NeuroImage 117 (2015) 184–190

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

The cortical surface area of the insula mediates the effect of *DBH* rs7040170 on novelty seeking

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ARTICLE INFO

Article history:
Received 9 December 2014
Accepted 14 May 2015
Available online 20 May 2015

Keywords:
Novelty seeking
Surface area
Cortical thickness
Insula
DBH

ABSTRACT

Novelty seeking (NS) is a personality trait important for adaptive functioning, but an excessive level of NS has been linked to psychiatric disorders such as ADHD and substance abuse. Previous research has investigated separately the neural and genetic bases of the NS trait, but results were mixed and neural and genetic bases have yet to be examined within the same study. In this study, we examined the interrelationships among the dopamine beta-hydroxylase (*DBH*) gene, brain structure, and the NS trait in 359 healthy Han Chinese subjects. We focused on the *DBH* gene because it encodes a key enzyme for dopamine metabolism, NS is believed to be related to the dopaminergic system and has been reported associated with *DBH* variation. Results showed a significant positive association between the cortical surface area of the left insula and NS score. Furthermore, the *DBH* genetic polymorphism at the SNP rs7040170 was strongly associated with both the surface area of the left insula and NS score, with G carriers having a larger left insula surface area and a higher NS score than AA homozygotes. Subsequent path analysis suggested that the insula partially mediated the association between the *DBH* gene and the NS trait. Our data provided the first evidence for the involvement of the insula in the dopamine–NS relationship. Future studies of molecular mechanisms underlying the NS personality trait and related psychiatric disorders should consider the mediation effect of the neural structure.

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Introduction

Novelty seeking (NS) is a personality trait characterized by a preference for exploratory and novel activities, avoidance of monotony and routine, and extravagance in approach to reward cues (Cloninger, 1987; Cloninger et al., 1993). This trait contributes to adaptive functioning. High NS individuals are impulsive, excitable, and quick-tempered, while low NS individuals are rigid, stoic, and slow-tempered (Cloninger, 1986; Cloninger et al., 1993). However, excessive NS has been linked to psychiatric disorders (Richter and Brandstrom, 2009), such as ADHD (Instanes et al., 2013; Jacob et al., 2014), pathological gambling (Kim and Grant, 2001) and substance abuse (Milivojevic et al., 2012), while reduced levels of NS are correlated with obsessive–compulsive disorders (Lyoo et al., 2001). A number of genetic and neuroimaging studies have attempted to examine the biological basis of NS, but results have been mixed and the combined genetic–neural mechanism of the NS remains to be explored.

Following Cloninger's model (Cloninger, 1986), much of the genetic work of the NS trait has focused on candidate genes affecting the dopamine (DA) system, and their genetic effects on NS (Davila et al., 2013; Montag et al., 2010; Munafo et al., 2008). In this study we focused on the *DBH* gene, located on chromosome 9q34. It encodes dopamine β-hydroxylase (DβH) protein (Kaufman and Friedman, 1965) and is a major quantitative trait locus of plasma DβH activity (Zabetian et al., 2001). DβH protein catalyzes the conversion of DA to norepinephrine (NE) (Levin et al., 1960) in synaptic vesicles and thereby influences extracellular DA level. Hence, one might speculate that variation in the *DBH* gene could impact NS by virtue of its effect on dopamine levels. This hypothesis has been supported by recent studies linking the *DBH* gene to NS (Hess et al., 2009) and several psychiatric disorders related to excessive NS, such as ADHD (Carpentier et al., 2013) and addiction (Preuss et al., 2013). However, the mechanism for these gene–behavior associations, especially neural structure as mediating factors (or neural endophenotypes (Goldberg and Weinberger, 2004; Meyer-Lindenberg and Weinberger, 2006)), remains unclear. Therefore, this study aimed to study the role of *DBH* gene on neural structure underlying NS. Our

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http://dx.doi.org/10.1016/j.neuroimage.2015.05.033
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results should help to better elucidate the influence of the *DBH* gene on NS as well as related neuropsychiatric disorders.

Neuroimaging studies have examined the correlation between NS and cortical volume in several brain regions (Gardini et al., 2009; Iidaka et al., 2006; Schilling et al., 2013b; Van Schuerbeek et al., 2011), however, these findings are mixed. Some research found that NS was associated with cortical volume in the middle frontal gyrus (Iidaka et al., 2006) and orbitofrontal cortex (Schilling et al., 2013b), whereas some others found associations with regions such as the posterior cingulate regions (Gardini et al., 2009; Van Schuerbeek et al., 2011) and cerebellum (Van Schuerbeek et al., 2011). These inconsistent results might be attributed to differences in sample size, methods, or statistical model specifications (Hu et al., 2011). Another possible issue is that most studies have examined cortical volume as a whole, while ignoring the two individual components that comprise it, cortical thickness and surface area. Cortical volume is the product of cortical thickness and surface area, which are genetically (Panizzon et al., 2009) and phenotypically (Winkler et al., 2010) independent. Moreover, these two measures are distinct aspects of the neural architecture and have different developmental trajectories (Lyall et al., 2014). Thus far, to our knowledge, the majority of structural neuroimaging studies of the NS trait have investigated the volume measure as a whole (Gardini et al., 2009; Iidaka et al., 2006), except for one study which estimated the cortical thickness measure but only focused on a facet of the NS trait (impulsiveness) (Schilling et al., 2013a). Given this gap in the literature, the respective contributions of surface area and cortical thickness to the NS trait should be investigated. This could not only help us to clarify the neural structure basis of the NS trait, but could also provide appropriate endophenotypes for imaging genetics studies (Winkler et al., 2010), to better understand the genetic–neural basis of the NS trait.

The aim of the present study was to examine the brain structure underpinnings of NS trait and to understand the gene–brain–behavior relationships among the *DBH* gene, brain structure, and the NS score. Therefore, we first evaluated the respective effects of cortical surface area and cortical thickness on the NS trait in a large healthy Han Chinese sample. Then we tested the association between the single nucleotide polymorphisms (SNPs) in and nearby the *DBH* gene and NS-related brain structures. Finally, to clarify the role of the brain in the complex interrelations, we performed path analyses to test whether brain structure served as a mediator between the *DBH* gene and the NS trait. We hypothesized that variations in the *DBH* gene would be related to cortical structure and NS score, and furthermore, that cortical structure would mediate the association between the genetic variations and NS score.

Material and methods

Subjects

Three-hundred and fifty nine healthy Han Chinese subjects (173 females, mean age = 19.4 ± 1.1 years) participated in the study. All subjects had no history of neurologic or psychiatric disorders, and were not taking any medications that could interfere with their ability to complete a questionnaire or provide structural MRI data. This study was approved by the Ethics Committee of School of Life Science and Technology at the University of Electronic Science and Technology of China. All participants gave informed written consent.

Genotyping

After blood sample collection, genomic DNA was extracted using the E.Z.N.A.™ Blood DNA Kit (Omega Bio-Tek, Georgia, US). All samples were genotyped using the standard Illumina genotyping protocol (Illumina, Inc). As described in Supplemental Materials Table S1, 51 SNPs located in or within 100 kb around the *DBH* gene on chromosome 9 were selected. These SNPs covered most of the linkage disequilibrium (LD) blocks in this region, as defined for the Chinese sample included in the HapMap Project (http://www.hapmap.org[phase 3]). Five of the 51 SNPs failed to pass minor allele frequency (MAF) > 0.05 and were excluded for further analyses. The remaining 46 SNPs met the criteria for Hardy–Weinberg equilibrium (HWE) $p > 0.01$ and genotype call rate > 0.98 and were included in subsequent analyses. When fewer than five participants were categorized as either heterozygotes or minor allele homozygotes for a SNP, the two genotype groups were combined in further analysis.

Novelty seeking measure

Each subject was asked to complete the Chinese version of the Temperament and Character Inventory-Revised (TCI-R) (Chen et al., 2011; Cloninger, 1994). This inventory was translated from English to Chinese and back translated and verified through a bilingual group discussion, and the resulting Chinese versions had high internal consistency (Chen et al., 2011). The NS subscale of the TCI-R measures individual differences in the extent to which a person is quick tempered, impulsive, extravagant, and disorderly versus rigid, stoical, and orderly (Cloninger et al., 1993). The total score on the NS subscale was used in the current study.

Image acquisition and preprocessing

MRI scans were performed with an MR750 3.0 Tesla magnetic resonance scanner (GE Healthcare). High-resolution 3D T1-weighted brain volume (BRAVO) MRI sequence was performed with the following parameters: TR = 8.16 ms, TE = 3.18 ms, flip angle = 7°, FOV = 256 mm × 256 mm, voxel size = 1 × 1 × 1 mm^3, and 188 slices. All the raw MRI data were inspected by two experienced radiologists who were blind to genotype information.

MRI data were analyzed with atlas-based FreeSurfer software (http://surfer.nmr.mgh.harvard.edu, version 5.3.0). The cortical surface was constructed through an automated procedure, involving segmentation of the white matter, classification of the gray/white matter boundary, inflation of the folded surface, and automatic correction of topological defects (Dale et al., 1999; Fischl and Dale, 2000). After the initial surface model had been constructed, measures of cortical surface area were calculated by computing the area of each triangle of a standardized tessellation. Then all of the individual reconstructed cortical surfaces were aligned to an average template with a surface-based registration algorithm. Quality control of scan images and segmentation was assured by visual inspection of the whole cortex of each subject and manual editing following the standard editing rules. Any inaccuracies in Talairach-transformation, skull stripping, and segmentation were also manually corrected, and re-inspected. A high correlation between these automatic measures and manual measures in vivo and ex vivo has been demonstrated (Desikan et al., 2006). Cortical thickness and surface area maps were then smoothed using a Gaussian kernel (20 mm FWHM).

Statistical analysis

After surface reconstruction, vertex-by-vertex analyses of cortical thickness and surface area were performed separately, by using a general linear model to estimate the association between the morphological measure at each vertex and the NS score. Gender and age were included as covariates to avoid potential confounding effects (Smith et al., 2007). Significance maps were then corrected for multiple comparisons with cluster-based Monte Carlo simulations with 5000 permutations (using the *FreeSurfer* program mri_glmfit-sim, corrected for two spaces). Finally, because thickness analysis did not yield any significant results, the region significantly correlated with the NS score (corrected $p < 0.05$) in the cortical surface area analysis, the left insula, was extracted. We mapped this region onto the average reconstructed surface for visual display,

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