

# INTRINSIC CONNECTIVITY NETWORKS AND PERSONALITY: THE TEMPERAMENT DIMENSION HARM AVOIDANCE MODERATES FUNCTIONAL CONNECTIVITY IN THE RESTING BRAIN

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**Abstract**—Recent functional imaging studies that examined functional connectivity in the resting brain have demonstrated various intrinsic connectivity networks (ICNs). Certain patterns of over- and underactivity in various ICNs have been hypothesized to form the neural basis of psychiatric disorders. Furthermore, activity in the ICNs does not reflect ongoing mental activity but the maintenance of neural circuits in a ready state suggesting not only relationships between ICNs and disorders but also correlations between ICNs and personality. In the present study, we assess the relationship between trait anxiety, a well established endophenotype of anxiety disorders, and functional connectivities within the insular salience ICN in a sample of healthy female subjects. Based on a previous study that demonstrated the functional relevance of the insular salience ICN for state anxiety, we used the harm avoidance scale from the Temperament and Character Inventory (TCI) as a trait marker to demonstrate increased functional connectivity within the insular salience ICN. Specifically, the functional connectivity between the anterior insula and the anterior cingulate and between the anterior insula and the dorsolateral prefrontal cortex were positively correlated with individual harm avoidance scores. The results fit into previous work, provide evidence for a potential biomarker of anxiety disorders and, most importantly, demonstrate a direct neural correlate of the personality trait harm avoidance in the absence of external stimulation. © 2013 IBRO. Published by Elsevier Ltd. All rights reserved.

**Key words:** anxiety, personality, resting state fMRI, harm avoidance, functional connectivity, insular salience network.

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**Abbreviations:** BOLD, blood oxygen level dependent; dACC, dorsal anterior cingulate; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; FWHM, full width at half maximum; ICN, intrinsic connectivity network; PFC, prefrontal cortex; SMA, supplementary motor area; SPM8, statistical parametric mapping; TCI, Temperament and Character Inventory.

## INTRODUCTION

The resting brain is never truly at rest. The analysis of functional magnetic resonance imaging (fMRI) data acquired in situations that do not impose any specific task condition on the subjects has revealed that slow oscillations of the blood oxygen level dependent (BOLD) signal show a high degree of coherence across different brain areas. The patterns of coherent neural activity appear to be stable across subjects and time (Damoiseaux et al., 2006) which has led to the assumption that the brain forms intrinsic connectivity networks (ICNs, Fox and Raichle, 2007). The functionally linked brain regions in ICNs are also connected by prominent white matter tracts (van den Heuvel et al., 2009). Hence, the ICNs seem to reflect a core organizational principle of the human brain.

Various ICNs have been identified using complementary methods (for review see van den Heuvel and Hulshoff Pol, 2010). Even though these ICNs can be uniquely identified by spatio-temporal synchrony in BOLD fluctuations at rest, they operate together to contribute to complex behavioral phenotypes (Raichle, 2011). Following a recent hypothesis (Sylvester et al., 2012), the ICNs' activity can be seen as dimensional, ranging from underactive to normal to overactive. Complex behavioral phenotypes such as personality or psychiatric disorders can be understood as a certain pattern of activity in various networks along this dimension.

A pressing question for the field is to clarify the psychological relevance of the ICN, both for behavior in the normal range and for psychopathology. For anxiety and anxiety disorders, activity in the insular network including insular, frontal, cingulate and subcortical regions such as thalamus and the basolateral amygdala nucleus of the amygdala (Beckmann et al., 2005; Luca et al., 2006; Baur et al., 2013) is thought to play a crucial role. It has been hypothesized that highly anxious individuals show overactivity in the insular ICN (Sylvester et al., 2012).

This hypothesis allows for the deduction of certain predictions for resting state activity. First, following the dimensional character of psychiatric disorders (Plomin et al., 2009), there should be similar relationships between the strength of these functional connectivities at rest and risk factors for or endophenotypes of the disorder in unaffected populations. Trait anxiety as a personality or temperament dimension is thought to

underlie anxiety disorders, either as a risk factor (Clark et al., 1994) or as an endophenotype with the disorder reflecting the endpoint of normal variation across the population. Thus, not only patients diagnosed with an anxiety disorder should show the pattern of activity at rest mentioned above. Also in healthy participants, anxiety levels in the normal range should co-vary with activity in the insular ICN.

In the present study we seek to test these predictions from the hypothesis by Sylvester et al. (2012) by looking at the relationship between trait anxiety and functional connectivities in the insular network. This ICN was first described by Seeley et al. (2007) who defined a seed region in the dorsal anterior insula and derived the insular ICN by correlating the BOLD time series from this seed region over the complete resting state run with the time series from all other voxels in the brain. The resulting functional connectivity map depicted the insular ICN which includes cortical areas including the dorsal anterior cingulate (dACC), the dorsolateral prefrontal cortex (DLPFC), the supplementary motor area (SMA) and the bilateral insula, as well as subcortical areas including thalamus, hypothalamus, the amygdala and striatal regions. Given the involvement of these regions in the processing of conflict and reward and in the monitoring of autonomic functions, the ICN was labeled “salience network”. The topology of the salience network was convergently validated using independent component analysis in an independent data set.

In a second step, Seeley et al. (2007) assessed the psychological relevance of the insular salience network. Before entering the MRI scanner, participants were questioned how anxious they were of the scanning session. The ratings on this single shot item were significantly associated with the activity of the salience network. Specifically, functional connectivities between the insular seed and two clusters in the dACC and the DLPFC were modulated by anxiety self-reports. The higher the pre-scan anxiety the stronger was the functional coupling between the insula and the two cortical sites. This positive relationship between state anxiety and functional connectivities in the insular ICN is in line with the prediction from the hypothesis by Sylvester et al. (2012) that overactivity in this ICN is an endophenotype of anxiety disorders. An important limitation of the study already pointed out by the authors is the possible confound between state and trait anxiety. It is unclear if the stronger connection of the insula during the resting state scan reflects only the current level of anxiety irrespective of a general behavioral disposition toward anxiety or if personality traits associated with heightened levels of anxiety account for these individual differences in the salience network.

In the present study, we thrive to overcome this limitation by testing for an association between functional connectivities within the insular ICN and harm avoidance. Harm avoidance as assessed by the Temperament and Character Inventory (TCI) by Cloninger et al. (1993) is a temperament variable that describes a heritable tendency to respond intensely to all kinds of aversive stimuli and to avoid punishment and non-reward (Cloninger, 1986). As

a behavioral disposition it mediates overly cautious, anxious, nervous, passive and pessimistic behavior. People scoring high on the harm avoidance dimension are thought to have a strong bias toward behavioral inhibition and describe themselves as pessimistically worrying in anticipation of the future, as passively avoidant due to fear of uncertainty and shyness of strangers, and as rapidly fatigued. The latter four aspects (“anticipatory worry”, “fear of uncertainty”, “shyness”, and “fatigability”) are reflected in four subscales of the harm avoidance construct allowing for a more fine grained perspective on individual differences in anxiety. Increased levels of harm avoidance have been reported in patients diagnosed with anxiety disorders (Ongur et al., 2005; Nery et al., 2008), rendering the temperament conceptually and empirically as an endophenotype of the disorders and making it an ideal candidate for the present study’s purpose. If the previously reported relationship between pre-scan anxiety and resting state connectivity in the insular salience network is a manifestation of a general behavioral disposition, individuals scoring high in harm avoidance should show similarly a stronger coupling between the insula and sites in the DLPFC and the anterior cingulate cortex (ACC).

## EXPERIMENTAL PROCEDURES

### Participants

Resting state fMRI data were acquired from  $N = 23$  female volunteers (age  $M = 22.48$ ,  $SD = 4.54$ ) after obtaining their informed written consent. All participants were free of any psychiatric or neurological condition as assessed by a screening questionnaire and had no contraindications to MRI. The study protocol was in accordance with the Declaration of Helsinki and approved by the local ethics committee of the University Clinics Bonn. Participants were recruited from psychology classes at the University of Bonn and had filled in the German translation of the TCI (Cloninger et al., 1993) upon recruiting. The TCI measures four temperaments (novelty seeking, harm avoidance, reward dependence, persistence) and three character dimensions (self-directedness, cooperativeness, self-transcendence) with 240 dichotomous items in total. For the present study, only the individual scores for harm avoidance (35 items) and its four subscales anticipatory worry (HA1, 11 items), fear of uncertainty (HA2, seven items), shyness (HA3, eight items) and fatigability (HA4, nine items) were analyzed. We chose to invite female participants only to control for possible gender effects. Because psychology classes at German schools are dominated by female students, not enough male participants could have been recruited for a balanced gender distribution in our sample.

### Image acquisition

From each participant, 240 T2\* weighted volumes were obtained on a Siemens Avanto 1.5T scanner (Siemens, Erlangen, Germany) at the Life & Brain Center Bonn in a single 12-min session. Participants were instructed to lie as still as possible with their eyes closed without thinking of anything in particular and without falling asleep. Each volume consisted of 38 slices (thickness: 3 mm, interslice gap: 1 mm, spatial resolution:  $3 \times 3 \times 3$  mm) scanned in ascending order (TR: 3.06 s, TE: 45 ms, Flip Angle: 90°, Field of View: 192 mm). Foam padding was used to constrain head movements.

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