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BDNF gene polymorphisms and haplotypes in relation to cognitive performance in Polish healthy subjects

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The brain derived neurotrophic factor (BDNF) is a neurotrophin that plays an important role in the cell survival, axonal and dendritic growth, and synaptic plasticity. BDNF gene polymorphisms, functional Val66Met mainly, were shown to influence human brain structure and cognition.

The aim of the study was to assess the relationship between twelve BDNF gene variants and their haplotypes and cognitive performance measured using the Wisconsin Card Sorting Test (WCST), the Trail Making Test (TMT), the Stroop Test which are to a large extent connected with prefrontal cortex activity. Our sample consisted of 460 healthy participants from Polish population. We detected possible association between five BDNF polymorphisms (rs11030101, rs10835210, rs2049046, rs2030324, rs2883187) and TMT_A. Additionally, one haplotype block made from eleven BDNF variants (rs2883187, rs1401635, rs2049046, rs2030324, rs11030101, rs10835210, rs1013402, rs1401635, rs1013402), as significant linkage disequilibrium appeared. We discovered possible relationships of CACCGCGTACG and CACCGCGTACG haplotypes with TMT_A and TMT_B performance respectively. Our results confirmed the involvement of BDNF in the regulation of psychomotor speed, working memory and executive function in healthy subjects measured by a task engaging visuoperceptual abilities.

Key words: brain derived neurotrophic factor, polymorphism, haplotype, cognition

INTRODUCTION

Research over the past two decades has highlighted the relationship of cognitive performance with the system of neurotrophins. Neurotrophins are a family of polypeptide growth factors with similar structures, involved in processes of brain development, differentiation and survival of neurons, synaptic plasticity and connectivity (Bath and Lee 2006). Neurotrophins group consists of: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin 4/5 (NT-4/5) (Barde et al. 1982, Leiberock et al. 1989). BDNF seems to play the most important role in the cognitive processes. It affects the development and activity of brain structures, predominantely hippocampus and prefrontal cortex (Lipska et al. 2001), by modulating the synaptic neurotransmission, affecting neuronal plasticity and proliferation of nerve cells (Figurov et al. 1996, Lu and Gottschalk 2000, Chen et al. 2004), and by regulating the processes of neuronal migration, i.e.: neuronal differentiation and preservation of modifications and changes of synaptic structures (Huang et al. 1999). BDNF also influences the development of dopaminergic (Altar et al. 1992, Shen et al. 1994), serotoninergic (White et al. 1994, Mamounas et al. 2000) cholinergic (Lindsay 1995, Lindvall et al. 1994) and GABAergic neurons (Ventimiglia et al. 1995). Furthermore, BDNF causes rapid postsynaptic reaction on ion channels and NMDA receptors (Levine et al. 1995).

BDNF gene is located on the short arm of chromosome 11 (Maisonpierre et al. 1991). It has a complex structure and regulation of expression. Pruunsild and others (2007) determined that the BDNF gene contains 11 exons and spans about 70 kb. They identified transcription start sites in 9 exons, each of which was associated with a functional promoter.

In the position 196 of the nucleotide sequence of the 3 'exon encoding the BDNF protein, there is a most widely studied functional polymorphism A/G, leading to the substitution of amino acid of valine to methionine at position 66 of the protein (refSNP Cluster Report: rs6265). An ancestral allele is Val and frequency of occurrence of the Met allele in different populations varies from 0% in

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African populations to 70% in Asian populations. In the Caucasian population frequency of the Met allele is approx. 20%. The rate of spread of the Met allele indicates a strong evolutionary selection of the genomic region, in which the polymorphism is located (Petryshen et al. 2010).

In recent years, studies have been conducted in order to analyze the relationship of Val66Met polymorphism with the structural and functional changes in the brain. In volumetric studies Met-carriers were found to have a hippocampal volume reduction in both healthy cohorts and psychiatric patients with schizophrenia, bipolar disorder, major depression and anxiety disorders (Pezewas et al. 2004, Szeszko et al. 2005, Bueller et al. 2006, Frodl et al. 2007, Chepenik et al. 2009, Mueller et al. 2013). These observations were confirmed in three meta-analytic reviews (Hajek et al. 2012, Kambeitz et al. 2012, Molendijk et al. 2012). However, the most recent meta-analyses showed no association between Val66Met polymorphism and hippocampal volumes neither in healthy subjects nor clinical groups (Harrisberger et al. 2014, 2015). The authors suggest that inconsistency of the results may be related to measuring techniques and sample sizes.

BDNF-dependent differences in structure of different cortical regions were also investigated. Healthy Met-carriers were found to have bilateral reductions of gray matter volumes in frontal lobes, predominately dorsolateral prefrontal cortex (Pezawas et al. 2004). It was confirmed by Nemoto and others (2006) in healthy subjects of the Japanese population who demonstrated a significant reduction in volume in the dorsolateral prefrontal cortex (DLPFC), moreover in anterior cingulate cortex (ACC), temporal lobe and parietal cortex correlated with age. These changes were greater in participants with the Met allele, mainly in women. Also, in the study of Matsuo a and colleagues (2009) the reduced volume of dorsolateral prefrontal cortex and anterior cingulate in Val/Met bipolar patients compared with Val/Val patients and healthy subjects was detected. In addition, Ho and others (2006) in a group of healthy American subjects and in patients with psychotic symptoms, showed the Met allele association with a lower volume of gray matter in the temporal and occipital lobes, while in Yang and colleagues (2012) study Met healthy adults homozygotes of Chinese population had smaller volumes of frontal, temporal, cingulate and insular cortices. Moreover, Montag and others (2009) found an association between the Met allele and smaller parahippocampal volumes, right amygdala, thalamus, fusiformus gyrus and several parts of the frontal gyrus in the group of healthy Caucasians. In his later study, he also revealed an epistasis effect of BDNF and DRD2 genes on gray matter volume of ACC. Participants with at least one Met allele of the BDNF and one A1 allele of the DRD2 were observed to have lowest gray matter volume of the ACC (Montag et al. 2010).

Functional neuroimaging studies have also addressed the *BDNF* association with the level of brain activation during cognitive performance. Most of the study investigated the hippocampus-related cognitive functions of memory and learning. The Met allele in heterozygous system was associated with abnormalities of the hippocampal and prefrontal activation in the course of neuropsychological testing (Bath and Lee 2006). In studies of Egan and colleagues (2003) Met allele carriers had a weaker hippocampal activation associated with poorer episodic memory compared to those with Val/Val genotype. Hariri and others (2003) when studying declarative memory in healthy adults observed the better performance and increased activation of the posterior hippocampal formation during encoding and retrieval of information in subjects with the Val allele. The study of Hashimoto and colleagues (2008) showed no effect of the Val66Met polymorphism on episodic memory in healthy Japanese subjects, but they observed the association of the Met allele with the decreased activity of the bilateral hippocampi and right parahippocampal gyrus. Moreover, van Wingen and others (2010) using face recognition task demonstrated sex-specific *BDNF* genotype effect on the amygdala activation during encoding, and on the prefrontal cortex and posterior cingulate cortex activity during memory retrieval. A larger contribution of these brain regions to the effective memory performance was observed in males with the Met allele compared to Val homozygotes, while there were no differences in females. The fMRI studies comparing the effect of Val66Met polymorphism on working memory in healthy subjects and patients with multiple sclerosis indicate the Met allele association with increased activation in the parieto-prefrontal network with simultaneous deactivation of the cortico-limbic regions. These results were obtained only in healthy subjects (Cerasa et al. 2010).

The results of previous research have also reported associations of Val66Met polymorphism with cognitive performance. Polish studies compared the results of Wisconsin Card Sorting Test, a task that is used as a standard diagnostic tool of executive functions (such as planning and set shifting) in bipolar patients with Val/Val and Val/Met genotypes. They revealed the significantly worse results in all test parameters in the group of patients with methionine allele (Rybakowski et al. 2003). In the other study of Rybakowski and colleagues (2006) Val homozygotes with schizophrenia have shown better performance on the N-back test, a task that measures attention and working memory. This relation was not observed in patients with bipolar disorder. The research of Gong and others (2009) on a large group of healthy Chinese young adults showed a better working memory for digits and spatial localization in people with Val/Val genotype. Similar results were obtained in the Caucasian population where Val homozygotes showed better associative memory and higher processing speed, with a

greater effect occurring in women (Raz et al. 2009). Met allele relationship with decreased efficacy of episodic memory in healthy subjects was also confirmed by study of Dempster and colleagues (2005). In addition, Goldberg and others (2008) and Montag and others (2014) found healthy Met-carriers compared to Val homozygotes presented bigger decline in recognition of previously learned verbal material after 24-hour and one-week delay, respectively. Moreover, Ho and colleagues (2006) found poorer verbal memory both in Met healthy volunteers and psychotic patients. The patients exhibited also visuospatial impairment. Similarly, in Zhang and others (2012) study, schizophrenic subjects and healthy controls with Met variant performed worse on visuospatial-constructional task. In addition, schizophrenic patients showed attention deficits. Furthermore, Val66Met polymorphism was also associated with intelligence. The Met carriers obtained significantly lower scores on tests of general intelligence, both in young Chinese female population (Tsai et al. 2004), as well as in older Caucasian adults (Miyajima et al. 2008). However, some of the studies have revealed a protective role of Met allele against neurocognitive deterioration in certain diseases (Oroszi et al. 2006) and in older age (Harris et al. 2006, Brooks et al. 2014).

Much lesser is known about the effect of other *BDNF* polymorphisms on brain structure and cognition in humans. Cathomas and others (2010) conducted the analysis of 55 single nucleotide polymorphisms (SNPs) with memory tested on the basis of reproduction of verbal material using neutral and emotional words. The results have not only confirmed the association of Val66 allele with better memory performance, but also reported that rs7127239, rs7125904, rs10835190 and rs10835218 reached the minimum level of statistical significance, which may constitute a prerequisite for their participation in memory processes. In turn, Laing and colleagues (2012) assessed the relationship of cognitive functions: psychomotor speed, attention and memory with rs6265, rs7103411 and rs7124442 polymorphisms. The results showed the relationship between rs7103411 polymorphism and memory. Moreover, gender-specific analyzes revealed the relationship of rs7103411 and rs6265 polymorphisms with psychomotor speed and memory in women.

Some publications have not found any associations between polymorphisms of *BDNF* gene and cognition. Hansell and others (2007) in a large cohort of healthy adolescents have found no relation between Va166Met polymorphism relation and memory, while Tsai and colleagues (2008) in the group of participants in late adulthood did not observed any relationship between this polymorphism in the normal process of aging and its associated attenuation of cognitive function. Meta-analysis of 23 studies on the relationship of Val66Met polymorphism with cognition showed no significant association with general cognitive ability, memory, executive function, visual processing and cognitive fluency (Mandelman and Grigorenko 2012). However, the authors suggest that further studies on larger, ethnically and age homogenous populations, including greater amount of BDNF gene polymorphisms, analysis of the haplotypes or its interactions with other genes should be carried out.

Therefore, the main goal of the present study was to verify the relationship between twelve *BDNF* gene polymorphisms and their haplotype and the results of neuropsychological tests connected to large extent with the activity of prefrontal cortex in 460 healthy subjects of Polish population.

METHODS

Participants

The study included 460 healthy volunteers (227 males and 233 females) aged 18–60 (*M*=36.18; *SD*=12.13) without history of any psychiatric disorder, substance abuse or serious somatic illnesses. All participants were Caucasians of Polish origin. We provided the written informed consent. Bioethics Committee of Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń approved the study.

Neuropsychological assessment

We assessed the neuropsychological performance using standard tests:

1) Wisconsin Card Sorting Test® Computer Version 4 (WCST:CV4™)-Research Edition (Heaton et al. 1993, http://www4.parinc.com). This is a widely used task to assess working memory, attention, conceptual thinking and executive functions of planning and set-shifting. In this test on the computer screen four exemplary card are presented. Based on a received feedback, the participant is asked to sort up to 128 cards appearing on the bottom of the computer screen in accordance with applicable, changing criteria.

The following parameters were assessed in the test: a) the percentage of perseverative errors (%P) – connected with inability to change previous set of reaction; b) the percentage of non-perseverative errors (%NP) – connected with attention inability to avoid distraction; c) the percentage of conceptual level response (%CONC) – connected with ability to utilize new information and previous experience to plan a conceptual reaction; d) the number of correctly completed categories (CC) – a measure of effectiveness of cognitive processes involved in the task; e) the number of cards to complete first category (1stCAT) – connected with an efficacy/speed of formulating logical conception.

2) Trail Making Test, TMT (Reitan 1955). The test consists of two parts, known as TMT_A and TMT_B. Both of them consist of 25 circles distributed over a sheet of paper. TMT_A task is to draw the lines to connect the numbers (from 1 to 25) in ascending order, in the shortest time possible. TMT_ B task is to connect the circles, but alternating between the numbers (from 1 to 13) and letters (from A to L), as quickly as possible, keeping the ascending order of numbers and letters. TMT_A requires visuoperceptual abilities and attentional search of visual field, whereas TMT_B reflects working memory, sustained and divided attention, and task-switching ability, while TMT B-A indicator by minimizing visuoperceptual and working memory demands, provides a good measure of executive control abilities and cognitive plasticity (Sanchez-Cubillo et al. 2009, Łojek and Stańczak, 2012). The time of performance on TMT_A is also a good measure of psychomotor speed. Neuroimaging data indicated that the performance on the TMT involves prefrontal areas of the brain, particularly the dorsolateral ones (Shibuya-Tayoshi et al. 2007, Kubo et al. 2008).

The following parameters were assessed in the test: a) the time of performance on A (TMT_A) and B parts (TMT_B) in seconds; b) the time difference between performance on both parts of the test (TMT_B-A) in seconds.

3) Stroop Color-Word Interference Test (Stroop 1935). It consists of two parts. In the first part (RCNb – Reading Color Names in Black) 50 words printed in black, meaning the names of seven colors (green, red, blue, pink, yellow, brown, black) are presented to the participant. The task is to read loud all the words, as quickly as possible. In the second part (NCWD – Naming Color of Word – different) the printout of same 50 names of 7 colors, printed in 4 different colors is presented to the subject. The names of colors do not correspond with the color of the print (e.g. the word "red" is printed in green). The task is to name the color of the print without reading what is written. RCNb part assesses the speed of reading – a measure of psychomotor speed and NCWd (Naming Color of Words – different) evaluates vigilance, selectivity of attention and executive control including the cognitive inhibition and monitoring of the performance, resistance to interference, as well as cognitive flexibility (Strauss et al. 2006, Badgaiyan and Posner 1998, Lezak et al. 2012). Neuroimaging results found the activation of the prefrontal cortex, cingulate cortex and other brain structures, including basal ganglia and cerebellum during the test performance (Badzakova-Trajkov et al. 2009, Tomaszewska et al. 2010).

The following parameters were assessed in the test: a) the time of performance of RCNb part (Stroop_I) and NCWd part (Stroop_II) in seconds – measures of psychomotor speed and attention; b) the time difference between performance on both parts of the test (Stroop_II-I) – linked with executive functions.

Genotyping

Genomic DNA was extracted from 10 ml of ethylene-diaminetraacetic (EDTA) acid-anticoagulated venous blood using the salting out method (Miller et al. 1988). Twelve SNPs have been genotyped in the BDNF gene based on Real-Time PCR 7900HT Fast System with molecular TaqMan probes The description of analyzed polymorphisms is given in Table I. Real-Time PCR System allows performing

Table I. Description of analyzed polymorphisms

SNP ID	chromosomal positon	MAF	Alleles	HWE	TaqMan assay ID	function
rs6265/Val66Met	27636492	0.17	G:A	0.75	C__11592758_10	exon
rs11030101	27637320	0.23	A:T	0.19	C___1751785_10	5'UTR
rs11030102	27638172	0.29	C:G	0.57	C__31701068_10	intron
rs1401635	27650567	0.37	C:G	0.02	C___8744367_10	intron
rs2049045	27650817	0.18	G:C	0.87	C__12035465_10	intron
rs10835210	27652486	0.36	C:A	0.11	C___1751795_10	intron
rs1013402	27668957	0.35	T:C	0.02	C___7468814_10	intron
rs2049046	27680351	0.40	A:T	0.20	C__12035467_10	intron
rs988748	27681321	0.22	C:G	1.805e-05	C___1197570_10	intron
rs2030324	27683491	0.43	T:C	0.26	C__12035468_20	intron
rs2030323	27685115	0.22	G:T	0.16	C__12035469_20	intron
rs2883187	27697668	NN	C:T	0.30	C___1197561_10	5'UTR

a risk analysis with the elimination of genotyping error. In addition, 10% of randomly selected samples were subjected to re-designation with nearly 100% compatibility. We used study by Petryshen and others (2009) to select gene variants for our investigation.

Statistical analysis

The concordance of the distribution of genotypes with the Hardy-Weinberg equilibrium and linkage disequilibrium analysis was done using Haploview v.4.0 program (Barrett et al. 2005, http://www.broadinstitute.org/). We investigated possible relationship between haplotypes and neuropsychological tests performance in PLINK (Purcell et al. 2007, http://pngu.mgh.harvard.edu/purcell/plink/). To determine haplotype blocks we used PLINK option: "plink --file mydat --blocks --out mydat --blocks". To evaluate haplotype frequencies we used the following command: "plink --file mydat --hap bdnf-blocks.blocks --hap-freq --out mydat" (Table II). To run association analyzes we used:

"plink --file mydat --pheno cog-pheno.txt --pheno-name TMT_A --hap TMT_A.blocks --hap-linear --mperm 10000 --out TMT_A". We investigated haplotype blocks for all phenotypes separately and then for the whole sample, as we got same results for all of them.

Table II. Haplotype frequencies

Locus	Haplotype	F
H1	TACGCCATAAG	0.176
H1	CTCGGAAAGCA	0.495
H1	CACGGCATAAG	0.029
H1	CACCGCGTACG	0.058
H1	CTCGGCAAGCA	0.022
H1	CAGCGCGTACG	0.189

Additionally, we explored how each single polymorphism influenced each cognitive outcome with generalized linear models (GLM) corrected for demographic covariates (i.e., age, sex and years of education), in (Statistica 10.0). In case of significant main effect for a given polymorphism, ANCOVA was complemented by contrast analysis for groups with different genotypes.

We are aware that the problem connected with the multivariate analysis is an issue of multiple comparisons. In case of correlated phenotypes (e.g. cognitive performance measurements) the principal component analysis (PCA) may be conducted. However, the neuropsychological tests usually measure more than one aspect of cognitive functions. While using PCA we may lose detailed insight into specific test parameters, even if they are correlated. Moreover these parameters are often expressed in different values (i.e. percentage of errors, number of correct responses, reaction time). Taking those into account we decided not to conduct the PCA in our work.

RESULTS

HWE analysis

Genotype distribution for nine polymorphisms was in concordance with the Hardy-Weinberg equilibrium. Due to the deviation from HWE (p>0,05) three polymorphisms (rs1401635, rs1013402, rs988748) were excluded from further SNP analysis.

In case of haplotypes analysis, HWE value was set as p>0,0000001 (Anderson et al. 2010). Therefore only polymorphism rs988748 was excluded from further analysis.

Polymorphisms and results of neuropsychological tests

Based on the obtained results, it can be concluded that among the considered measures of cognitive functions, only TMT A time performance was related to the *BDNF* polymorphisms included in the study, as follows (Table III):

1) Polymorphism rs11030101: $F_{2,437}$=4.157, P=0.016, η^2p=0.019.
   The performance time of TT homozygotes was significantly longer compared to TA and AA genotypes ($F_{1,437}$ =8.014, P<0.005).
   Age: $F_{1,437}$ =110.152, P<0.001, η^2p=0.201.
   Education: $F_{1,437}$=2.250, P=0.134, η^2p=0.005.
2) Polymorphism rs10835210: $F_{2,438}$=4.546, P=0.011, η^2p=0.020.
   The performance time of AA homozygotes need was significantly longer compared to AC and CC genotypes ($F_{1,438}$=8.855, P<0.003).
   Age: $F_{1,438}$ =109.565, P<0.001, η^2p=0.200.
   Education: $F_{1,438}$=2.141, P=0.144, η^2p=0.005.
3) Polymorphism rs2049046: $F_{2,437}$=3.784, P=0.023, η^2p=0.017.
   The performance time of AA homozygotes was longer compared to AT and TT genotypes ($F_{1,437}$=7.295, P<0.007).
   Age: $F_{1,437}$=111.422, P<0.001, η^2p=0.203.
   Education: $F_{1,437}$=1.917, P=0.167, η^2p=0.004.

Table III. Results of TMT_A (in seconds) in groups with different genotypes

Polymorphism	Genotype		
rs11030101	TT	TA	AA
M (SD)	24.41 (9.00)	21.99 (7.10)	22.38 (7.75)
M adjusted	24.38	22.24	22.14
N	113	236	96
rs10835210	AA	AC	CC
M (SD)	24.68 (9.27)	21.93 (7.01)	22.50 (7.73)
M adjusted	24.61	22.28	22.18
N	101	242	103
rs2049046	AA	AT	TT
M (SD)	24.39 (8.88)	21.97 (7.21)	22.46 (7.50)
M adjusted	24.32	22.30	22.18
N	116	236	93
rs2030324	GG	GA	AA
M (SD)	24.40 (8.90)	21.87 (7.14)	22.59 (7.57)
M adjusted	24.36	22.22	22.31
N	121	233	91
rs2883187	AA	AG	GG
M (SD)	24.36 (8.94)	21.87 (7.14)	22.55 (7.54)
M adjusted	24.36	22.21	22.25
N	121	233	92

4) Polymorphism rs2030324: $F_{2,437}$=4.133, P=0.017, η^2p=0.019.
   The performance time of GG homozygotes was significantly longer compared to GA and AA genotypes ($F_{1,437}$=7.616, P<0.006).
   Age: $F_{1,437}$=107.968, P<0.001, η^2p=0.198.
   Education: $F_{1,437}$=2.024, P=0.155, η^2p=0.005.
5) Polymorphism rs2883187: $F_{2,438}$=4.183, P=0.016, η^2p=0.019.
   The performance time of AA homozygotes was significantly longer compared to AG and GG genotypes ($F_{1,438}$=7.816, P<0.005).
   Age: $F_{1,438}$=109.143, P<0.001, η^2p=0.199.
   Education: $F_{1,438}$=2.066, P=0.151, η^2p=0.005.

The performance on TMT_A was to a greater extent explained by age than polymorphisms. The size effect, as measured by the coefficient of the partial eta square of age variable was large in all cases, while effect for polymorphisms was small. Years of education have not explained a statistically significant results in TMT_A. In our study the relation between BDNF polymorphisms and TMT_A performance was neither modified by gender.

Haplotypes and results of neuropsychological tests

The analysis revealed one block of haplotype. Strong linkage disequilibrium was observed between 11 studied polymorphisms (Fig. 1).

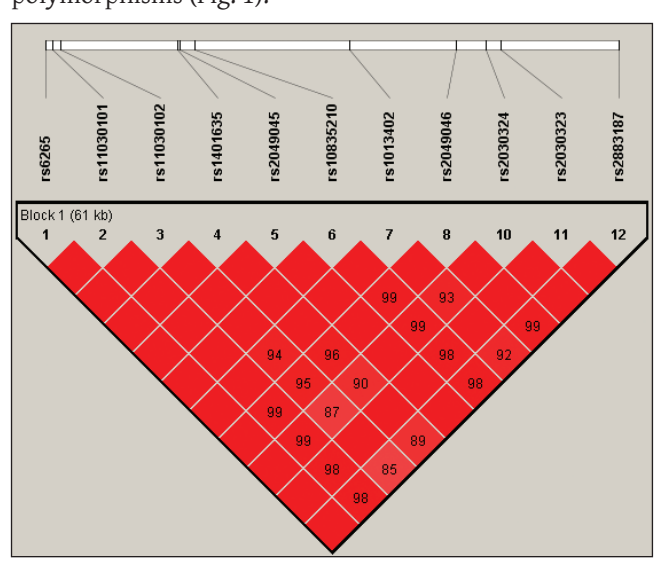

Fig. 1. Relative positions and LD estimates between polymorphisms. Colored squares correspond to D'values with numerical estimates given within squares.

We found the association of haplotypes: CTCGGAAAGCA with a longer time of performance on TMT_A (F=0.495, B=1.12, t=4.26, P=0.034) and CACCGCGTACG with a shorter time of performance on TMT_B (F=0.058, B=–5.74, t=4.42, P=0.036). No association with other cognitive measures was observed.

DISCUSSION

Previous research on relations between the BDNF gene polymorphisms and cognition focus primarily on hippocampus-dependent cognitive domains, mainly on long-term memory and learning (Kambeitz et al. 2012). However, the influence of *BDNF* on brain structure and function was also observed in different cortical regions (Pezewas et al. 2004, Matsuo et al. 2009, Yang et al. 2012). In our study we concentrated on the relation between *BDNF* polymorphisms and haplotypes with neuropsychological measures engaging predominantly prefrontal cortex, an area associated with higher cognitive functions, such as working memory, executive attention, planning, set-shifting (Bath and Lee 2006).

The analysis of the associations between nine *BDNF* polymorphisms and the results of well-known neuropsychological tests (WCST, TMT and Stroop test) showed significant relationship between five of them and the performance on TMT_A. This task to the greatest extent is assessing psychomotor speed of attentional search of visual field. Psychomotor speed has been related to velocity of nerve conduction, speed of information processing and data retrieval from memory (Jensen 1993). It influence the efficacy of most cognitive domains (Lezak et al 2012). The *BDNF* polymorphisms were found to be related to psychomotor or processing speed in previous studies (Miyajima et al. 2008, Cathomas et al. 2010, Laing et al. 2012). In our study better results were recorded in homozygotes for the alleles with a higher frequency in the population for all five polymorphisms (rs11030101, rs10835210, rs2049046, rs2030324, rs2883187). Similarly, most of the studies of Val66Met found homozygotic Val/Val variant to be more beneficial for cognitive functioning in different cohorts (Egan et al. 2003, Rybakowski et al. 2006, Gong et al. 2009), except for elderly (Harris et al. 2006, Brooks et al. 2014) who however were not included in this study.

Given that the examination of single polymorphism may result in overlooking some information, the analysis of haplotype was suggested to improve genotyping efficiency and assessment of gene effect on specific function (Hong et al. 2011). In our study, we identified one block of haplotype and revealed the association of CTCGGAAAGCA haplotype with better results of TMT_A, confirming the impact of *BDNF* gene on psychomotor speed. In addition, it showed the relation of CACCGCGTACG haplotype with a worse performance on TMT_B. In previous study, better performance on TMT_B test was found to be associated with *BDNF* Met66 allele and connected with larger left cerebellum, right precuneus, left superior frontal gyrus and bilateral hippocampal volumes, while worse results on TMT were connected with larger brainstem and bilateral posterior cingulate cortex volumes in older adults (Brooks et al. 2014).

TMT_B is considered as a tool to measure working memory and executive performance such as set-shifting, inhibition and cognitive flexibility (Marqués-Iturria et al. 2014). However we found no association between BDNF polymorphisms and haplotypes and other neuropsychological tests, i.e. WCST and Stroop, used to measure these cognitive domains. It is in line with the studies of Oral and others (2012) and Han and colleagues (2015), who also applied several tasks to measure executive functioning and similarly to us found association of BDNF serum level only with TMT_B. Our hypothesis is that it may be connected with the specificity of the task which applies psychomotor speed and visuo-perceptual abilities (Sanchez-Cubillo et al. 2009) It may be assumed that BDNF is related to executive performance through those cognitive abilities.

Some research found BDNF genetic effect on cognition to be gender-specific (Matsuo et al. 2009, Raz et al. 2009, van Wingen et al. 2010, Laing et al. 2012). In our study the relation between BDNF polymorphisms and TMT_A performance was not modified by gender. It also needs to be noticed that size effect of polymorphisms on TMT_A performance was much smaller than the effect of age. In contrast to several studies (Hong et al. 2011, Kambeitz et al. 2012), the functional polymorphism Val66Met was found to have no relation with cognitive functions measured in our study. The number of inconsistent reports within the literature assessing the effects of the Val66Met polymorphism in both healthy and clinical samples emphasizes that phenotypic associations can be subtle and are susceptible to nuisance variance and noise. Additionally, differences in allelic frequency between populations, suggests ethnicity-specific effect of this variant (Notaras et al. 2015). The genetic influence on cognition may be also less pronounced in healthy subjects even in Caucasian populations which was shown to be more susceptible to the effect of the *BDNF*, whereas in clinical groups and in older subjects genotype may be an important factor mediating the ability of effective cognitive compensation.

CONCLUSIONS

In general, the results of our study has revealed the associations between *BDNF* polymorphisms and haplotypes with the results of TMT, a task considered to be connected with prefrontal cortex activity. However, we found no relations between *BDNF* and other neuropsychological tests engaging prefrontal area of the brain. We assumed that it

may be related to the visuo-motor specificity of the TMT. Our study confirms also the value of continued research employing neuropsychological assessment to enhance the knowledge of molecular mechanisms associated with cognition.

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