ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Research paper Acta Neurobiol Exp 2010, 70: 86–94

Influence of dopaminergic and serotoninergic genes on working memory in healthy subjects

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Working memory is an ability to keep information in short-term memory and manipulate them "on line". Working memory is also involved in complex frontal executive functions. The role of dopaminergic system in modulating working memory processes in prefrontal cortex is well established. Also the role of serotoninergic receptors is postulated. The purpose of this study was to assess the association between the polymorphisms of dopaminergic (DRD1, DRD3, DRD4, COMT) and serotoninergic (SERT – serotonin transporter, 5HT2A, 5HT2C) genes' polymorphisms and performance on WCST in 200 volunteers from the Polish population. We found the association between DRD1, DRD4, COMT and SERT genes polymorphisms and the performance on WCST. The results obtained in the study indicate that dopaminergic and serotoninergic genes may play a role in modulating the executive function and working memory processes in healthy subjects. The pattern of this influence may be different in males and females. Moreover, the relationship between the efficacy of prefrontal cognitive function and genes polymorphisms may differ between healthy subjects and schizophrenic patients.

Key words: Wisconsin Card Sorting Test, dopaminergic and serotoninergic genes, working memory, healthy subjects

INTRODUCTION

Working memory is an ability to keep information in short-term memory and manipulate them "on line". Working memory is also involved in complex frontal executive functions (Baddeley 2000, D'Esposito et al. 2000, Fletcher and Henson 2001). Working memory deficit in schizophrenic and bipolar patients, as well as in their first-degree relatives indicates the genetic mechanism underlying its function. Currently it is proposed as a cognitive endophenotypic marker of vulnerability to these illnesses (Borkowska and Rybakowski 2001, Everett et al. 2001, Gottesman and Gould 2003, Glahn et al. 2004, Zalla et al. 2004, McIntosh et al. 2005).

The role of dopaminergic system in modulating working memory processes in prefrontal cortex is well established (Seamans and Yang 2004). Many studies demonstrated the significance of activity of D1 dopamine receptors in determining the efficacy of the "on-line" processes, whereas interaction of D1 and D2 receptors influences the overall efficacy of working memory (Goldman-Rakic 2000, Goldman-Rakic et al. 2004). The association between the polymorphism of DRD1 receptor gene and the performance on Wisconsin Card Sorting Test (WCST) in schizophrenic patients was demonstrated (Rybakowski et al. 2005). Laszy and coauthors (2005) postulated the role of D3 dopamine receptors in the processes of memory and learning. Szekeres and colleagues (2004) found the correlation between the results on WCST and the polymorphism of DRD3 gene. The experimental study on the dopamine receptor D4 antagonists has demonstrated their beneficial influence on

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Received 08 June 2009, accepted 26 February 2010

working memory (Zhang et al. 2004). Also the interaction of DRD4 and NMDA in the prefrontal cortex may play a significant role in determining cognitive efficiency by modulating synaptic plasticity (Wang et al. 2003).

It has been shown that the correlation between the amount of dopamine in the prefrontal cortex and cognitive performance can be represented as an inverted U, which means that overflow as well as deficiency of dopamine may have a negative impact on cognitive functions, particularly on working memory (Arnsten and Li 2005). One of the most studied factors that modulate the dopamine levels in prefrontal cortex is catechol-O-methyltransferase (COMT). The Met variant of this enzyme shows a 3–4 times lower activity leading to the increased dopamine level (Lachman et al. 1996, Chen et al. 2004). Numerous studies investigated the influence of COMT on prefrontal function measured by WCST (Egan et al. 2001, Malhotra et al. 2002, Rosa et al. 2004, Bruder et al. 2005, Rybakowski et al. 2005, 2006, Barnett et al. 2007a). Sambataro and coworkers (2009) demonstrated that the effect of Val108(158)Met polymorphism on activity and functional connectivity of brain regions involved in working memory network increases with age**.** There is also an evidence for a sexually dimorphic influence of COMT (Sazci et al. 2004, Harrison and Turnbridge 2008).The other polymorphisms of COMT are also postulated to have an influence on prefrontal cognitive functions (Meyer-Lindenberg et al. 2006, Diaz-Asper et al. 2008), as well as interaction between COMT and DRD4 (Alfimova et al. 2007) or DRD2 polymorphisms (Xu et al. 2007).

The role of the serotonin system in the evolution of human cognitive capacities was supported by changes in the supply of this neurotransmitter to the frontal cortex (Raghanti et al. 2008). The serotonin transporter (SERT) plays an essential role in serotonergic neurotransmission as it determines the quality and duration of the serotonin signal in the synaptic cleft. The 5HT receptors play also an important role in brain development and memory processes (Meneses et al. 1997, Menses 1999, van Kesteren and Spencer 2003) and may be a target for cognitive enhancement (Roth 2004). It was demonstrated that memory performance may be correlated with SERT density in the dorsolateral prefrontal cortex, orbitofrontal cortex, and parietal cortex which are implicated in memory function. (McCann et al. 2008). The 5HT function also modulates dopaminergic activity (Nocjar 2002). Regulatory role of serotonin-dopamine interactions in cognition and the prefrontal

Table I

Results of WCST in relation to –48A/G polymorphism of DRD1 gene (X ± SD)

DRD1 genotype	Total		
WCST	A/A	A/G	G/G
%P	7.69 ± 2.4	8.36 ± 3.4	8.26 ± 2.6
%NP	8.26 ± 4.2	7.52 ± 4.0	7.67 ± 3.3
%CONC	81.52 ± 7.8	81.52 ± 7.9	81.23 ± 6.5
CC	6.00 ± 0.0	6.00 ± 0.2	6.00 ± 0.1
1stCAT	13.78 ± 6.2	13.87 ± 6.5	13.26 ± 5.0
	Females		
WCST	A/A	A/G	G/G
%P	8.00 ± 2.9	8.34 ± 3.3	8.30 ± 2.7
%NP	9.77 ± 4.7	7.84 ± 4.2	7.83 ± 4.2
%CONC	78.69 ± 8.5	81.48 ± 7.1	80.43 ± 8.0
CC	6.00 ± 0.0	5.96 ± 0.2	6.00 ± 0.0
1stCAT	16.00 ± 7.6*	14.11 ± 6.4	12.33 ± 4.1
	Males		
WCST	A/A	A/G	G/G
%P	7.30 ± 1.6	8.39 ± 3.4	8.22 ± 2.5
%NP	6.30 ± 2.4*	7.13 ± 3.7	7.53 ± 2.3
%CONC	85.21 ± 4.9*	81.57 ± 8.8	81.89 ± 4.9
CC	6.00 ± 0.0	5.96 ± 0.3	5.97 ± 0.2
1stCAT	10.9 ± 0.6**	13.59 ± 6.6$^{\#}$	13.97 ± 5.6

*Difference A/A vs. A/G $P<0.05$; **A/A vs. A/G $P<0.01$; $^{\#}$ A/G vs. G/G

Table II

Results of WCST in relation to polymorphism –521C/T of DRD4 gene (X ± SD)

DRD4 genotype	Total		
WCST	C/C	C/T	T/T
%P	7.50 ± 2.7	8.58 ± 3.1	8.25 ± 2.9
%NP	6.92 ± 2.9	8.04 ± 4.1	7.28 ± 3.6
%CONC	83.02 ± 6.0	80.45 ± 7.7	82.22 ± 7.2
CC	6.00 ± 0.0	5.95 ± 0.3	5.99 ± 0.1
1stCAT	13.08 ± 5.3	13.7 ± 5.9	13.74 ± 6.1
	Females		
WCST	C/C	C/T	T/T
%P	7.48 ± 3.3	8.58 ± 3.3	8.47 ± 2.7
%NP	7.67 ± 3.3	9.00 ± 4.7	6.75 ± 3.9#
%CONC	81.52 ± 6.5	79.7 ± 8.17	82.39 ± 6.9
CC	6.00 ± 0.0	5.98 ± 0.2	5.97 ± 0.2
1stCAT	12.91 ± 5.5	14.33 ± 6.1	13.42 ± 5.8
	Males		
WCST	C/C	C/T	T/T
%P	7.53 ± 2.0	8.59 ± 3.1	8 ± 3.2
%NP	6.00 ± 2.1*	7.16 ± 3.3	7.88 ± 3.1
%CONC	84.88 ± 5.0	81.14 ± 7.3	82.03 ± 7.7
CC	6.00 ± 0.0	5.93 ± 0.3	6.00 ± 0.0
1stCAT	13.3 ± 5.4	13.2 ± 5.7	14.1 ± 6.5

*Difference C/C vs. T/T $P<0.05$; #T/T vs. C/T $P<0.05$

cortex and the striatum as a neuroanatomical substrate for these interactions, are postulated. Experimental data revealed that disruption of serotonin neurotransmission results in a facilitative effect on the processing of mnemonic information by refrontal cortex and the striatum which are under strong, functional DA modulation, while increased serotonin neurotransmission has a detrimental effect on cognitive functions connected with these brain structures (Olvera-Cortés et al. 2008) Neuroanatomical findings in schizophrenic patients revealed an altered 5HT2A serotoninergic receptors distribution in prefrontal cortex (Dean 1996, Dean and Hayes 1996). Üçok and colleagues (2007) found a correlation between the results of WCST and polymorphism of 5HT2A receptors' gene.

Relatively few studies examined the relationship between polymorphisms of dopaminergic and serotoninergic receptors' genes and prefrontal cognitive functions in healthy subjects.

The purpose of this study was to assess the association between the polymorphisms of dopamine and serotonin systems' genes and working memory in healthy subjects. The association between dopaminergic (DRD1, DRD3, DRD4, COMT) and serotoninergic (SERT – serotonin transporter, 5HT2A, 5HT2C) genes' polymorphisms and performance on WCST in the Polish population was assessed.

METHODS

Subjects

The study included 200 healthy volunteers (100 males and 100 females) aged 18–60 (mean 34.4 + 11.7) years with no history of any psychiatric disorder, substance abuse or serious somatic illnesses. All subjects were assessed using the Polish version of M.I.N.I Plus scale (Lecrubier et al. 1997) for excluding presence of any serious mental health problems. The Bioethics Committee of Nicolaus Copernicus University Torun, Collegium Medicum in Bydgoszcz, approved the study. Informed consent was received from all participants after the aim and procedure of the study were fully explained to them. All subjects were Caucasians of Polish origin.

Neuropsychological assessment

Working memory evaluation was made using the Heaton and coauthors (1993) computerized version of

WCST. The following domains of WCST were measured: (1) the percentage of perseverative errors (%P) – connected with inability to change reaction due to ignorance of relevant stimuli; (2) the percentage of non-perseverative errors (%NP) – connected with attention inability to avoid distraction; (3) the percentage of conceptual level response (%CONC) – connected with ability to utilize new information and previous experience to create conception; (4) the number of correctly completed categories (CC) – connected with effectiveness of measured cognitive function; (5) the set to complete first category (1stCAT) – connected with speed of formulating logical conception.

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). The polymorphisms of interest were amplified by PCR-RLFP method.

The following polymorphisms were determined using cited methods: -48 A/G of DRD1 (Cichon et al. 1994), Ser9Gly of DRD3 (Lannfelt et al. 1992), -521C/T of DRD4 (Jönsson et al. 2001), Val108(158)Met of COMT (Li et al. 1996), ins/del of SERT (Stoltenberg et al. 2002), T102C of 5HTR2A (Du et al. 2000), C68G (Cys23Ser) of 5HT2C (Lappalainen et al. 1995).

Statistics

For statistical evaluation The Shapiro-Wilk test was used to evaluate the normality of the variables' distribution. In case of normal distribution one-way ANOVA was applied. Otherwise non-parametric tests of Friedman ANOVA and U Mann-Whitney were used. All statistical analyses were performed using Statistica 7.0 package (STATSOFT, Poland). The concordance of genotypes with Hardy-Weinberg equilibrium was assessed using „Utility Programs for Analysis of Genetic Linkage" (Copyright © 1988 J. Ott).

RESULTS

The analysis of -48A/G polymorphism showed that women with A/A genotype obtained significantly worse results comparing to those with G/G one in WCST-1stCAT, while males with A/A and A/G genotypes performed better in this parameter of WCST

Table III

Results of WCST in relation to polymorphism Val108(158)Met of COMT gene (X ± SD)

COMT genotype	Total		
WCST	Met/Met	Val/Met	Val/Val
%P	8.31 ± 3.1	8.1 ± 2.9	8.55 ± 3.2
%NP	7.36 ± 4.2	7.87 ± 3.7	7.36 ± 3.7
%CONC	81.95 ± 7.8	81.2 ± 7.1	81.4 ± 8.1
CC	6.00 ± 0.0	5.95 ± 0.3	6.00 ± 0.0
1stCAT	13.15 ± 4.8	13.7 ± 6.0	13.93 ± 6.6
	Females		
WCST	Met/Met	Val/Met	Val/Val
%P	8.75 ± 3.7	8.35 ± 3.0	8.13 ± 2.9
%NP	9.38 ± 4.1	7.98 ± 4.3	7.42 ± 4.5
%CONC	78.94 ± 8.0	80.62 ± 7.7	81.96 ± 7.5
CC	6.00 ± 0.0	5.97 ± 0.2	6.00 ± 0.0
1stCAT	13.50 ± 3.7	13.97 ± 6.2	13.93 ± 6.6
	Males		
WCST	Met/Met	Val/Met	Val/Val
%P	8.00 ± 2.8	7.78 ± 2.7	9.00 ± 3.5
%NP	5.96 ± 3.7	7.74 ± 2.9**	7.3 ± 2.7*
%CONC	84.04 ± 7.1	81.9 ± 6.4	80.83 ± 8.8
CC	6.00 ± 0.0	5.94 ± 0.3	6.00 ± 0.0
1stCAT	12.9 ± 5.4	13.36 ± 5.7	14.00 ± 6.6

*Difference Met/Met vs. Val/Val $P<0.05$;
**Met/Met vs. Val/Met $P<0.005$

Table IV

Results of WCST in relation to polymorphism ins/del of SERT gene (X ± SD)

SERT genotype	Total		
WCST	s/s	s/l	l/l
%P	7.95 ± 3.6	8.42 ± 3.1	8.12 ± 2.7
%NP	8.50 ± 4.8	7.35 ± 3.5	7.77 ± 3.7
%CONC	81.65 ± 7.9	81.34 ± 7.1	81.60 ± 7.3
CC	6.00 ± 0.0	5.96 ± 0.2	6.97 ± 0.2
1stCAT	12.65 ± 5.4*	12.74 ± 4.6##	15.04 ± 6.9
	Females		
WCST	s/s	s/l	l/l
%P	8.55 ± 4.3	8.55 ± 3.0	8.02 ± 2.9
%NP	10.64 ± 5.5**	6.89 ± 3.4	6.28 ± 4.3
%CONC	78.90 ± 8.1	81.68 ± 6.9	80.74 ± 8.0
CC	6.00 ± 0.0	5.98 ± 0.2	5.98 ± 0.2
1stCAT	14.00 ± 7.1	12.27 ± 3.7#	15.07 ± 6.9
	Males		
WCST	s/s	s/l	l/l
%P	7.22 ± 2.5	8.29 ± 3.2	8.26 ± 2.6
%NP	5.89 ± 1.6	7.85 ± 3.6	7.03 ± 2.6
%CONC	85.00 ± 6.5	80.98 ± 7.4	82.83 ± 6.1
CC	6.00 ± 0.0	5.95 ± 0.3	5.97 ± 0.2
1stCAT	11.00 ± 2.8*	12.24 ± 5.4	15.00 ± 7.0

*Difference s/s vs. l/l $P<0.05$; **s/s vs. l/s $P<0.05$;
s/l vs. l/l $P<0.05$; ##s/l vs. l/l $P<0.01$

compared to G/G. Moreover male homozygotes A performed better in WCST-%NP and %CONC compared to those with G/G genotype (Table I).

The analysis of -521C/T polymorphism of DRD4 demonstrated that males with T/T genotype performed worse than those with C/C one, while in females, T/T genotype was connected with better performance comparing to females with T/C genotype on WCST-%NP (Table II).

Table III shows the results the analysis of Val108(158) Met polymorphism of COMT gene. The correlation with results of WCST in this case was observed only in the male group where genotype Met/Met was connected with significantly better results in WCST-%NP than other genotypes.

The analysis of ins/del polymorphism of SERT gene showed that subjects with l/l genotype obtained worse results in WCST-1stCAT than in other genotypes (Table IV). Moreover, in females, s/s genotype was connected with worse results in WCST-%NP comparing to l/s genotype, while l/s one was related to better results in WCST-1stCAT comparing to l/l. Also in males, l/l genotype was connected with worse results in WCST-1st CAT.

We found no correlation between the polymorphisms: Ser9Gly of DRD3 gene, T102C of 5HTR2A gene, C68G (Cys23Ser) of 5HT2C gene and the results of WCST in healthy subjects.

DISCUSSION

The -48A/G polymorphism of DRD1 has been postulated to modulate transcription activity of this gene (Cichon et al. 1994). Our analysis showed different pattern of influence in males and females. The impact in the male group was more significant and observed in more domains. Women with A/A genotype obtained significantly worse results comparing to those with G/G one in WCST-1stCAT, while males with A/A and A/G genotypes performed better in this parameter of WCST compared to other genotypes. The study of this polymorphism in schizophrenia showed that G/G genotype was connected with the worst results in all domains of WCST (Rybakowski et al. 2005). Also in our study we found that G/G genotype in healthy males was connected with worse results in WCST-%NP, %CONC, 1stCAT, while female group with G/G genotype obtained better results in WCST-1stCAT compared to A/A.

We found no correlation of Ser9Gly polymorphism of DRD3 with results on WCST. DRD3 are located mostly

in limbic structures, hippocampus and hypothalamus (Levesque et al 1992) that may cause their possible larger influence on long-term memory processes than those of working memory. The serine variant of the protein shows a higher affinity for dopamine (Lundstrom and Turpin 1996). The results of previous cognitive studies were ambiguous. Szekeres and coauthors (2004) have found that schizophrenic patients with Ser/Ser genotype performed better in WCST-%P and CC comparing to Ser/Gly one, but work of Rybakowski and others (2005) did not confirm these findings.

The analysis of -521C/T polymorphism of DRD4 gene showed that allele C has a 40% higher transcription activity that allele T (Okuyama et al. 1999). In this study we found the relation between this polymorphism and the results in WCST-%NP. Similarly to the case of DRD1 gene polymorphism, the influence of DRD4 differed according to gender. Males with T/T genotype performed worse than those with C/C one, while in females, T/T genotype was connected with better performance compared to females with T/C genotype on WCST-%NP. In the Polish study, no association between WCST performance and this polymorphism in schizophrenic patients was found (Rybakowski et al. 2005).

Our study demonstrated that Met/Met genotype of Val108(158)Met polymorphism of COMT gene was connected with significantly better results in WCST-%NP compared to other genotypes, but only in males. The previous studies showed that metionine allele of COMT gene is related to better performance on WCST, especially in %P parameter (Egan et al. 2001, Malhotra et al. 2002, Rosa at al. 2004). The metaanalysis of Barnett and colleagues (2007a) have confirmed association of Met homozygotic genotype with better performance in WCST-%P in healthy subjects. They also indicated that the influence of COMT gene might be greater in populations other than Caucasian. The studies postulated the interaction between COMT activity and sex (Gogos et al. 1998). Sazci and coworkers (2004) demonstrated that the influence of Val108(158)Met polymorphism of COMT is more significant in schizophrenic women, while Barnett and others (2007b) showed that COMT genotype effect on IQ is significantly higher in boys than in girls. We found no correlation between this polymorphism and performance on WCST in healthy women. Sambataro and coauthors (2009) showed that Val/Val genotype in older subjects is connected with increased activity in dorsolateral prefrontal cortex and decreased activity in ventrolateral prefrontal cortex comparing to Met/Met genotype in younger subjects. In schizophrenia, the metionine allele was found to be related to better performance in WCST-CC in study of Bruder and colleagues (2005), while Rybakowski and coworkers (2005) observed the association of Val/Val genotype with better results in WCST-%P in male schizophrenic patients, but with worse results in WCST-%NP in females with schizophrenia. The studies of Bilder and coauthors (2002) and Stefanis and others (2004) showed no correlation between COMT gene's polymorphism and performance on WCST in schizophrenia.

The analysis of serotoninergic genes showed the correlation only in case of ins/del polymorphism of SERT. Subjects with l/l genotype obtained worse results in WCST-1stCAT than in other genotypes. Borg and colleagues (2009) have found significant association between SERT genotype and performance in the Wisconsin Card Sorting Test. Subjects with the s allele performed better compared to the l homozygotes. The study of Bosia and others (2010) showed an association between SERT polymorphism and executive functions and inversely with sustained attention. The l/l genotype was connected with better executive and poorer attention performances. We also observed a different pattern of correlation in males and females what indicates that serotonin may have a sexually dimorphic influence on cognition. In females, s/s genotype was connected with worse results in WCST-%NP comparing to l/s genotype, while l/s one was related to better results in WCST-1stCAT comparing to l/l. In males, l/l genotype was connected with worse results in WCST-1st CAT.

We found no correlation between polymorphisms: T102C of 5HT2A and Ser23Gly of 5HT2C genes and performance on WCST. It may indicate lack of influence of these polymorphisms on prefrontal cognitive function in healthy subjects.

CONCLUSIONS

The results obtained in the study indicate that dopaminergic and serotoninergic genes may play a role in modulating the executive function and working memory processes in healthy subjects. The pattern of this influence may be different in males and females. Moreover, the relationship between the efficacy of prefrontal cognitive function and genes polymorphisms in healthy subjects may differ from that reported in schizophrenic patients.

ACKNOWLEDGEMENT

The study was supported by grant no. P05B123 26 (Ministry of Science and Higher Education, Poland).

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