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The Role of the Brain-Derived Neurotrophic Factor C270T Polymorphism in Executive Functioning

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Abstract

Neurotrophins such as brain-derived neurotrophic factor (BDNF) play an important role in the proliferation and survival of cholinergic, dopaminergic, and serotonergic neurons. With high BDNF gene expression in the hippocampus and prefrontal cortex, BDNF is a regulatory factor for building and maintaining cognitive reserves. The recently identified BDNF C270T polymorphism is understudied, especially in non-clinical samples. In this study, 106 adults completed a battery of executive function measures and were genotyped using real-time polymerase chain reaction. Results indicated that the C/T group (n = 42) outperformed the C/C (n = 62) group on measures of cognitive flexibility. No genotype effects emerged for domains of abstract reasoning, planning/task initiation, response inhibition, self-monitoring, fluency, or working memory. Although the mechanism of C270T gene expression as it relates to BDNF

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availability is still unknown, we speculate that the C/T polymorphism modulates phasic dopamine activity in the prefrontal cortex to achieve enhanced cognitive flexibility.

Keywords: genetic polymorphism, executive functions, neuropsychological tests, brain-derived neurotrophic factor, dopamine

1 Introduction

Neurotrophic factors (NTFs) are a family of peptides that contribute to the development and maintenance of specific cells in the nervous system. During early stages of embryonic development, NTFs promote neuronal survival by inhibiting apoptosis, with the net result of this “neural Darwinism” [1] being survival of only the most successful synaptic connections. After maturity when apoptotic mechanisms are dormant, NTFs continue to have a role in the nervous system by fostering dendritic branching and development of axon collaterals [2]. These two forms of neuroplasticity permit neuronal flexibility to reorganize when appropriate (e.g., in the context of learning; after neural insult). Recent studies suggest that age- or genetic-related variation in NTF levels contribute to neurodegeneration, prompting exploration of NTF gene-cognition relationships in the context of Alzheimer’s disease and other dementias [3]. Indeed, NTF regulation of synaptic plasticity well into adulthood implicates these peptides as potential modulators of cognitive ability across all ages.

One particular NTF, brain-derived neurotrophic factor (BDNF), has received considerable attention in the literature for its trophic effects on cholinergic, dopaminergic, and serotonergic neurons. Consistent with findings of high BDNF gene expression in the prefrontal cortex (PFC) and hippocampus [4], human and nonhuman animal studies indicate a role of BDNF in long-term memory and

executive function domains [5]. The BDNF gene, located on chromosome 11p13, consists of four short 5' exons and one 3' exon [6]. Several polymorphisms have been identified, including a dinucleotide repeat $(GT)_n$ polymorphism, a Val66Met (196G/A) polymorphism, -374A/T and -256G/A polymorphisms, and a C270T substitution. Of these, the C270T polymorphism is understudied, especially in non-clinical samples. To date, research has identified relationships between the C270T polymorphism, particularly the T allele, and late-onset Alzheimer's disease [7], familial Parkinson's disease [8], and schizophrenia [9], but no study has examined whether cognitive differences exist between genotype groups outside the context of psychiatric illness.

This study explores patterns of cognitive performance as a function of the C270T polymorphism in a community sample of adults. Given the role of BDNF in executive functioning, we focused specifically on this cognitive domain in assessment. Executive functioning refers to mental processes that permit goal-oriented behavior, which include abstract reasoning, planning and task initiation, response inhibition, self-monitoring, cognitive flexibility, fluency, and working memory. In light of research that indicates relationships between intelligence and executive functioning [10], intellectual functioning was also assessed as a potential confounding variable. Without knowing the intracellular mechanisms by which C270T exerts an influence on BDNF, it is difficult to predict a priori whether C or T allele carriers will demonstrate a cognitive advantage, and, if so, in which executive function domain(s). Investigation into whether such behavioral differences exist and neuropsychological characterization of those differences, however, may provide insight into functional and structural intergroup differences at the level of the brain and thereby guide future molecular research. The present study set out to assess a range of executive functioning skills in normal, healthy controls using standardized, validated neuropsychological tests with known neural correlates that have not previously been evaluated in the context of this genotype.

2 Methods

The sample included 109 genetically-unrelated, right-handed adults (70 women) recruited through online advertisements. Participants ranged in age from 18 to 64 years (*M* = 32.3, *SD* = 13.2), with 84.9% reporting their ethnicity as European American/Caucasian, 6.6% as Asian-American, 4.7% as Black/African-American, and 1.9% as Latina(o)/Hispanic. Educational achievement ranged from 11 to 26 years (*M* = 15.8, *SD* = 2.6), indicating nearly complete college education on average. Written informed consent was obtained per participant, and the experimental protocol was approved by the local Institutional Review Board. Rule-out criteria included English as a second language, color-blindness, presence of a diagnosed psychiatric illness and/or history of psychiatric treatment, history of significant neurological illness or brain injury, history of medical conditions with known cognitive or emotional sequelae, substance abuse history, and recent use of psychoactive substances.

DNA extraction was completed with the Gentra Puregene Blood Kit (Qiagen: Valencia, California, USA). Genotyping for C270T was completed by molecular pathology staff at Dartmouth-Hitchcock Medical Center (Lebanon, New Hampshire, USA). Quantitative real-time polymerase chain reaction (qPCR) was performed using the ABI Assay-on-Demand system using allele-specific probes and primers run on the ABI PRISM 7500 (Applied Biosystems, Foster City, California, USA). Each reaction underwent an initial denaturation step at 50˚C for 2 minutes, and the PCR reaction ran at an annealing temperature of 95˚C for 10 minutes, followed by 40 cycles of 92˚C for 30 seconds, alternating with 60˚C for 1 minute.

Neuropsychological tests included the Wechsler Abbreviated Scale of Intelligence (WASI) [11], several subtests from the Delis-Kaplan Executive Function System (D-KEFS) [12] including the Color-Word Interference Test, Word Context Test, Verbal Fluency Test, Figural Fluency Test, Trail Making Test, and the Tower Test, the Spatial Span and Digit Span subtests of the Wechsler

Memory Scale, Third Edition (WMS-III) [13], the Paced Auditory Serial Addition Test (PASAT) [14], the Connors' Continuous Performance Test, Second Edition (CPT-II) [15], and the Wisconsin Card Sorting Test, Computer Version 4 (WCST:CV4) [16]. Test order was such that presentation of verbal and nonverbal material was as counterbalanced as possible.

The WASI is a four-component intelligence test. The Vocabulary subtest assesses crystallized verbal knowledge by requiring the participant to define words that vary in level of difficulty. In the Block Design subtest, which examines visual information processing, the participant replicates abstract shapes using colored cubes. The Similarities subtest assesses level of verbal abstract thinking by asking the individual to relate together two different objects, actions, or concepts. In the Matrix Reasoning subtest of nonverbal reasoning, the participant selects a geometric figure that will complete a sequenced visuospatial pattern. The Vocabulary and Similarities subtests compose the Verbal IQ, and the Block Design and Matrix Reasoning subtests compose the Performance IQ. These two quotients, in turn, yield the Full Scale IQ. Subtest and superordinate values were normalized from raw scores based on available age norms [11].

The Color-Word Interference Test is a measure of cognitive flexibility and response inhibition. The first two trials assess the individual's baseline speed of color naming and word reading. The third trial, in which the participant identifies the ink color of a word whose semantic meaning is incongruent with the ink color itself, indexes response inhibition in that the participant must inhibit the prepotent response of word-reading. In the fourth trial, the individual follows the same rules, unless the stimulus is surrounded by a box in which case the participant must verbalize the semantic meaning of the word instead of naming its ink color. Therefore, the fourth condition requires the individual to switch flexibly between two rules, thereby utilizing cognitive flexibility. Completion time scores are converted to scaled scores based on available norms [12].

The Word Context Test is an assessment of abstract thinking, requiring the

related skills of deductive reasoning and hypothesis testing, in which the participant deduces the meaning of neologisms based on contextual clues. For each target word, the participant is given clue sentences with the goal that the participant derives the correct meaning by the last sentence. The variable of interest is the number of sentences answered consistently correct, which is transformed to a scaled score based on available norms [12].

The Verbal Fluency Test has three conditions. Condition 1 (Letter Fluency) asks the individual to generate as many words as possible that begin with a specified letter of the alphabet in three trials of 60 seconds each. In Condition 2 (Category Fluency), the individual generates words that belong to a designated semantic category (e.g., animals) as quickly as possible in two trials of 60 seconds each. Condition 3 (Category Switching) assesses cognitive flexibility, as the participant generates words belonging to two different semantic categories as quickly as possible within 60 seconds but with the task demand of alternating between categories per response. The Figural Fluency Test is similar in that it has three, 60-second conditions, the first two of which assess fluency and the last of which assesses cognitive flexibility. In Conditions 1 and 2, the individual must create as many unique designs as possible using four straight lines to connect dots presented on paper. In Condition 3, the participant continues to draw unique designs but alternates between types of dots when making connections. In all cases, the raw score is the number of correct, unique designs completed within the time limit. Raw scores are converted to scaled scores based on available norms [12].

The Trail Making Test is comprised of five trials. Trial 1 measures visual scanning speed, Trial 2 measures number sequencing speed, Trial 3 measures letter sequencing speed, and Trial 5 measures motor speed. The trial that assesses cognitive flexibility, and therefore the one of interest here, is Trial 4, in which the individual connects numbers and letters on a sheet of paper in an alternating, ascending fashion. Time to completion is transformed into a scaled score based on

test-specific norms [12].

The Tower Test is a non-verbal assessment of spatial planning that requires participants to assemble towers using differently-sized wooden pieces that can be placed on vertical pegs. Individuals replicate a picture of a tower shown in a stimulus booklet in as few moves as possible but under the conditions that they move only one piece at a time and cannot place bigger pieces atop smaller pieces. Individuals are scored based on the time at which they make their first move, how many moves are made to complete the task, the number of rule violations, and the time in which they complete the task. Raw scores are converted to scaled scores based on available norms [12].

In the Spatial Span subtest, the experimenter uses a three-dimensional plastic board with raised cubes to present a series of spatial patterns. For the first task (Forward Condition), the experimenter points to a series of blocks on the board at a rate of one block per second. The participant must then point to the same series in the same order. This process is repeated as the number of blocks in a given series gradually increases. The second task (Backward Condition) is the same, except that the participant must point to the series of blocks in the reverse order. The Spatial Span total score is the number of accurate trials in both conditions. Digit Span also involves a Forward and Backward Condition. In the Forward Condition, the experimenter reads aloud a series of digits at a rate of one digit per second. The participant must then repeat the digits in the same order. The Backward Condition is the same, except that the participant must repeat the digits in the reverse order. The Digit Span total score is the number of accurate trials in both conditions. Raw scores are converted to scaled scores based on available norms [13].

The PASAT is an auditory test of working memory. Single digit numbers are presented at the rate of one every three seconds (Trial 1) or one every two seconds (Trial 2), with 60 stimuli presented per condition. Individuals must add the numbers in pairs, such that each number is added to the one preceding it.

Accuracy scores are converted to *z*-scores based on available norms [14].

The CPT-II is a computerized measure of visual sustained attention and inhibition in which participants must respond to frequent non-target stimuli and inhibit a response to infrequent target stimuli. Although many variables are computable, three were selected for analysis. The number of commission errors was chosen as an index of response inhibition. Two other variables were chosen as indices of self-monitoring skill: changes in reaction time over the course of the test (Reaction Time Block Change) and changes in response consistency (Hit Standard Error Block Change). In all cases, raw values are converted to *T*-scores compared to normative values [15].

The WCST:CV4 is a computerized assessment of abstract thinking and cognitive flexibility. Participants are shown four target cards on a computer screen, each with a different geometric shape, number of shapes, and color of shapes. The participant is then shown a novel card and asked to match the new card to one of the four target cards. Individuals are not told the principle by which they should make their matches, but they are given feedback after each selection. After ten correct responses, the matching criterion changes unbeknownst to the participant. Participants must acknowledge the change in order to get future matches correct. Variables selected for analyses included: the total number of trials correctly matched (Total Trials Correct raw score) and the number of successfully matched categories (Categories Completed raw score) as two indices of planning, the number of repeated incorrect answers (Perseverative Errors *T*-score) as an index of response inhibition, and the proportion of consecutive correct responses occurring in runs of three or more (Conceptual Level Response *T*-score) as an index of insight into the correct sorting principles. When possible, scores were normed according to age [16].

Multivariate analyses of variance (MANOVA) with genotype as a grouping factor were conducted separately for domains of abstract reasoning, planning/task initiation, response inhibition, self-monitoring, cognitive flexibility,

fluency, and working memory. Given that a relationship between C270T genotype and cognitive phenotype has not been established in the literature, we did not apply a Bonferroni correction for multiple comparisons; adjusting the threshold for significance might inappropriately increase the possibility that a real effect is missed among the data [17].

3 Results

The sample consisted of 63 individuals with the C/C genotype, 43 with the C/T genotype, 2 with the T/T genotype, and 1 individual whose genotype was undetermined. To maximize power, only individuals with C/C and C/T genotypes were included for analysis, leaving a sample of 106 individuals (68 women). The genotype frequencies in the present sample are consistent with those reported elsewhere [9]. The sexes were comparably distributed across genotype groups (χ^2 with Yates' Continuity Correction = .62; df = 1; p = ns). Similarly, the groups were comparable in terms of age, level of education, as well as Verbal, Performance, and Full Scale IQ (all p = ns).

Neuropsychological variables are shown in Table 1. There was no significant skewness in the dependent variables. Of the MANOVAs conducted to analyze differences across cognitive categories, there was an effect of C270T genotype on cognitive flexibility, Wilks' λ = .89, $F(5,98)$= 2.45, p = .03. Tests of between-subjects effects indicated that C/T group outperformed the C/C group in D-KEFS Category Switching scaled score, $F(1,102)$ = 12.14, p = .001, partial eta^2 = .11, and D-KEFS Category Switching Accuracy scaled score, $F(1,102)$ = 11.75, p = .001, partial eta^2 = .10. The groups performed equivalently on the other cognitive flexibility measures.[1] No differences emerged across groups for any other executive function domain (all full model p = ns).

Table 1: Performance on executive functioning measures by genotype

	C/C group	C/T group
Domain/Measure	*M (SD)*	*M (SD)*
Intelligence		
WASI VIQ standard score	108.0 (12.5)	108.3 (9.8)
WASI PIQ standard score	111.2 (13.2)	113.9 (12.9)
WASI FIQ standard score	111.0 (12.7)	112.3 (10.6)
Abstract Reasoning		
D-KEFS Word Context Correct SS	11.4 (2.4)	11.9 (1.9)
WASI Similarities *T*-score	54.7 (6.9)	53.0 (6.6)
WCST Conceptual Level *T*-score	48.8 (9.9)	49.1 (8.4)
Planning/Task Initiation		
WCST Categories raw score	5.8 (1.0)	5.8 (.89)
WCST Total Trials Correct raw score	70.5 (10.6)	71.7 (9.0)
D-KEFS Tower Total Achievement SS	10.9 (2.6)	11.8 (2.5)
D-KEFS Tower Mean First Move SS	11.1 (1.7)	11.1 (2.4)
D-KEFS Tower Move Accuracy Ratio SS	9.7 (2.3)	10.0 (2.0)
Response Inhibition		
WCST Perseverative Errors *T*-score	51.0 (11.3)	52.2 (11.6)
D-KEFS Color-Word Inhibition SS	10.7 (2.3)	10.5 (2.3)
CPT-II Commission Errors *T*-score	55.0 (12.1)	50.1 (11.7)
Self-Monitoring		
CPT-II RT Block Change *T*-score	49.5 (6.4)	49.6 (10.4)
CPT-II Hit SE Block Change *T*-score	55.0 (11.3)	52.6 (10.1)
D-KEFS Tower Total Rule Violations %	82.2 (31.3)	86.4 (28.7)
Cognitive Flexibility		
D-KEFS Category Switch SS	11.9 (3.3)	14.1 (2.9)
D-KEFS Category Switch Accuracy SS	11.6 (3.3)	13.6 (2.5)
D-KEFS Color-Word Switch/Inhibit SS	11.0 (2.1)	11.1 (2.6)
D-KEFS Design Fluency 3 SS	12.5 (2.8)	12.9 (2.6)
D-KEFS Trail Making Trial 4 SS	11.2 (2.1)	11.6 (1.8)
Fluency		
D-KEFS Letter Fluency Total SS	12.7 (3.1)	12.5 (3.4)
D-KEFS Category Fluency Total SS	13.4 (3.0)	14.9 (3.1)
D-KEFS Design Fluency 1 SS	11.5 (2.7)	12.7 (2.3)
D-KEFS Design Fluency 2 SS	11.7 (2.2)	12.4 (2.5)
Working Memory		
WMS-III Spatial Span Total SS	11.9 (2.5)	11.9 (2.3)
WMS-III Digit Span Total SS	11.1 (2.6)	11.2 (2.3)
PASAT Condition 1 *z*-score	-.17 (1.0)	-.19 (1.1)
PASAT Condition 2 *z*-score	-.16 (.95)	-.23 (.93)

Note: WASI = Wechsler Abbreviated Scale of Intelligence; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; FIQ = Full Scale Intelligence Quotient; D-KEFS = Delis-Kaplan Executive Function System; SS = scaled score; WCST = Wisconsin Card Sorting Test; CPT-II = Conners' Continuous Performance Test, Second Edition; WMS-III = Wechsler Memory Scale, Third Edition; PASAT = Paced Auditory Serial Addition Test.

5 Conclusion

This is the first investigation of executive functioning in a non-clinical sample as a function of the BDNF C270T polymorphism. Of the domains assessed, cognitive flexibility emerged as a point of difference such that the C/T group outperformed the C/C group on the D-KEFS Category Switching test, a finding that was not confounded by age, gender, education, or IQ differences. As a dual-task measure of verbal fluency and set-shifting, this test requires rapid retrieval from semantic knowledge and cognitive flexibility to shift between two semantic categories. The lack of intergroup discrepancy on the other verbal fluency subtests suggests that the locus of difference between groups is cognitive flexibility as opposed to verbal fluency [12]. Given this finding, it is important to address how the C270T genotype influences BDNF to result in cognitive flexibility differences. Although much is known about the functional mechanisms associated with other BDNF-related genes such as the Val66Met polymorphism [18], the molecular nature by which C270T exerts an influence on BDNF and, subsequently on brain structure and function, is unknown. It is possible that C270T has a direct effect on cognition via changes in BDNF alone, but it is also possible that it mediates an effect through other genes or through downstream changes in other neurotransmitter systems. Although speculative, there is reason to suspect that one key downstream mediator to link BDNF and cognitive flexibility is the prefrontal dopaminergic system.

As a component of cognitive control, cognitive flexibility is essential for goal-oriented action by allowing an individual to switch between goals in response to environmental changes. Cognitive stability, however, is also needed for goal-oriented behavior in that it maintains relevant information and shields the goal state from distraction. Several theorists propose that the balance between cognitive flexibility and stability is determined by tonic versus phasic dopamine release in the PFC [e.g., 19]. Phasic dopamine is thought to aid the updating and resetting of representations in the PFC via D_2 receptors, thereby permitting a flexible response style with the activation of new goal states. Alternatively, tonic dopamine is thought to enhance the stability of working memory traces via D_1 receptors. Given the present data, we suggest that an indirect effect of the BDNF C/T polymorphism is stimulation of phasic dopamine activity at D_2 receptors. Non-human animal data suggest that phasic dopamine transmission in orbitofrontal and medial PFC via D_2 receptor binding is critical for set-shifting tasks involving rapid rule reversal [20] akin to the neuropsychological test used here, and human neurogenetic imaging studies corroborate the association between cognitive flexibility ability and D_2 receptor activation [21]. Although evidence suggests that these D_2 receptors are localized in striatal dopaminergic neurons whose efferents terminate in these prefrontal regions [e.g., 22], there is additional support for a role of D_2 receptors located directly in orbitofrontal and medial PFC in guiding behavioral flexibility [23,24].

Neurotrophic factors are known to foster neuroprotection of dopaminergic neurons, and research is beginning to characterize the interactions between BDNF and dopamine circuits. BDNF influences dopamine release in striatal regions [25], which subsequently alters prefrontal dopamine catabolism via basal ganglia-thalamocortical loops [26]. One result of this potentiated dopamine output, and the one we propose is the means by which the BDNF C270T genotype modulates cognitive flexibility, is increased activity in the D_2 orbitofrontal-striatal circuit.

In addition to clarifying the molecular basis of altered BDNF function by C270T with transgenic animal models, as next research steps it is important to characterize other differences between C/C and C/T groups in humans. Structural and functional neuroimaging is useful to determine if there are concomitant alterations in key brain regions. For example, for the BDNF Val66Met polymorphism, Pezawas and colleagues [4] have shown that heterozygous Met allele carriers (i.e., those with less activity-dependent BDNF secretion) have decreased volume in the hippocampus, dorsolateral PFC, and caudate nucleus relative to Val allele carriers (i.e., those with more BDNF secretion). Additional research has uncovered functional differences between these groups, such as reduced hippocampal activation during memory tasks [27] and reduced functional connectivity with the hippocampus during implicit fear processing [28] for Met allele carriers. Whether similar intergroup distinctions exist for C270T genotypes is unknown.

With larger sample sizes, future studies should also replicate and extend the finding reported here, including determination of whether age and gender moderate the influence on cognitive flexibility. More sophisticated psychometric assessment will be useful to parse cognitive flexibility from other components of cognitive control [29] given the importance of this distinction to the tonic/phasic dopamine hypothesis and given that stable and flexible processing task demands are confounded in many neuropsychological measures. As the genotype reported here captures 11% of the variance in cognitive flexibility, there remain other explanatory variables to elucidate. It will be constructive to consider gene-gene interactions between C270T and other genes, particularly those linked to dopaminergic control, as genetic interdependencies between BDNF and dopaminergic systems would not be unexpected in the repertoire of human individual differences in cognition.

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