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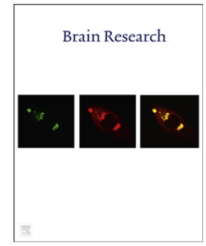

Research Report

Functional network organizations of two contrasting temperament groups in dimensions of novelty seeking and harm avoidance

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ABSTRACT

Novelty seeking (NS) and harm avoidance (HA) are two major dimensions of temperament in Cloninger's neurobiological model of personality. Previous neurofunctional and biological studies on temperament dimensions of HA and NS suggested that the temperamental traits have significant correlations with cortical and subcortical brain regions. However, no study to date has investigated the functional network modular organization as a function of the temperament dimension. The temperament dimensions were originally proposed to be independent of one another. However, a meta-analysis based on 16 published articles found a significant negative correlation between HA and NS (Miettunen et al., 2008). Based on this negative correlation, the current study revealed the whole-brain connectivity modular architecture for two contrasting temperament groups. The *k*-means clustering algorithm, with the temperamental traits of HA and NS as an input, was applied to divide the 40 subjects into two temperament groups: 'high HA and low NS' versus 'low HA and high NS'. Using the graph theoretical framework, we found a functional segregation of whole brain network architectures derived from resting-state functional MRI. In the 'high HA and low NS' group, the regulatory brain regions, such as the prefrontal cortex (PFC), are clustered together with the limbic system. In the 'low HA and high NS' group, however, brain regions lying on the dopaminergic pathways, such as the PFC and basal ganglia, are partitioned together. These findings suggest that the neural basis of inhibited, passive, and inactive behaviors in the 'high HA and low NS' group was derived from the increased network associations between the PFC and limbic clusters. In addition, supporting evidence of topological differences between the two temperament groups was found by analyzing the functional connectivity density and gray matter volume, and by computing the relationships between the morphometry and function of the brain.
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1. Introduction

The Temperament and Character Inventory (TCI), based on one of the most prevalent personality models, with four biologically based temperament dimensions and three psychosocially based character dimensions (Cloninger, 1987; Cloninger et al., 1993), has been widely used for investigating the neurobiological correlates of personality in multimodal neuroimaging and gene studies. Among the four temperamental traits, novelty seeking (NS) and harm avoidance (HA) are reported to have more evidence supporting for their psychometric validity and biological basis, compared to the validity of the traits of reward dependence and persistence, and therefore are most extensively studied (Miettunen et al., 2008). HA and NS reflect individual's automatic behavioral responses to the environmental stimuli of danger and novelty and are responsible for inhibition and activation of behaviors, respectively (Cloninger, 1987). More specifically, Cloninger describes the temperament dimension as the individual differences of the behavioral activation system (BAS) and the behavioral inhibition system (BIS). The BAS governs responses to positive and rewarding stimuli, resulting in approach behavior and is closely related to NS, whereas the BIS may give rise to inhibition of response and avoidance behavior and is related to HA in Cloninger's model (Caseras et al., 2003; Cloninger et al., 1993). NS and HA are known to be associated with distinct neurochemical substrates: NS with low basal dopaminergic activity and HA with high serotonergic activity. In addition, several genetic studies of functional polymorphisms support Cloninger's claim that the temperament dimensions of NS and HA have a genetic basis (Cloninger, 1987).

The temperament dimensions in Cloninger's model were originally proposed to be independent of one another (Cloninger, 1987). However, a meta-analysis based on 16 published articles on the relationship between the dimensions of the TCI found a significant negative correlation between HA and NS (Miettunen et al., 2008). This result implies that there is an interaction between the neural systems related to each temperamental construct, and the BAS and BIS can be described as antagonistic to each other (De Fruyt and Van De Wiele, 2000; Zuckerman and Cloninger, 1996). Some studies have also shown that individuals with strong BAS-related personality traits, such as NS, show diminished processing of aversive cues, indicating inhibition from the BAS on the BIS. The BIS-related personality traits, such as HA, are expected to modulate responsiveness of the BAS, through behavioral inhibition (Newman et al., 1985; Patterson et al., 1987; Zuckerman and Cloninger, 1996; De Fruyt and Van De Wiele, 2000; Ávila, 2001; Kennis et al., 2013). This might be the reason that NS and HA are negatively correlated in subjects in the above-mentioned studies. Therefore, it is natural to divide individuals into two representative groups with combinations of two temperamental traits: high HA and low NS versus low HA and high NS, instead of just describing their HA and NS scores separately, to emphasize the interaction between temperamental phenotypes.

With the development of brain imaging techniques, numerous neuroimaging studies have been conducted to investigate the neurobiological basis of human temperaments. In voxel-based morphometry (VBM) studies, researchers have found anatomical regions that are significantly correlated with the temperamental traits using a multiple regression method. For example, the HA was found to be positively correlated with the gray matter (GM) volume in the left orbitofrontal cortex (OFC), right angular gyrus, left amygdala, and right middle temporal gyrus (Iidaka et al., 2006) and negatively correlated with the GM volume in the left prefrontal cortex (PFC) and right hippocampus (Yamasue et al., 2008), and the NS was found to be positively correlated with the GM volume in the left middle frontal gyrus (MFG) (Iidaka et al., 2006). In a diffusion tensor imaging study, the fiber connections among the striatum, hippocampus, and amygdala could predict individual differences in the NS (Cohen et al., 2009). In addition, NS was positively correlated with fiber connections from the OFC and amygdala to the striatum, and HA was positively associated with the fiber connectivity from the PFC to the striatum (Lei et al., 2014). Furthermore, several neurofunctional studies have reported that several brain regions were associated with the traits of HA and NS. For example, the HA score was correlated with the connectivity between the PFC and the insula (Markett et al., 2013), and between centromedial amygdala subregions and frontal cortices associated with emotional processes (Li et al., 2012). According to Haier et al. (1987), the neurobiological basis of the BAS includes the PFC, amygdala, and basal ganglia (BG), while the neurobiological basis of the BIS consists of the OFC, septo-hippocampal system, and hypothalamus. Taken together, we can summarize that the important brain regions for the neural correlates underlying the temperaments are the PFC, limbic structure, and BG territories.

Until recently, personality studies using neuroimaging data were performed within the framework of a linear regression model and focused on finding brain regions that were linearly correlated with temperamental dimensions. However, since the human personality consists of multidimensional traits composed of various cognitive, emotional, and behavioral characteristics interconnecting with each other, it may be postulated that a wide array of cerebral circuits mediate the individual variability, and the study of human brain networks related to personality traits has been seen to be necessary. Under this background, modular analysis of neuroimaging data within a graph theoretical framework has been growing rapidly and could potentially provide new insights into a better understanding of whole human brain network organizations for various personality groups (Boccaletti et al., 2006; Bullmore and Sporns, 2009). For example, Davis et al. (2013) investigated modular architecture in a functional network (FN) for different impulsivity groups, i.e., low, intermediate, and high impulsivity. Because the 'connectome' is one of the encouraging frameworks for brain researchers to understand how the brain works, studying the patterns of regional association under the graph theoretical framework, rather than focusing on the local brain activity under the general linear model framework, can advance our understanding of the neural correlates of personality.

The aim of the present study was to identify the characteristics of the modular organization of FN that make each temperamental group different: 'high HA and low NS' versus 'low HA and high NS' groups. In the current study, we hypothesized that different patterns of functional connections (i.e., modular organizations) among the PFC, BG, and limbic regions during the brain's resting-state constitute the neural basis of personality that characterizes the 'high HA and low NS' and 'low

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