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Featured Article

A dopamine receptor genetic variant enhances perceptual speed in cognitive healthy subjects

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Abstract

Introduction: Cognition is under strong genetic control, yet the specific genes are unknown.

Methods: One hundred and fifty-three cognitive healthy European subjects from the Reference Abilities Study (RANN) were genotyped for 1,160 variants within 446 neuropsychiatric genes. Adjusted linear regression models evaluated the association between the genetic variants and four reference abilities (Vocabulary, Episodic Memory, Perceptual Speed, and Reasoning).

Results: One hundred and fifty-nine variants nominally were found significant in the RANN cohort and re-evaluated in an independent cohort of 868 cognitive healthy subjects from the Religious Orders Study and Rush Memory Aging Project. Meta-analysis yielded a Bonferroni adjusted statistically significant association between perceptual speed and a variant located in the promoter of the dopamine receptor D4 gene, rs3756450 ($\beta = 0.23$, standard error $= 0.05$, $P_{meta} = 2.3 \times 10^{-5}$).

Discussion: Our data suggest that genetic variation in a dopamine pathway gene influences perceptual speed performance in cognitively healthy individuals.

Keywords: Cognitive performance; Cognitive healthy subjects; Candidate genes SNP association; Meta-analysis; Dopamine pathway

1. Introduction

A significant proportion of the differences observed in cognitive performance is attributable to genetic variability. Cross-sectional and longitudinal twin studies have consistently shown strong genetic influences on cognitive performance, in both normal variation and in the extremes of the normal distribution [1,2]. Results from a meta-analysis of 23 independent twin studies also showed that heritability estimates vary across the different specific domains [3].

Several studies have reported genetic associations with a priori biological relevant genes for cognition; however, results have not been consistently replicated [4–13]. Genetic-agnostic approaches through genome-wide association analysis (GWAS) have also been reported for different cognitive tasks [14–21]. GWAS studies have examined cognition in the context of pathologic cognitive variation, that is, Alzheimer's disease (AD) [22–28], and also in normal variation in healthy adults. Some of the loci reported in recent GWAS of cognitive function in middle and older nondemented subjects have been previously associated with AD [15–17], suggesting a possible genetic overlap between normal and

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pathologic cognitive variation in older age. However, some other studies have reported that many loci previously implicated in Late Onset Alzheimer's Disease (LOAD) were not associated with any cognitive domain [28,29] or AD pathology [30]. To better understand the natural disease resistance to brain neurodegeneration, increasing number of genetic studies are focusing on cognitive healthy individuals. The identification of genetic variants influencing cognitive function in nondemented cohorts can elucidate molecular mechanisms for preventing or delaying cognitive decline.

Among the main limitations of GWAS are the small genetic effects of the identified variants and the very stringent multiple testing correction needed to achieve genome-wide significance ($P \leq 6 \times 10^{-8}$) [31]. Alternative gene identification approaches include hypothesis-driven gene-based analysis, that is, candidate gene(s), which rely on already available experimental data that support the involvement of the genes being tested. The use of smaller focused single-nucleotide polymorphism (SNP) arrays represents a practical approach where SNPs cover a limited number of biological candidate genes. Such focused SNP arrays offer the advantages of lower cost and lower false discovery rate, especially in situations where a data set may have inadequate power for GWAS because of either size or other reasons [32].

The candidate gene approach has been questioned because of nonreplication of results and limits on its ability to include all possible causative polymorphisms [33]. However, rigorous epidemiologic principles, as previously described [33], may considerably improve its success. In addition, efforts from different human genome sequencing initiatives, such as 1000 genome sequencing project, provide extensive high coverage data information (genomic, transcriptomic, epigenomic, and proteomics) that will helpfully contribute to overcoming the shortcomings of the candidate gene approach [34].

Our candidate gene approach focused on genes previously investigated [32] based on their roles as functional domains important in psychiatric neurogenetics. Neurobiological studies of addiction, mood disorders, and psychoses have established the importance of mechanisms such as reward, stress resiliency, and executive cognitive control [35]. Among the implicated molecular networks and genes integral to those processes are signaling networks, stress/endocrine genes, and key neurotransmitter systems including dopamine (DA), serotonin, glutamate, γ-amino butyric acid (GABA), and acetylcholine.

We investigated whether SNPs tagging genes that are key players in different neurologic molecular networks (pharmacogenomics, pharmacodynamics, and behavioral) may influence individual performance on four previously reported reference abilities (RAs): episodic memory, fluid reasoning, perceptual speed, and vocabulary.

2. Methods

2.1. Study samples

Subjects were recruited from two different cohorts. Three hundred twenty-nine participants were recruited from the community for the Reference Ability Neural Network (RANN) study (referred to as RANN sample), of which only those with Caucasian ancestry ($n = 153$) were considered for analysis purposes, and 868 Caucasian participants from the Religious Orders Study and Rush Memory and Aging Project (ROSMAP sample).

2.2. RANN sample

2.2.1. Study participants

The RANN study includes healthy adults for whom cognitive assessment and MRI imaging are available. Subjects were free of medical or psychiatric conditions that could affect cognition. Detailed description of the cohorts can be found elsewhere [36].

2.2.2. Computation of cognitive phenotypes from neuropsychology data

A battery of 12 neuropsychological tests was selected to assess cognitive functioning in four cognitive domains: episodic memory, reasoning ability, perceptual speed, and vocabulary. Previous analyses demonstrated that the included tasks described latent unique latent variables for the four cognitive domains [37,38]. There were some missing data for the neuropsychological measures, but we decided to be as inclusive as possible. We therefore calculated average z-scores within each domain over all the three measures that were available; a missing value for the domain z-score was assigned only when all three measures were missing. All measures were adjusted such that a larger value indicated better performance, that is, completion times were flipped in sign. The measures that made up the domain z-scores all showed high correlation, lending good support for internal consistency, as can seen subsequently.

Three *memory* measures were based on subscores of the Selective Reminding Task (SRT) [39]. Participants in this task were initially asked to read a list of 12 words and then asked to recall as many as they could. For the following five trials they were reminded of the words that they did not report and were asked to again recall all the words in the list. Words are considered to enter long-term storage from the point when they are recalled twice in a row without reminders. The long-term storage subscore (SRT_LTS) is the sum over all words of the number of trials when each word was in long-term storage. Continuous long-term retrieval (SRT_CLRT) is the sum over all words of the number of trials for which the word was continuously recalled. The third memory measure was the number of words recalled on the last trial (SRTLast).