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Moderating Effects of Harm Avoidance on Resting-State Functional Connectivity of the Anterior Insula

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MODERATING EFFECTS OF HARM AVOIDANCE ON RESTING-STATE

FUNCTIONAL CONNECTIVITY OF THE ANTERIOR INSULA

by

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ABSTRACT

MODERATING EFFECTS OF HARM AVOIDANCE ON RESTING-STATE
FUNCTIONAL CONNECTIVITY OF THE ANTERIOR INSULA

by

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The University of Wisconsin-Milwaukee, 2018
Under the Supervision of Associate Professor Christine L. Larson, Ph.D.

As an index of behavioral inhibition and an individual's propensity to avoid, rather than seek, potentially dangerous situations, harm avoidance has been linked to internalizing psychopathology. Altered connectivity within intrinsic functional neural networks has been linked to internalizing psychopathology; however, less is known about the effects of harm avoidance on functional connectivity within and between these networks. Importantly, harm avoidance may be distinguishable from trait anxiety and have clinical relevance as a risk factor for psychopathology. To this end, the current study aimed to examine associations between harm avoidance and resting state functional connectivity. A sample of undergraduate students (n=92) completed a resting state functional magnetic resonance imaging (fMRI) scan and self-report measures of harm avoidance and trait anxiety. Results indicated a main effect of harm avoidance on functional connectivity, such that higher harm avoidance was associated with decreased connectivity between the right anterior insula and clusters in the precuneus/PCC, left lateral parietal lobe, and left superior/middle frontal gyrus. Higher harm avoidance was also associated with decreased connectivity between the left anterior insula and precuneus/PCC. There were no effects of trait anxiety on functional connectivity of the anterior insula. Overall, the results indicate that individual differences in harm avoidance relate to disruptions in internetwork connectivity that may contribute to deficits in appropriately modulating attentional focus.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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Research in personality has long been interested in understanding the latent structure of personality traits and linking these traits to psychological and biological systems (Cloninger, 1993; DeYoung et al., 2010; Watson, Clark, & Harkness, 1994). In pursuit of this line of work, research has shed light on complex interactions of heritable and stable traits associated with patterns of emotional and behavioral processes, neurobiological features, and clinical phenotypes (Kennis, Rademaker, & Geuze, 2013; Watson et al., 1994; Watson, Clark, & Chmielewski, 2008). Personality encompasses a wide range of observable, long-standing traits, including several broad, higher-order factors (e.g., positive emotionality, negative emotionality) comprised of a number of more specific, lower-order traits.

Among these primary, lower-order traits, harm avoidance has been of interest in psychopathology research, as a disposition for harm avoidance may be an underlying feature common to internalizing psychopathology (e.g., anxiety, depression). Harm avoidance has broadly been characterized by fear of uncertainty, anticipatory worry, shyness, and fatigability (Cloninger, 1993), and higher harm avoidance has been observed in depressive (Abrams, Yune, Kim, & Jeon, 2004; D. J. Smith, Duffy, Stewart, Muir, & Blackwood, 2005) and anxious psychopathologies (Ettelt et al., 2008; Starcevic, Uhlenhuth, Fallon, & Pathak, 1996; Wachleski et al., 2008). However, although harm avoidance is highly correlated with internalizing psychopathology, some have argued that there is a clear distinction between the two constructs, with an emphasis on harm avoidance more specifically as a motivational tendency that subserves approach-avoidance behaviors (Sylvers, Lilienfeld, & LaPrairie, 2011; Tellegen & Waller, 2008). For instance, while the general experience of anxiety may involve feelings of fear and a desire to escape, the cause of this anxiety may be poorly understood by the individual; Tellegen and Waller (2008) argue that harm avoidance captures an individual's propensity to avoid, rather

than seek, physically dangerous situations that elicit fear. As such, harm avoidance may be characterized better as trait fear, rather than trait anxiety (Sylvers et al., 2011). Individual differences in harm avoidance have been proposed to be consequent to variability in arousal regulation, which may further indicate susceptibility to affective disorders (Hariri et al., 2005; Zuckerman & Kuhlman, 2000). Thus, given the clinical relevance of this behavioral inhibition, examining individual differences in harm avoidance and its supporting neurobiological features may provide insight into mechanisms of risk for internalizing psychopathology.

Although the neural systems implicated in anxiety and depression have been studied extensively (see Etkin & Wager, 2007; Hamilton et al., 2012), less is known about whether these features are unique to psychopathology, or may relate to personality traits, such as harm avoidance, relevant to internalizing symptoms. As personality describes persistent patterns of individuals' behavioral response patterns, it is likely that these traits may be reflected in the brain's functional architecture, and may be distinguishable from the patterns observed in relation to internalizing symptomatology. Moreover, neural signatures of harm avoidance that are separable from actual symptoms may have implications on risk for internalizing psychopathology, playing a mechanistic role. Specifically, as harm avoidance describes a persistent pattern of avoidance in response to dangerous, fear-inducing situations, this behavioral pattern could contribute to exacerbation of internalizing symptoms as highly harm avoidant individuals fail to learn avoided situations may be safe or rewarding and, subsequently, become more fearful or inhibited.

To this end, neuroimaging studies have identified intrinsic functional organization within the brain, with certain brain regions demonstrating consistently greater activity during different states. In particular, analysis of fMRI during resting state and during cognitive tasks has revealed

two spatially distinct, anti-correlated networks: the default mode network and the task-positive network (which can further be differentiated into salience and central executive networks; Damoiseaux et al., 2006; Fox et al., 2005). The default mode network (DMN) consists of a number regions demonstrated to be active during wakeful, resting states (i.e., a "default" brain state), and includes key nodes such as the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), precuneus, and inferior parietal lobule (Buckner, Andrews-Hanna, & Schacter, 2008; Menon, 2011). These neural regions generally subserve internally focused or cued processes, including self-referential processing, thinking about others, and episodic memory (Buckner et al., 2008; Gusnard, Akbudak, Shulman, & Raichle, 2001; Uddin, Kelly, Biswal, Castellanos, & Milham, 2008). In contrast, the regions comprising the central executive network (CEN) have been shown to come online during performance of cognitively demanding tasks. This network includes a set of regions consistently engaged during processes requiring endogenous attention and goal-directed task performance, such as the dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex (PPC; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Seeley et al., 2007; Sridharan, Levitin, & Menon, 2008). Taken together, the DMN and CEN demonstrate an antagonistic relationship, wherein increases in regions of one network correspond to proportionate decreases in the other (and vice versa) and are dependent on cognitive demands and task difficulty.

Although these macro-scale networks are consistently identified across broad samples, individual differences in communication between regions within and between networks have been demonstrated to relate to disease states, traits, and overt behaviors (Adelstein et al., 2011; Manoliu et al., 2014; Menon, 2011; Wang et al., 2015). Additionally, such disruptions in

3

network connectivity are also informative in understanding aberrant activation in key regions of these networks implicated in task-related brain activation.

Aberrancies related to task-related activity and functional connectivity of the DMN have been of significant interest in psychopathology research. Most notably, much of the extant literature has focused on links between the DMN and depression, as the DMN has been proposed to subserve passive, self-referential processing that is likely disturbed in depression (e.g., excessive rumination, negative attributions to self; Buckner et al., 2008; Whitfield-Gabrieli & Ford, 2012). Indeed, studies of functional connectivity have consistently identified patterns of DMN activity that differ in depressed compared to control patients (Belleau, Taubitz, & Larson, 2014; Broyd et al., 2008; Greicius et al., 2007). Hamilton and colleagues (2011) also demonstrated that increased dominance of DMN activity was associated with higher levels of maladaptive, depressive rumination in individuals with depression. As a result of this mounting evidence, aberrant DMN activity and increased connectivity between regions of the DMN and subgenual prefrontal cortex has been proposed as a neural substrate of depression (Hamilton, Farmer, Fogelman, & Gotlib, 2015). Examination of the DMN in anxiety has also revealed atypical function. For instance, decreased functional connectivity in regions such as the PCC and precuneus has been associated with greater anxiety (Coutinho et al., 2016), and regional cerebral blood flow to the DMN increases during anticipatory anxiety (Simpson, Drevets, Snyder, Gusnard, & Raichle, 2001). In response to emotional stimuli, patterns of activation within the PCC, mPFC, and precuneus have also been demonstrated to distinguish patients with anxiety disorders from healthy controls (Gentili et al., 2009; Zhao et al., 2007).

Altered functioning within the CEN in internalizing psychopathology has also provided insight into potential neural correlates underlying deficits in cognitive functioning commonly

observed in anxiety and depressive disorders. Prior research has suggested that in individuals with high trait anxiety, impairments in executive control correspond to deficient recruitment of core regions of the CEN, such as the dlPFC (Basten, Stelzel, & Fiebach, 2011; Bishop, 2008; Pacheco-Unguetti, Acosta, Callejas, & Lupiáñez, 2010). Decreased functional coupling within the CEN has also been demonstrated in patients with social anxiety disorder, compared to healthy controls (Liao et al., 2011; Qiu et al., 2011).

However, although abundant evidence has implicated abnormal activity within the DMN and CEN as it relates to various traits and disease states, relatively little attention has been given to the dynamic interplay of these networks. To this end, research on intrinsic functional neural networks has suggested that the antagonistic relationship between the DMN and CEN is facilitated by a separate network: the salience network (Goulden et al., 2014; Menon, 2015). The salience network (SN) - including the anterior insula, dorsal anterior cingulate cortex (dACC), amygdala, ventral striatum, and substantial nigra/ventral tegmental area - appears to play a critical role in modulating brain states, initiating the switch between DMN and CEN (Menon, 2015: Seeley et al., 2007). Specifically, the SN has been proposed to detect the saliency of incoming information in order to appropriately direct attention. For instance, information that is surprising, rewarding, or emotionally engaging may be perceived as salient and trigger the SN to focus spotlight of attention (Menon, 2015). The perceived salience of stimuli can thus have significant repercussions on attentional allocation and how internal and exogenous cues are processed. Moreover, functional connections between the SN and CEN have been demonstrated to underlie actual performance of cognitive tasks (Fang et al., 2016).

Within the SN, the anterior insula has been particularly noteworthy, as emerging evidence implicates the anterior insula as having a causal role in alternating between DMN and

CEN states (Sridharan et al., 2008). Traditionally, the insula has been viewed as a limbic region and has been shown to play an important role in a number of cognitive and affective functions, including interoceptive awareness, emotional processing, and disgust (Menon & Uddin, 2010; Singer, Critchley, & Preuschoff, 2009; Stein, Simmons, Feinstein, & Paulus, 2007). Furthermore, across all functional neuroimaging research, the anterior insula is among the most frequently activated regions (Craig, 2009; Menon, 2015; Nelson et al., 2010). The ubiquitous involvement of the insula in often disparate functions has prompted this more recent conceptualization of the insula as a core hub of the SN (Menon & Uddin, 2010; Sridharan et al., 2008). In response to a salient stimulus, the anterior insula (particularly the right anterior insula) is responsible for signaling engagement of cognitive control systems (i.e., CEN) while suppressing default mode activity (Sridharan et al., 2008). Given this causal role for the anterior insula in switching between central executive and default mode networks, inefficient communication between the anterior insula and nodes of either or both of these regions may result in difficulties shifting out of internally-focused processing and subsequently contribute to weaker performance on cognitively demanding tasks.

Evidence has also linked activity within the SN and anterior insula in particular, to psychopathology. Notably, compared to healthy controls, individuals with depression have demonstrated decreased intra-network connectivity within the SN and decreased inter-network connectivity between the SN and DMN (Manoliu et al., 2014).Within anxiety disorders, hyperactivity of the insula appears to be a common feature (Mataix-Cols et al., 2004; Paulus & Stein, 2006; Wright, Martis, McMullin, Shin, & Rauch, 2003); amygdala and insula reactivity to emotional stimuli has also been found to be positively related to self-reported trait anxiety, neuroticism, and anxiety sensitivity (Stein et al., 2007). Increased connectivity within regions of

the SN has also been found to relate to anxiety (Baur, Hänggi, Langer, & Jäncke, 2013; Sylvester et al., 2012). Thus, evidence suggests that altered functioning of the SN and anterior insula is relevant to internalizing psychopathology; moreover, given the role of the right anterior insula in attentional switching, this disruption in SN may have profound downstream effects on appropriately integrating salient information to initiate CEN or DMN engagement.

Less is known about the specific relations between the SN and harm avoidance, however, several neuroimaging studies have revealed associations between harm avoidance and anterior insula functioning. Markett and colleagues (2013) demonstrated a positive association between harm avoidance and connectivity within the SN between the anterior insula and dACC. However, this study was specifically interested in connectivity within the insular SN and limited its analysis to primarily regions of interest within the SN. Interestingly, the authors also found increased connectivity between the anterior insula and dlPFC (typically considered a node of the CEN) was positively correlated with harm avoidance, although this association was inconsistent across cluster and ROI-based analyses. The role of the anterior insula in harm avoidance has also been examined in risk-taking decision making behavior. Paulus and colleagues (2003) found increased right anterior insula activation when participants made risky versus safe choices. Moreover, the degree of insular activation was modulated by subjects' degree of harm avoidance, such that higher scores on this trait corresponded to greater magnitude of insula activation. Thus, several neuroimaging studies have supported an association between the anterior insula and harm avoidance; yet, to date, research has failed to investigate how complex internetwork communication may be modulated by individual differences in harm avoidance.

In addition, the limited research on associations between harm avoidance and functioning of the anterior insula is further muddied by differences in construct definition, as overlap

between measures of trait anxiety and harm avoidance is common. While Tellegen's (1982; Tellegen & Waller, 2008) definition emphasizes a propensity for behavioral avoidance based on a hypersensitivity to danger, others have defined harm avoidance more broadly (Cloninger, 1993), somewhat conflating trait fear and trait anxiety. Indeed, it has been suggested that trait fear and trait anxiety are largely independent (if somewhat overlapping) constructs that are likely supported by different neurobiological systems (Sylvers et al., 2011). As a measure of behavioral avoidance and trait fear, harm avoidance may point to a mechanism for better understanding internalizing symptoms and the functional neural networks supporting these symptoms. For instance, it is feasible that high levels of harm avoidance may increase the saliency of dangerous situations and subsequently affect appropriate recruitment of neuronal networks; given the disruptions in DMN, CEN, and SN intra- and internetwork connectivity seen in internalizing psychopathology, such a pattern could potentially confer risk for these disorders.

The goal of the current study was to examine the associations between harm avoidance and resting state functional connectivity. Given the role of the SN's right anterior insula in modulating DMN versus CEN states, the anterior insula was selected as a seed region in order to examine functional connectivity with both the DMN and CEN, as well as within the SN. Although the extant literature suggests that the right anterior insula, in particular, is critical in switching between the DMN and CEN (Goulden et al., 2014; Sridharan et al., 2008), other studies have not differentiated across hemispheres (Markett et al., 2013) or have indicated left hemispheric effects related to trait and state anxiety (Baur et al., 2013; Dennis, Gotlib, Thompson, & Thomason, 2011). Accordingly, both left and right anterior insula were examined as seed regions to support examination of lateralized function and connectivity. As research has detailed associations between harm avoidance and symptoms of internalizing psychopathology,

the current study also examined the association between trait anxiety and anterior insula-seeded resting state functional connectivity to examine any differences in connectivity as a function of trait anxiety compared to harm avoidance. Given the extant literature, we hypothesized that harm avoidance would be (1) positively correlated with connectivity between the anterior insula and other regions of the SN, and (2) negatively correlated with connectivity between the anterior insula and regions of the DMN and CEN. Similar results were anticipated for the analyses examining connectivity in relation to trait anxiety, however we hypothesized that the effects may be more robust given that trait anxiety includes measurement of symptoms directly relevant to potential deficits in attentional switching (e.g., difficult to control worry). We also hypothesized that effects of harm avoidance and trait anxiety on functional connectivity would be stronger for the right anterior insula.

Method

Participants and Procedure

Ninety-nine undergraduate students aged 18-26 (69 female) were recruited from the University of Wisconsin-Milwaukee research subject pool. Seven subjects were excluded for poor neuroimaging data quality (i.e., excessive motion during rest scan), resulting in a final analyzable n of 92. Participants were excluded from participation if they were left-handed, had any contraindications to magnetic resonance imaging (e.g., irremovable metal in body, pregnancy), or had a history of significant head trauma, neurological disorder, bipolar disorder, or psychotic disorder. Participants provided written informed consent after reviewing the study procedures. All procedures were approved by the University of Wisconsin-Milwaukee and Medical College of Wisconsin Institutional Review Boards. Participants were compensated with course credit and cash payment for their participation.

Measures

      Harm avoidance. Harm avoidance was assessed using the harm avoidance subscale from the Multidimensional Personality Questionnaire (MPQ; Tellegen, 2003). The harm avoidance scale of the MPQ consists of 28 dichotomous self-report items. Nine items are true-false statements (e.g., "I would not like to try skydiving"). For the remaining 19 items, the respondent is asked to choose which of two situations they would like least (e.g., "Of the following two situations I would like least: (a) Walking a mile when it's 15 degrees below zero, (b) being near a volcano when it's about to erupt"). Notably, the MPQ harm avoidance dimension has demonstrated good specificity compared to other personality measures of harm avoidance, which may map onto traits such as negative emotionality or neuroticism rather than a predisposition for behavioral inhibition (Waller, Lilienfeld, Tellegen, & Lykken, 1991).

      Trait anxiety. The Trait version of the Spielberger State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) was used to measure trait anxiety. The STAI consists of 20 self-report items rated on a four-point scale. The STAI has demonstrated good psychometric properties, including high test-retest reliability and internal consistency (Barnes, Harp, & Jung, 2002).

      MRI data acquisition. Imaging data was collected on a 3.0 Tesla short bore GE Signa Excite MRI system at the Medical College of Wisconsin. Functional T2*-weighted echoplanar images (EPI) were collected for the resting state scan in a sagittal orientation: repetition time (TR)/echo time (TE)=2000/25ms; FOV=24mm; matrix=64x64; flip angle=77°; slice thickness=3.5mm. Participants were instructed to remain still and to keep their eyes open while data was collected for five minutes.

For coregistration of the functional data, high resolution spoiled gradient recalled (SPGR) images were also acquired (TR/TE=8200/3.2ms; FOV=240mm; matrix=256x224; flip angle=12°; voxel size=0.9375 x 0.9375 x 1mm).

MRI data analysis

Resting state fMRI data was analyzed using the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). In preprocessing, EPI data was slice-time corrected to adjust for non-simultaneous slice acquisition within each volume. Images were corrected for head movements using a six-parameter (rigid body) linear transformation. Images were transformed to Montreal Neurological Institute space (MNI 152) and spatially smoothed to minimize effects of anatomical variability (FWHM=6mm). Linear detrending and temporal bandpass (0.01-0.1 Hz) filtering were performed to remove low-frequency drifts and high-frequency physiological noise (Cordes, Haughton, & Arfanakis, 2001; Fox et al., 2005). Nuisance covariates including head motion parameters (and their first order derivatives), white matter signal, and cerebrospinal fluid signal were regressed out (Cole, Smith, & Beckmann, 2010).

Motion correction procedures in resting state functional connectivity analyses have become a prominent concern, as research has demonstrated that these analyses are particularly susceptible to spurious noise and distance-dependent changes in signal correlations caused by small head movements (Power, Schlaggar, & Petersen, 2015). To reduce confounding effects of motion, frame-wise displacement (FD) was computed. Volumes with FD>0.3mm were 'scrubbed' (i.e., excluded from further analysis), and participants with excessive motion (<4 minutes of useable data) were excluded from analyses (Power et al., 2015).

Seed-to-voxel analyses were conducted to measure functional connectivity. For first-level analysis, the left (-44, 13, 1) and right anterior insula (47, 14, 10) were selected as seed ROIs.

Mean BOLD time series were extracted from these seed regions and correlated with the time course of each voxel of the brain, resulting in a three-dimensional correlation coefficient (r) map for each subject and each seed. Normalized Fisher-transformed correlation maps were used for group analysis. Second-level seed-to-voxel analyses were conducted to allow for between-subjects comparisons. Subject connectivity maps were entered into a second-level general linear model to compare functional connectivity patterns as associated with (1) MPQ-harm avoidance and (2) STAI-trait anxiety scores. Sex was included as a covariate in the model. The statistical threshold was set at $p<.05$ and corrected for multiple comparisons. The height threshold was set at $p<.001$ (uncorrected) and cluster-size threshold at $p<.05$ (FDR-corrected).

Results

Participant characteristics

Participant characteristics are provided in Table 1. There was a significant sex difference in harm avoidance, $t(90) = -5.63$, $p < .001$, such that women reported higher levels of harm avoidance ($M = 18.84$, $SD = 4.59$) than men ($M = 13.25$, $SD = 3.87$). There were no significant differences in age or trait anxiety between males and females. Harm avoidance and trait anxiety were not significantly correlated in the sample ($r = .15$, $p = .16$). Additional information regarding sample characteristics can be found in the Appendix.

	Mean (SD) or %
Sex	
Female	69.6%
Male	30.4%
Age	20.85 (2.26)
MPQ Harm Avoidance	17.14 (5.07)
STAI Trait Anxiety	40.85 (10.77)

Table1. Sample Characteristics. MPQ, Multidimensional Personality Questionnaire; STAI, Spielberger State-Trait Anxiety Inventory.

Functional connectivity results

  After adjusting for age, results indicated a main effect of MPQ harm avoidance on functional connectivity of both anterior insula seeds. These results are reported in Table 2 and Figures 1 and 2. For the right anterior insula, harm avoidance was negatively associated (i.e., stronger anticorrelations) with connectivity to clusters located in the precuneus/PCC (8, -54, 22; cluster size k = 1025), left lateral parietal cortex (-48, -76, 42; cluster size k= 105), and left superior and middle frontal gyrus (-26, 14, 58; cluster size k = 88). For the left anterior insula, harm avoidance was negatively associated with connectivity to a cluster in the precuneus/PCC (8, -32, 8; cluster size k = 432).

  There were no main effects of STAI trait anxiety on functional connectivity of the left or right anterior insula.

Region	k	$t_{(89)}$	pFDR-corrected	Peak coordinates (MNI)		
				x	y	z
Right anterior insula seed						
Precuneus/PCC	1025	4.85	<.001	8	-54	22
Lateral parietal cortex (L)	105	4.16	.021	-48	-76	42
Superior/middle frontal gyrus (L)	88	4.07	.027	-26	14	58
Left anterior insula seed						
Precuneus/PCC	432	4.98	<.001	8	-32	8

Table2. Functional Connectivity Results. Regions demonstrating decreased functional connectivity with increased harm avoidance.
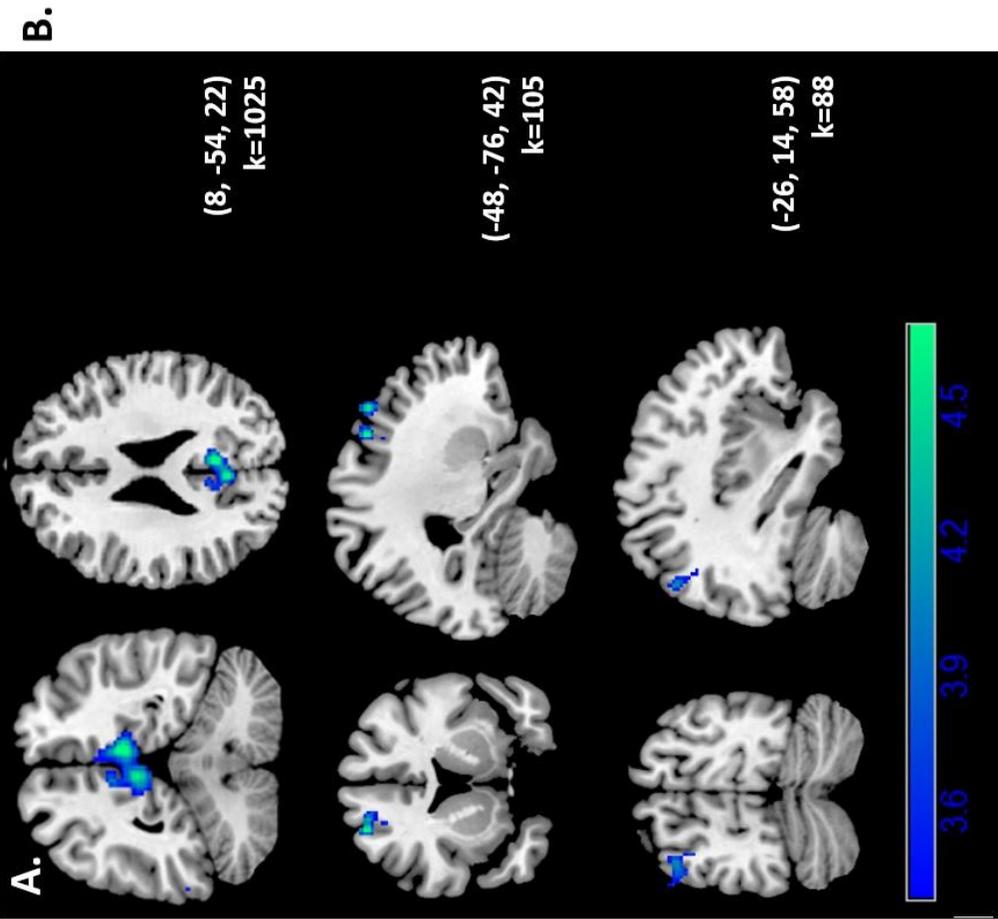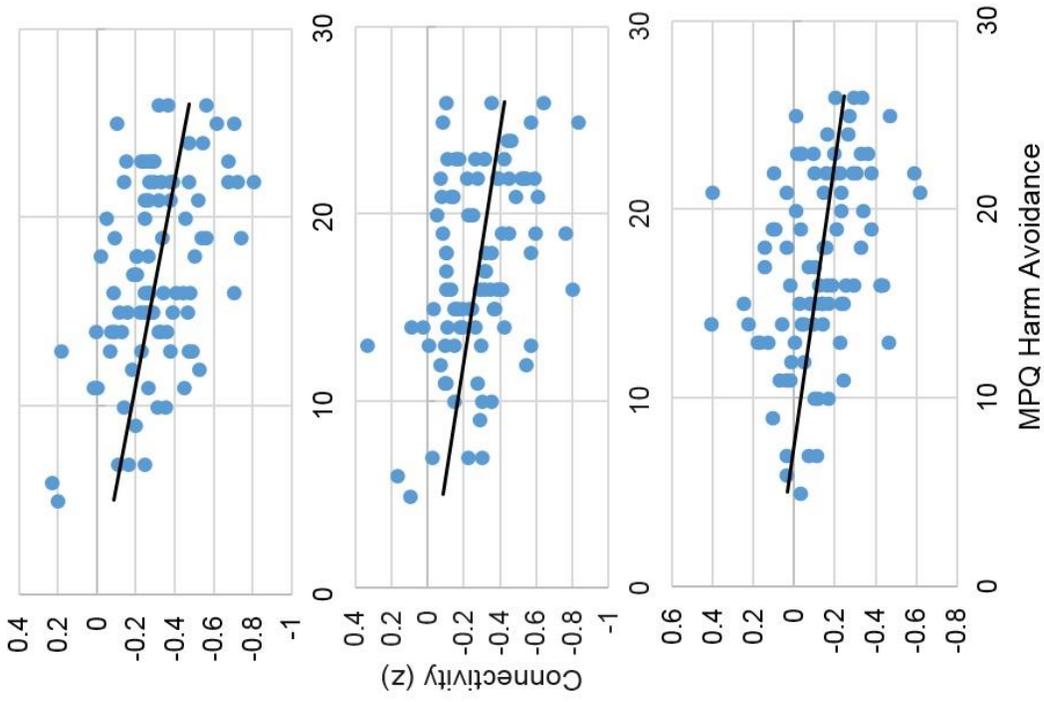
Figure1. Functional Connectivity Results – Right Anterior Insula Seed. A. Main effect of harm avoidance. Clusters showing significantly decreased connectivity to right anterior insula seed with higher harm avoidance scores ($p < .05$ FDR-corrected, adjusted for sex). Peak coordinates reported in MNI space, k = size of cluster (number of voxels). **B.** Scatterplots depict cluster functional connectivity (Fisher's z) plotted against harm avoidance scores from the MPQ.

14

Figure2. Functional Connectivity Results – Left Anterior Insula Seed. **A.** Main effect of harm avoidance. Clusters showing significantly decreased connectivity to left anterior insula seed with higher harm avoidance scores ($p < .05$ FDR-corrected, adjusted for sex). Peak coordinates reported in MNI space, k = size of cluster (number of voxels). **B.** Scatterplots depict cluster functional connectivity (Fisher's z) plotted against harm avoidance scores from the MPQ.
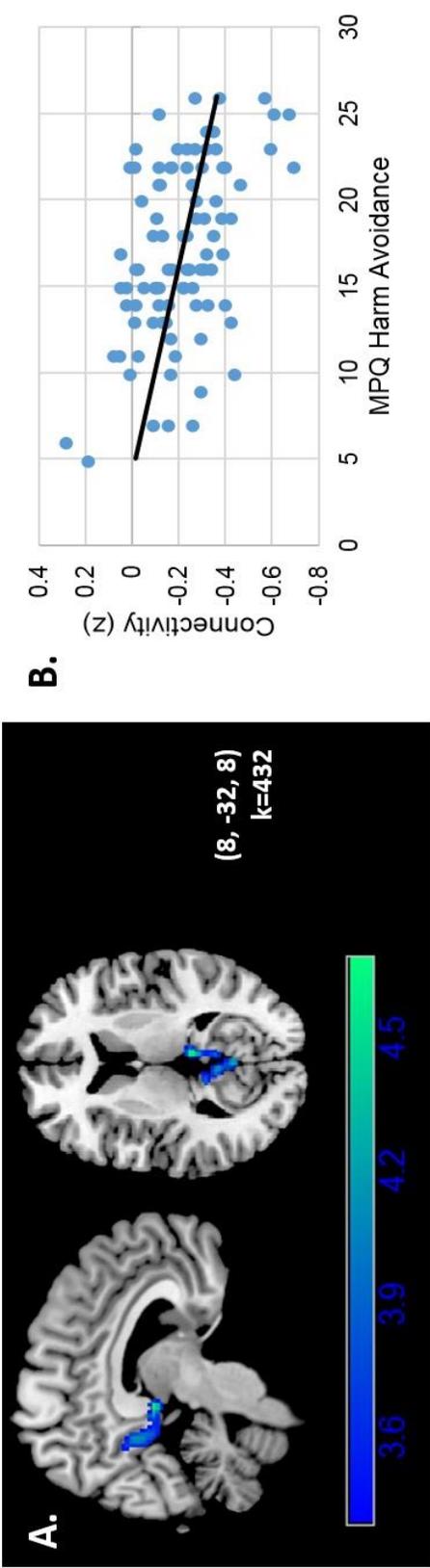
Discussion

The current study aimed to examine the associations between harm avoidance and resting state functional connectivity of the anterior insula. Results indicated that higher levels of harm avoidance were associated with significantly decreased connectivity between the anterior insula and several clusters located within the default mode and central executive networks. Effects of harm avoidance on connectivity were observed primarily based on the right anterior insula seed, consistent with research indicating the causal role of the anterior insula in modulating brain states is right lateralized (Goulden et al., 2014; Sridharan et al., 2008); however, decreased connectivity between the left anterior insula and precuneus/PCC was also observed. Notably, no significant differences in connectivity were observed relative to individual differences in trait anxiety. Harm avoidance and trait anxiety were also not significantly correlated with each other. Thus, these findings support the notion that harm avoidance is a separable construct from general trait anxiety, and it appears that these processes are supported by different neurobiological substrates.

Moderating effects of harm avoidance were observed on internetwork connectivity between the SN's anterior insula and DMN and CEN. Most notably, increased harm avoidance was associated with lesser connectivity (specifically, larger anticorrelations) between the anterior insula and DMN, including a large cluster within the precuneus/PCC. The precuneus/PCC has been established as a key node of the DMN (Fransson & Marrelec, 2008; Utevsky et al., 2014). Notably, while at rest, the precuneus/PCC has demonstrated higher metabolic activity than any other region of the brain (Gusnard & Raichle, 2008), suggesting that the precuneus/PCC is critical to the general internally-focused processes relevant to the DMN. Moreover, aberrant DMN activity and connectivity is common in internalizing psychopathology relevant to harm

avoidance (Hamilton et al., 2011; Whitfield-Gabrieli & Ford, 2012). Deficits in deactivation of the precuneus/PCC during task states has also been observed in individuals with social phobia (Gentili et al., 2009). While anticorrelated activity between these regions is normal in healthy individuals (Fox et al., 2005; Uddin et al., 2008), it is possible that the increased magnitude of these anticorrelations reflects impairment in effectively allocating attention to other stimuli when the SN has identified behaviorally-relevant stimuli. Consistent with this idea, research has demonstrated that greater anticorrelations between the SN and DMN are associated with difficulties with emotion regulation (Rabany et al., 2017). As such, elevations in harm avoidance may be associated with deficits in attentional shifting, or a tendency to get 'stuck' in internally-focused/self-referential thought facilitated by the DMN (Buckner et al., 2008) when faced with potential danger. Additional disruptions in internetwork connectivity likely further contribute to this deficit in attentional shifting for those high in harm avoidance, as connectivity was also reduced between the anterior insula and left lateral parietal cortex (part of the DMN) and left middle and superior frontal gyrus (part of the CEN).

Surprisingly, harm avoidance was not associated with increased connectivity between the anterior insula and other regions of the SN. Given the role of the SN in detecting the importance of incoming information in order to direct attentional resources (Menon, 2015), it had been hypothesized that perhaps increased attention to dangerous/threatening stimuli for those high in harm avoidance would have downstream consequences for how attentional resources are allocated. In light of the current findings, it may be that individual differences in harm avoidance do not affect the initial perceived salience of incoming information, but rather result from excess apprehensive self-focused thought that ultimately interferes with appropriate interpretation of this information. For instance, when faced with a potentially dangerous situation, the perceived

salience of this information is not necessarily influenced by harm avoidance; instead, individuals

high in harm avoidance may struggle to disengage from or down-regulate negative self-focused

thought about the stimuli (e.g., thoughts about possible bodily harm). As the current findings

reflect functional connectivity while at rest inside the scanner, it is also possible that enhanced

connectivity within the SN may only be present while in the actual presence of threat.

Contrary to a priori hypotheses, trait anxiety was not associated with any differences in

connectivity of either the left or right anterior insula. One possible explanation for a lack of

findings related to trait anxiety is that the sample comprised relatively healthy undergraduate

students. Thus, anxious symptoms may not have been significantly elevated enough to

correspond to differences in functional connectivity. It may be beneficial to examine whether

trait anxiety relates to disrupted insular functional connectivity in clinical samples and whether

these patterns differ from those related to harm avoidance. Alternatively, the current study may

have failed to observe a main effect of trait anxiety on functional connectivity given the selection

of the anterior insula as a seed region. In anxiety research, the extant literature has largely

focused on the functional connections between the amygdala and prefrontal regions, such as the

ventromedial prefrontal cortex, proposed to downregulate hyperactive amygdala activity (Hahn

et al., 2011; Kim et al., 2010; Kim et al., 2011). It is possible that trait anxiety is better

characterized by disrupted communication between the amygdala and these inhibitory regions,

rather than in dynamic interplay of DMN and CEN. The STAI has also previously been criticized

for its heterogeneity, as items of the STAI have been shown to map onto separate constructs

related to anxiety/worry and sadness/self-deprecation (see Bieling, Antony, & Swinson, 1998).

In light of the current findings, disrupted connectivity between the insula and DMN and CEN

may be more relevant to the specific behavioral propensities captured by harm avoidance, while

broader indices of trait anxiety may modulate different functional connections within the brain. Future work would likely benefit from further disentangling the complex features of internalizing psychopathology in order to better understand more precise neural mechanisms implicated in different facets of these phenotypes (e.g., cognition, behavior).

The current study has several limitations. First, the resting state fMRI scan was five minutes in duration. Emerging evidence has indicated that longer resting state scans produce more reliable data (Birn et al., 2013). Second, while the resting state design of the study helps provide initial evidence regarding the associations between harm avoidance and the interplay of intrinsic functional neural networks (as well as its discriminability from trait anxiety), future work would likely benefit from utilizing task-based designs to examine the functional connections between the anterior insula and DMN/CEN during tasks that may require attentional switching or simulate real-world behavioral inhibitory tendencies. Finally, the current study utilized a convenience sample comprising healthy college students. Although the sample included a good range of variability in regards to the harm avoidance and trait anxiety measures, it would likely be beneficial to have samples including those with clinical levels of internalizing symptoms in order to better characterize the potential mechanistic role of harm avoidance in these disorders. In addition, it would also be informative to examine the neurobiological correlates of harm avoidance for those *low* in harm avoidance, as this is also likely maladaptive and leads to reckless, harmful behavior. Indeed, harm avoidance has been found to be negatively correlated with components of psychopathy (e.g., antisocial behavior, callousness; Gaughan, Miller, Pryor, & Lynam, 2009; Levenson, Kiehl, & Fitzpatrick, 1995).

Overall, the results suggest that increased harm avoidance is associated with disrupted functional connections between the anterior insula and regions of the DMN and CEN, suggesting

individuals high in harm avoidance may experience difficulties in appropriately modulating attention between internally and externally focused processes. These findings were distinct from trait anxiety, for which there were no significant effects on anterior insula connectivity. As such, the behavioral inhibitory tendencies captured by harm avoidance may be uniquely relevant to individuals' attentional switching abilities. Future work would likely benefit from continuing to disentangle the underlying neurobiological systems relevant to harm avoidance and its distinguishability from higher order personality traits (e.g., neuroticism) and anxiety.

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Appendix

Psychopathology

Current diagnosis of a number of internalizing and externalizing psychopathologies was assessed using the MINI International Neuropsychiatric Interview (MINI 6.0.0; Sheehan et al., 1998), a brief, structured diagnostic interview. Trained doctoral students in clinical psychology administered the assessment, and diagnoses were made according to DSM-IV criteria. Diagnostic breakdown of the sample is reported in Table A1. Seven participant indicated current comorbid internalizing and externalizing psychopathology. Of those with current internalizing psychopathology only, five of eight met criteria for more than one internalizing disorder. Of those with externalizing psychopathology only, 11 of 21 met criteria for both an alcohol and substance use disorder.

Associations between psychopathology and harm avoidance

A one-way ANOVA was conducted to compare the effects of psychiatric diagnosis on harm avoidance and trait anxiety. Given the overall low prevalence of current psychopathology in the sample, participants were grouped into the following categories: healthy controls (n=56), internalizing only (n=8), externalizing only (n=21), and comorbid internalizing and externalizing psychopathology (n=7).

There was a significant effect of diagnosis on harm avoidance, $F(3,88) = 3.424$, $p = .021$. Post hoc comparisons using Scheffe's test indicated that harm avoidance scores were significantly higher for individuals with internalizing psychopathology only ($M =21.63$, $SD = 2.97$) compared to individuals with externalizing psychopathology only ($M = 15.19$, $SD = 5.19$). There were no significant differences reported relative to healthy controls ($M = 17.30$, $SD =$

5.05) or those with comorbid internalizing and externalizing psychopathology ($M = 16357$, SD =3.87),

There was also a significant effect of diagnosis on trait anxiety, $F(3, 88) = 4.088$, $p = .009$. Post hoc comparisons using Scheffe's test indicated that trait anxiety scores were significantly higher for those with comorbid internalizing and externalizing psychopathology ($M = 50.71$, $SD = 12.55$) compared to healthy controls ($M = 38.61$, $SD = 10.10$). There were no significant differences reported relative to individuals with internalizing ($M = 47.25$, $SD = 12.91$) or externalizing ($M = 41.10$, $SD = 8.80$) psychopathology only.

Diagnosis	n
Internalizing	*15*
Depression	5
Panic disorder	2
Agoraphobia	7
Social anxiety disorder	4
OCD	2
PTSD	4
GAD	7
Externalizing	*28*
Alcohol abuse/dependence	21
Substance abuse/dependence	17
None	*56*

TableA1. Current Psychiatric Diagnoses. OCD, Obsessive-compulsive disorder; PTSD, Posttraumatic stress disorder; GAD, Generalized anxiety disorder.