=Center for Epidemiologic Studies Depression Scale. $p<0.05$, cluster size 150.

Table 21 Brain Regions Showing Decreased PCC Seed Connectivity in Association with Higher CES-D Scores

Brain Region	MNI Coordinates	BA	K_E	t value	p value
Postcentral Gyrus	-38 -26 50		140	3.83	0.000
	-34 -36 50		23	3.23	0.001
	-58 -12 26	3	42	3.10	0.001
Subgyral Frontal Lobe	30 -22 50		22	3.11	0.001
	42 -8 26		57	3.09	0.001
Precuneus	20 -70 28		28	3.11	0.001
	-22 -50 44		42	3.10	0.001
Inferior Frontal Gyrus	46 6 32		28	3.11	0.001
Inferior Parietal Lobe	66 -28 30	40	29	3.19	0.001
Mid Temporal Gyrus	-60 -58 0		28	3.17	0.002
Inferior Temporal Gyrus	-58 -48 -2		28	3.05	0.002
Precentral Gyrus	46 -6 38	6	57	2.71	0.003
Cuneus	-18 -90 20	18	24	2.97	0.002

Note. MNI=Montreal Neurological Institute, BA=Brodmann area. $p<0.005$, cluster size 20.

7.0 DISCUSSION

7.1 RESULTS RELATED TO THE PRIMARY HYPOTHESES

The primary goal of the current study was to establish that functional connectivity strength within the default mode RSNN varies in association with RSA levels. The secondary, more exploratory goal of this research was to ascertain whether the association between the default mode RSNN and resting RSA was related to self-focused cognition. This hypothesis was also not supported. Functional connectivity strength within the default mode RSNN did not vary in association with one's level of self-focused cognition and activity within the default mode RSNN did not commonly covary with RSA and self-focused cognition.

Notably, there is some controversy in the literature regarding statistical threshold choice. Thus, we took care in examining relationships among our variables of interest across a range of accepted statistical thresholds (i.e., from $p<0.05$, cluster size 100 to $p<0.0001$, cluster size 25). Although several analyses at lower statistical thresholds showed some significant relationships, these results were of small effect size and largely lacked conceptual significance. Specifically, some results showed functional connectivity with regions such as the occipital lobe or other brain regions clearly unrelated to our hypotheses. Other results were indicative of signal noise (e.g., functional connectivity was observed with the corpus callosum) rather than true neural activity. Most importantly, these results observed at lower statistical thresholds lost significance once corrected for family wise error. As such, we conclude that all of our findings were generally lacking in significance and not supportive of our hypotheses.

Our lack of supportive findings was rather surprising because the literature detailed in the Introduction quite strongly supported at least a relationship between functional connectivity strength within the default mode RSNN and RSA. However, we failed to find an association between these variables using two separate analytic approaches, one using more stringent criteria for assessing default mode RSNN functional connectivity and another using more liberal criteria. As such, the lack of association between default mode RSNN functional connectivity strength and RSA appears reliable. Given the smaller amount of literature supporting associations between 1) default mode RSNN functional connectivity strength and openness to feeling and 2) conjoint relationships between default mode RSNN functional connectivity, RSA, and openness to feeling, it is less surprising that our analyses, merely exploratory to begin with, assessing these relationships were not significant.

It might be suggested that our lack of significant findings was due to methodological errors, specifically in isolating the default mode RSNN and in recording RSA. However, data are to the contrary. Firstly, we isolated a valid default mode RSNN that included all of the brain regions typically associated with the network, see Analytic Approach I for further elaboration of this point; Figure 3 depicted a "typical" default mode RSNN functional connectivity map, similar to those obtained by several other researchers, suggesting that the approach used and results obtained in the current study were valid and reliable (Birn, et al., 2006; Fransson, 2006; Greicius, et al., 2003b; Long, et al., 2008; Waites, et al., 2005; H. Yan, et al., 2009). We also based our choice of PCC seed region on a substantial literature base (see Isolation of the Default Mode RSNN for additional information) and even added a supplementary analysis in which another network was isolated for comparative purposes (see Supplementary Analyses), allowing us to determine that incorrect seed region choice was not likely the reason for our null findings.

Although there are several ways to isolate the default mode RSNN in addition to the seed-based approach used in this study (one of the most popular methods aside from the seed-based approach is ICA, described in the Introduction), the literature suggests that, regardless of the statistical methodology used to isolate the default mode RSNN, the results are typically highly correlated (Egizio, 2010; Long, et al., 2008). Thus, using another method to isolate the default mode RSNN likely would not have altered our results. Finally, while participants in this study were not particularly instructed to keep their eyes open or closed during the baseline neuroimaging protocol, research suggests that the functional connectivity among brain regions forming the default mode RSNN isolated using various statistical methods and with eyes open/closed/fixated is, in general, moderately reliable ($r = 0.69$) when examined within subjects (Damoiseaux, et al., 2006; Honey, et al., 2009; Meindl, et al., 2009; Shehzad, et al., 2009; Van Dijk, et al., 2010).

Regarding the recording of RSA, some of our data was less reliable than desired, but analyses conducted with participants who had particularly reliable data produced similar results. Also, we replicated the common finding that older age is significantly associated with lower RSA. Overall, it is not likely that errors in default mode RSNN isolation or RSA recording accounted for our failure to support our hypotheses.

All this being said, some methodological confounds may have negatively affected our findings. RSA data was recorded neither simultaneously with default mode RSNN functional connectivity nor in the same postural stance (i.e., RSA was recorded while participants were seated whereas scanning was conducted when they were supine). It is possible that the relationship between the variables is time-sensitive, influenced by environmental context, and bodily posture, rendering it best captured with contemporaneous measures.

Specifically, participants underwent imaging on average 4 weeks prior to RSA collected; the two measures were not simultaneously assessed. As such, it is possible that participants' RSA in the laboratory environment, a more familiar, less threatening place, may have been different from their RSA in the less-familiar, possibly more threatening scanner. Research suggests that RSA levels fluctuate as a function of laboratory tasks, thus it is possible that they may change in association with recording setting, particularly if settings are perceived as qualitatively different (Porges, Doussard-Roosevelt, & Maiti, 1994; Spalding, et al., 2000). It is also possible that RSA and the default mode share a very time-sensitive, contemporaneous relationship only captured with simultaneous recording. Drawing on the greater default mode RSNN literature, research shows that the default mode RSNN is quite sensitive to changes in an individual's level of arousal. Expressly, there is decreased functional connectivity among the regions of the default mode RSNN while participants sleep and there are increases and decreases reported in default mode RSNN functional connectivity while participants are under the influence of various types of anesthesia (Nallasamy & Tsao, 2011; Samann, et al., 2011; Stamatakis, Adapa, Absalom, & Menon, 2010). Since we know that participants' levels of arousal and engagement/interest in experimental protocols may change across experimental settings, this is more evidence that researchers who wish to study the default mode RSNN in conjunction with physiological measures should assess default mode RSNN activity and such physiological measures contemporaneously for optimal results indicative of their concordance.

Furthermore, while the assessment of resting RSA via ECG is fairly passive, requires little participant engagement, and is likely not overly threatening, the process of being scanned and trying to relax at one's "baseline" state in such a foreign environment calls into question how comparable the "resting baseline" RSA data and scanning data we obtained is. Did we really

obtain a resting baseline in both settings, or, did we get at qualitatively different cognitive states? While contemporaneous measurement of RSA during scanning would partially address this problem, it would be most useful to also have participants complete a debriefing interview in which they are surveyed about how relaxed, calm, and at rest they felt during the protocol; relatedly, they should be questioned as to whether they actually allowed their minds to wander without ruminating on any particular topic. Future research examining these variables simultaneously must be undertaken to better understand and expand upon these potential relationships.

Regarding bodily posture and RSA, research has established that individuals' RSA levels are lower during experimental manipulations such as the head-up tilt than they are while individuals are supine (Brown, Bryant, Mundel, & Stannard, 2008; Elstad, Toska, Chon, Raeder, & Cohen, 2001; Freeman, 2006). Thus, there is likely discord between our participants' RSA levels in the laboratory versus in the scanner, possibly sharing differential relationships with default mode RSNN functional connectivity strength. In order to optimally parse out relationships between default mode RSNN functional connectivity strength and RSA measures should be recorded simultaneously, if the equipment is compatible, or at least with participants in the supine position during ECG recording.

In addition to these methodological considerations concerning RSA, there are alternative experimental designs we could have used to test our hypotheses. For example, it is possible that functional connectivity is not related to RSA and that the activity of particular brain regions at rest, assessed individually, is more relevant. This hypothesis could be tested by examining regional deactivation maps in which resting baseline neuroimaging data is mathematically subtracted from resting state data to produce so-called "deactivation maps." Brain regions

isolated in these maps commonly show higher levels of activity during the resting protocol than during the task-engaged protocol, effectively "deactivating" during the task-engaged protocol. Perhaps correlating the activity within such "deactivated" brain regions with RSA would be a useful approach. Moreover, most prior studies of self-focused cognition were task-based (see the Self-Focused Cognition section for more details). If participants engaged in a task such as relaxation training while in the scanner and also having peripheral cardiovascular recordings conducted, their brain deactivation and cardiovascular functioning could be compared to measures collected during a control, baseline scanning protocol.

Additionally, although there was adequate variance in our openness to feeling measure, (suggesting that relationships between it, RSA, and default mode RSNN functional connectivity should have been detectable, if present) openness to feeling is only one measure of self-focused cognition. It is possible that other survey measures of this construct tapping into different dimensions described in the Introduction such as the personal experience of emotions, decision-making, or bodily awareness may relate differently to RSA and default mode RSNN functional connectivity.

Despite all of the different avenues for future research described above, we must address the possibility that default mode RSNN connectivity strength just is not associated with RSA, contradicting our primary hypothesis. There are several reasons why the two variables may not be related. First of all, researchers first conceptualized the default mode RSNN as a set of brain regions whose task was to support various neural homeostatic processes such as neuronal repair and cellular metabolism (Fukunaga, et al., 2008; Gusnard, et al., 2001; Raichle, et al., 2001). Although researchers have never directly tested this hypothesis, it guided early work in the field of default mode RSNN study. This original theory, if it is an accurate characterization of the

default mode RSNN's functional purpose, does not necessarily entail that the default mode RSNN should be involved in peripheral bodily functions like cardiovascular regulation, or RSA output more specifically. Within this framework, it is not surprising that we failed to find an association between default mode RSNN functional connectivity strength and RSA.

Secondly, much of our argument supporting a relationship between the default mode RSNN and RSA was based on the fact that several brain regions are commonly associated with these variables. While such brain structural overlap is promising, it does not indicate a definitive association between the default mode RSNN and RSA. Research demonstrates that brain regions have many different functions; for example, Table 1 details how the pACC is involved in autonomic function as well as other emotional and cognitive processes. As such, it may be overly simplistic to assume that, just because the default mode RSNN includes many brain regions associated with RSA, the default mode RSNN's functional purpose is related to RSA output. It could just as easily be associated with the emotional or cognitive processes listed. Furthermore, neural functional connectivity research is in its infancy and it is possible that, when brain regions work together as a functional network, the network as a whole takes on a new purpose or processing capacity that supersedes the functionality of its component brain regions.

In conclusion, unpublished research (Egizio, et al., 2011) shows relationships between default mode functional connectivity strength and measures of baroreflex function. Specifically, the bilateral cerebellum, right VMPFC, right anterior insula and mid-ACC showed increased PCC-seed connectivity associated with higher baroreflex sensitivity (BRS; a measure of the magnitude of heart rate (HR) responses corresponding to systolic blood pressure (SBP) changes), controlling for activity within the fourth brain ventricle, age, gender, resting SBP, and smoking status ($p<0.005$, cluster size 50). Also, the right pons, left cerebellum, midline pACC, and right

VMPFC showed increased PCC-seed connectivity associated with a greater baroreflex effective index value (BEI; a measure of how often SBP changes are met with appropriate compensatory changes in HR), controlling for activity within the fourth brain ventricle, age, gender, resting SBP, and smoking status ($p<0.005$, cluster size 50). The participant sample comprised 99 adults who were close in age and gender distribution to participants in the current study (see Table 5 for the current study (Primary Database) and mean age=40, SD=6.08, 47 male for the unpublished study); they also met inclusion criteria identical to that used in the current study, had similar smoking status' skewed towards no history of smoking, and had similar body mass indices (BMI; see Table 5 for the current study (Primary Database) and mean BMI=3.32, SD=0.18 for the unpublished study). However, participants in the unpublished study had significantly greater SBP values ($t= -5.35$, $p>0.001$), but comparable DBP values (current study SBP mean=113.30 mmHg, SD=8.93 and DBP mean=73.34 mmHg, SD=7.28; unpublished study SBP mean=121.35 mmHg, SD=10.07 and DBP mean=73.38 mmHg, SD=7.11).

It is quite interesting that we were able to detect associations between default mode RSNN connectivity strength and measures of baroreflex function, but not between default mode RSNN connectivity strength and RSA, a measure presumptively related to baroreflex function. Research suggests that the resting baseline correlation between RSA (quantified using the peak-to-valley method) and BRS is approximately 0.60, $p<0.05$ (Reyes del Pasoa, Langewitzb, Roblesc, & Pérezc 1996). However, the physiological relationship between baroreflex function and RSA is not necessarily one-to-one; although the baroreflex influences RSA, in part, RSA levels are also determined by such variables as central respiratory drive, central and peripheral chemoreflexes, respiratory rate and depth, and pulmonary stretch mechanisms (Egizio, Eddy, Robinson, & Jennings, 2010). Indeed, the Reyes del Paso and colleagues (1996) noted that following beta-

adrenergic blockade, when heart period is predominantly under vagal control, RSA did not significantly predict heart period variability. However, BRS predicted more than 97% of heart period variability. The authors did not interpret this finding, citing the preliminary nature of their results (their sample only comprised nine male participants), but it does beg the question of whether RSA levels and baroreflex function can dissociate. Such dissociation seems possible since RSA levels are multiply determined and no research, to our knowledge, has systematically examined the variance in RSA accounted for by *each* variable contributing to RSA levels/output.

Other explanations for our finding that default mode RSNN functional connectivity strength and baroreflex function covary while default mode RSNN functional connectivity and RSA do not include 1) that participants in the baroreflex functioning study had significantly greater SBP values than participants in the current RSA study, 2) postural considerations and 3) timing and contextual considerations. Regarding the first point, the differences in SBP can suggest potential baseline differences in cardiovascular functioning between the samples, accounting for the divergent findings. However, research suggests that blood pressure measurements taken using a forearm cuff (as done in the current study) often dissociate from those obtained using a Finometer due to various physiological factors (Bogert & van Lieshout, 2005). Thus, differences in the recording device used may also account for variance in SBP values. Regarding the second point, postural considerations, participants in the current study underwent RSA recordings while seated in the laboratory. Conversely, scanning was conducted while participants were supine. As previously noted, research has established that individuals' RSA and blood pressure levels are lower during experimental manipulations such as the head-up tilt than they are while individuals are supine (Brown, et al., 2008; Elstad, et al., 2001; Freeman, 2006). Thus, there is likely discord between our participants' RSA levels in the laboratory versus in the scanner, possibly sharing

differential relationships with default mode RSNN functional connectivity strength. Notably, such a postural confound is absent in the unpublished baroreflex functioning study. In order to optimally parse out relationships between default mode RSNN functional connectivity strength, RSA, and BRS, all measures should be recorded in a single study (as such data is not available to us in the current study), preferably simultaneously if the equipment is compatible, or at least with participants in the supine position during all physiological recordings. Finally, regarding timing and postural considerations, participants in the baroreflex study had their cardiovascular functioning assessed closer in time to scanning than did participants in the current study, potentially maximizing temporal concordance between peripheral physiological and brain activity measurements. Also, baroreflex function was assessed while participants were in a simulated scanner, likely minimizing environmental/contextual confounds. Overall, it may be possible that the default mode RSNN is indeed more involved in blood pressure control mechanisms than it is in vagal output, but additional research assessing the relationship among default mode RSNN activity, RSA, and baroreflex function controlling for the many confounding factors listed above is needed to support this theory.

7.2 ANCILLARY RESULTS

7.2.1 Correlations

Despite the null findings described above, significant correlations were found between the mean pACC and 1) mean VMPFC, 2) mean retrosplenial cortex, and 3) mean temporoparietal cortex. There were also significant correlations between the mean VMPFC and mean temporoparietal junction. These results suggest that activity within the primary default mode RSNN brain regions of interest covaried, as would be expected, and that the pACC may be a "hub" region particularly important in that covariation.

Interestingly, we found a significant positive correlation between openness to feeling and the CES-D. The literature suggests that an inverse relationship between the variables should be expected (Costa, et al., 2005; Heisel, et al., 2006). That said, the correlation we detected was of quite small effect size and, consequently, may not be particularly reliable (Cohen, 1992). Also, several correlations of small effect size between our main independent variables (RSA, openness to feeling, and the CES-D) and our covariates were reported in Table 10. Some relationships were particularly marginal and not likely reliable. Specifically, RSA and openness to feeling were correlated at $p=0.042$ and this relationship did not persist in the Optimal Openness to Feeling Database that included more participants and, consequently, had greater statistical power (see Table 9). Age and alcohol consumption were correlated at $p=0.031$ and IQ and BMI at $p=0.041$, as well. Our results do suggest that participants with lower IQ scores engage in less healthy behaviors (e.g., smoking and possibly poor diet/nutrition as suggested by their higher BMIs), a finding in keeping with previous literature (Muennig, et al., 2011). Also replicating prior research, we observed a significant inverse relationship between age and RSA (Jennings & Yovetich, 1991). Relatedly, we replicated an association between older age and increased

alcohol consumption, though this result should be interpreted cautiously since the mean amount of alcohol consumption was quite minimal in our sample (see Table 5) (Kalapatapu, Paris, & Neugroschl, 2010). Our finding that men had significantly higher IQ scores than women is not unusual as the literature suggests that IQ is not consistently higher for either gender, a result possibly due to methodological differences between studies (Vogel, 1990). Finally, increased alcohol consumption is typically associated with higher BMI (Grucza, et al., 2010); this finding makes it difficult to interpret our inverse result, but our result should be viewed cautiously since the mean amount of alcohol consumption was quite minimal in our sample.

7.2.2 Analytic approach I

While the relationship between the CES-D and BA 30 was unreliable in the current study, the relationship between RSA and BA 30 appeared to be. However, this result is difficult to interpret since BA 30 represents only a small portion of the brain and a fraction of one of our areas of interest, the retrosplenial cortex (BAs 29 and 30). No previous literature, to our knowledge, has reported a relationship between BA 30 and a measure of cardiovascular function and we did not predict a relationship between RSA and the retrosplenial cortex. Moreover, BA 30 only accounted for about five percent of the variance in RSA and the p values associated with this effect were 0.035 and 0.036 in the Primary Database and in the Optimal RSA Database, respectively. These statistics suggest that the result is rather marginal. Overall, this is an interesting, exploratory finding that warrants additional research to 1) replicate it and 2) better understand and expand upon its functional significance.

7.2.3 Analytic approach II

Our lack of significant associations between PCC seed functional connectivity and participants' CES-D scores may, initially, appear at odds with literature suggesting that depression is

associated with both increased and decreased default mode functional connectivity (R. Bluhm, et al., 2009; Broyd, et al., 2008; Greicius, et al., 2007a; Sheline, et al., 2010). However, all prior research explored these relationships with participant samples who were clinically depressed and, in some cases, taking anti-depressant medications. Our participants denied current and past diagnosis of depression and reported quite low levels of depressive symptomatology (mean (square root)=2.46, SD=1.40). Given this very substantial difference in participant characteristics and the minimal variance in depressive symptoms reported by our participants, it is not surprising that we did not replicate previous research findings.

7.2.4 Supplementary analyses

Our analyses examining how functional connectivity within the BA 25/RSA network varied in association with RSA, openness to feeling, and CES-D scores were undertaken to determine whether seed region choice played a role in whether we found evidence to support our hypotheses. Unfortunately, our results with this network mirrored our results with the default mode RSNN. This suggests that our null findings were not due to seed region choice and that our variables of interest are just not associated with brain activity in the manner we predicted. That said, it is surprising that we failed to find at least a significant association between RSA and the BA 25/RSA network, since that network was specifically generated to examine functional connectivity within brain regions purported to be very important in vagal output. Since such a network and analytic strategy has not been described in the literature before, to our knowledge, it is difficult to interpret this finding. However, our lack of a significant association may well be due to the same methodological issues that potentially affected our default mode RSNN and RSA analyses (e.g., that RSA was not recorded simultaneously during scanning and that participants

were seated during RSA recording but supine during scanning). As such, research addressing these methodological confounds may produce more supportive results.

7.3 OVERALL CONCLUSIONS

Generally, the current study did not support the hypotheses that default mode RSNN functional connectivity is related to RSA levels, openness to feeling, or that it mediates a relationship between the latter two variables. The lack of relationship between functional connectivity strength within the default mode RSNN and RSA is particularly surprising in light of a sound literature base supporting a hypothetical relationship. But, given the smaller amount of literature supporting associations between 1) default mode RSNN functional connectivity strength and openness to feeling and 2) conjoint relationships between default mode RSNN functional connectivity, RSA, and openness to feeling, it is less surprising that our analyses, merely exploratory to begin with, were not significant.

While we do not believe our lack of significant findings is associated with methodological *errors*, we do assert that methodological *confounds* may have negatively impacted our research. In particular, our RSA data was recorded neither simultaneously with default mode RSNN functional connectivity nor in the same postural stance (i.e., RSA was recorded while participants were seated whereas scanning was conducted when they were supine); it is possible that the relationship between the variables is time-sensitive, influenced by environmental context, and bodily posture, rendering it best captured with contemporaneous measures.

In general, we do not believe our null findings in this particular study should preclude future research in this area. Many of our analyses in Analytic Approach II showed significant relationships between our variables of interest and default mode RSNN functional connectivity

strength at liberal thresholds, suggesting that our hypotheses have the potential to be supported. Addressing the confounding factors detailed previously in the Discussion may help us obtain positive results in future studies. Moreover, research demonstrating that default mode RSNN functional connectivity is associated with baroreflex function (a measure physiologically related to RSA) is also promising.

Taken together, future research concomitantly analyzing relationships between default mode RSNN functional connectivity strength, RSA, and baroreflex function, all preferably recorded simultaneously if the equipment is compatible (or at least with participants supine during all physiological recordings/in a simulated scanner and recordings taken in close temporal proximity to scanning), might provide more rich, informative results about how the default mode RSNN may be associated with cardiovascular function. We hope to conduct such additional research using Peter Gianaros, PhD's data as it addresses many of these confounds. Specifically, Dr. Gianaros' data includes a larger participant sample, providing greater statistical power. He also took Finapres measurements during a simulated scanning protocol, addressing environmental/contextual and postural confounds that may influence peripheral physiological recording. Additionally, the time between participants' simulated and real scanning sessions was shorter than the several-month interval common in the current study. Finally, his Finapres data allows us to examine and compare relationships between default mode RSNN functional connectivity strength and both baroreflex function and RSA. Comparing results gleaned from his data with those of the current study would provide a rich basis for understanding the relationship between default mode RSNN functional connectivity and cardiovascular function.

Overall, while the current research did not support our predicted associations, it provided valuable information that may help refine research questions and analytic techniques to be used

in future studies. This study represents the first foray into complex RSNN research, attempting to link neural functional connectivity to peripheral physiology and psychological functioning. This work showed that such research is not easy to conduct and particularly demonstrated that researchers must try to minimize potential confounds as they design their research protocols.

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