Polymorphisms of the SNAP-25 gene and performance on the Wisconsin Card Sorting Test in anorexia nervosa and in healthy adolescent participants.

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Summary

Aim. The synaptosomal associated protein of 25 kD (SNAP-25) gene plays an integral role in the synaptic transmission as a part of the soluble N-ethylmaleimide-sensitive fusion protein (NSF) attachment receptor (SNARE). Several studies have suggested a possible involvement of SNAP-25 in learning and memory. Also in earlier studies a possible involvement of this protein in psychiatric disorder has been shown. As neurocognitive impairment is postulated in the pathology of anorexia nervosa and considered to be a putative endophenotype according to studies we investigated the influences of different SNAP-25 polymorphisms on Wisconsin Card Sorting Test (WCST) in patients and healthy controls.
Methods. We estimated an association between three polymorphisms of SNAP-25 gene and performance on the Wisconsin Card Sorting Test, measuring prefrontal cortex functions, in 61 anorexia nervosa patients.
Results. No significant differences in WCST performance were found between patients and controls. Correlation analysis showed that in patient's group value of BMI interfered on number of perseverative errors in the Wisconsin Card Sorting Test. No significant differences in Wisconsin Card Sorting Test performance were found as to three analyzed polymorphisms (rs362552, rs8636, rs363050) on the SNAP-25 gene.
Conclusions. These data suggest that polymorphisms of snap-25 gene may be not involved in the set shifting impairment in anorexia nervosa patients and healthy controls in Polish adolescents.

Wisconsin Card Sorting Test, SNAP-25 gene, anorexia nervosa, healthy subjects

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ABBREVIATIONS: ADHD – attention deficit hyperactivity disorder, AN – anorexia nervosa, DNA – deoxyribonucleic acid, DSM-IV – Diagnostic and Statistical Manual, 4th edn., EDTA – ethylenediaminetetraacetic acid, HC – healthy controls, ICD-10 – International Classification of Disease, 10th edn, IQ – intelligence quotient, MAF – minor allele frequency, PCR – polymerase chain reaction, PFC – prefrontal cortex, SCID-I – Structured Clinical Interview for DSM-IV Axis I Disorders, SNAP-25 – the synaptosomal associated protein of 25 kD, SNARE – soluble N-ethylmaleimide-sensitive factor attachment protein receptors, WCST – Wisconsin Card Sorting Test,

INTRODUCTION

The synaptosomal associated protein of 25 kD (SNAP-25) belongs to the SNARE superfamily of membrane proteins (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) and it is one of the core proteins involved in the regulation of neurotransmitter (catecholamine) release. SNAP-25 represents a multifunctional protein involved in the control of secretion by multiple interactions with syntaxin-1 and synaptobrevin/VAMP2 [1], synaptotagmin I and various ion channels [2, 3]. SNAP-25 gene has been mapped to chromosome 20p12-p11.2, a susceptibility region for ADHD [4]. Two alternative transcript variants encoding different protein isoforms have been described for this gene and SNAP25 is differentially expressed in the mammalian brain in neocortex, hippocampus, anterior thalamic nuclei, substantia nigra, and cerebellar granular cells [5]. The association of several single nucleotide polymorphisms of this gene with ADHD, IQ and schizophrenia has been demonstrated in case-control studies [6, 7, 8, 9].

Performance on the Wisconsin Card Sorting Test (WCST) may be regarded as a neuropsychological marker of working memory efficiency, depending on the activity of prefrontal cortex PFC [10]. In several study, the AN group showed significantly impaired set-shifting in the WCST, both total errors and perseverative errors [11, 12, 13, 14, 15]. In recent years such deficits have been proposed as a cognitive endophenotype for molecular-genetic studies, as they are also present in healthy first-degree relatives of patients [16].

Snap25 expression exhibit developmentally and anatomically distinct patterns in mouse brain [17, 18]. Decreased expression of Snap25 mRNA in the in the prefrontal cortex PFC was obserwed [19]. Also some evidence showed that variations in SNAP25 gene are associated with an increased gene expression level in prefrontal cortex in human brain [20, 21].

Because SNAP-25 plays a role in neurotransmitter release and some studies implicate that alterations in SNAP-25 gene expression in PFC, thus we hypothesized that impaired performance on WCST in anorexia nervosa may show an association with SNAP-25 gene. The present study aims to investigate whether SNAP-25 gene plays a role in performance on WCST in anorexia nervosa patients in comparison with healthy controls.

SUBJECTS AND METHODS

Participants

The study was performed on 61 patients with anorexia nervosa (AN) female patients (mean age 16 years) and 49 healthy controls (HC) (women only – mean age 15 years). Groups were matched for age, ethnicity and education level. Demographic features of the group patients and healthy controls are shown in Tab. 1.

All patients were hospitalized at inpatient clinic, Department of Child and Adolescent Psychiatry, University of Medical Sciences, Poznań. Consensus diagnosis by two psychiatrists was made for each patient using Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1996). Healthy controls were recruited from volunteers in junior high school and college in Poznań. These persons were not related to the patients. Inclusion criteria for the HC group were no personal or family history of any

Table1. Demographic description of group of patients with anorexia nervosa (AN) and group of healthy control persons (HC) (means +/- S.D.)

	N	Age (years)	SD	BMI *	SD	BECK **	SD	Education (years)	SD	Age of onset (years)	SD	Duration of illness (months)	SD
AN	61	15.85	2.16	14.35	1.55	14.36	10.11	9.78	2.08	13.48	2.16	2.20	1.79
HC	49	15.32	2.16	20.54	1.95	8.93	7.95	9.98	2.16				

Statistical significant differences between group of patients and controls

*p<0.000

**p=0.027

psychiatric illness or eating disorders. Information was achieved on the basis of short interview filled out by parents. The study was approved by the Ethics Committee, University of Medical Sciences, Poznań. All patients, controls and their guardians gave informed consent, after the nature of the procedures had been fully explained to them and their parents. Exclusion criteria for both groups included: documented organic injuries of central nervous system, serious somatic disorders, as well as the use of pharmacotherapy at the time of the study which might affect on the behavior and cognitive function, and co-existing schizophrenia and bipolar disorder.

Cognitive test

The WCST is a standard test for assessing working memory and executive functions, mostly connected with PFC. The computer version of WCST designed by Heaton et al. (1993), with instructions in Polish, was used in this study [22]. As the test uses colored stimuli, all patients were screened for a possible color blindness which was not found in any of them. The following domains of WCST were measured, reflecting various aspects of cognitive functions such as: the percentage of perseverative errors (WCST-P); the percentage of nonperseverative errors (WCST-

Genotyping

In the first-step screening analysis we selected three tag SNPs (rs362552, rs8636, rs363050) of SNAP-25 gene published previously. The included polymorphisms fulfilled the following criteria: minor allele frequency (MAF) above 0.10 and genotypic correlation (ϱ) across the genotypes of maximal 0.85, to avoid redundancy. DNA was extracted from blood samples using the salting out protocol [26]. The selected polymorphisms of SNAP-25 gene were genotyped using the TaqMan single-nucleotide polymorphism (SNP) allelic discrimination method with the ABI 7900HT system. In the Real-Time PCR reaction the commercially available TaqMan Genotyping assays (Applied Biosystems, Foster City, CA) were used (Tab. 2).

Statistics

The Shapiro-Wilk test was used to evaluate the normality of the variables' distribution. Due to lack of normal distribution in our data, non-parametric tests were used: U Mann-Whitney test for comparing two groups and Kruskal-Wallis test for more than two groups. To illustrate the differences in performance of all domains of WCST between patients and healthy controls the average values were also placed. All statisti-

Table 2. Description of analyzed polymorphisms and TagMan Probe used in genotyping procedure

Gene	SNP ID	TaqMan Probe	[VIC/FAM] allele	Chromosomal position	Validation
SNAP25	rs362552	C_2488312_10	[C/T]	Ch 20: 10296217	
	rs8636	C_339355_10	[C/T]	Ch 20: 10287742	CRCh37 – (genome build 37.1)
	rs363050	C_329097_10	[A/G]	Ch 20: 10234257	

NP); the number of correctly completed categories (WCST-CC); the percentage of conceptual level responses (WCST-%conc) and the set to the first category (WCST-1st cat). These five domains of WCST have been used in our previous works on the molecular genetics of prefrontal function [23, 24].

The cognitive test was performed in anorexia patients during acute intensity of symptoms (extremely low body weight -BMI≤15, lack of menstruation and disturbed social functioning [25]) in the first week of hospitalization.

cal analyses were performed using Statistica 8.0 package (STATSOFT, Poland). The nominal level of statistical significance was determined at p< 0.05. The concordance of genotypes with Hardy-Weinberg equilibrium was assessed using "Utility Programs for Analysis of Genetic Linkage" (Copyright 1988 J.Ott).

RESULTS

The results of cognitive prefrontal test in whole group of patients with AN compared to a group of healthy control subjects are shown in Tab. 3.

Table 3. The results of the Wisconsin Card Sorting Test in group of patients with anorexia nervosa (AN) compared with a group of healthy controls

	ANO N=61	CON N=49	p
WCST-P	14.85 ± 14.68	14.00 ± 9.21	0.854
WCST-NP.	11.65 ± 6.51	13.06 ± 8.94	0.814
WCST%CONC	69.72 ± 17.08	66.55 ± 19.41	0.448
WCST-CC	5.45 ± 1.42	5.14 ± 1.58	0.101
WCST 1st CAT	20.18 ± 24.49	18.61 ± 20.61	0.837

WCST-P: the percentage of perseverative errors; WCST-NP: the percentage of nonperseverative errors; WCST-CC: the number of correctly completed categories; WCST-%conc: the percentage of conceptual level responses; WCST-1st CAT: the set to the first category.

No significant differences in Wisconsin Card Sorting Test performance were found between patients and controls. Correlation analysis showed that in patient's group value of BMI interfered with a number of perseverative errors in the WCST. Patients with low BMI made more perseverative errors (BMI 13.78+/-1.45; WCST-P 11.84+/-5.22 p=0.042, r2=0.324).

The distributions of genotypes for all SNAP-25 gene polymorphisms were in Hardy–Weinberg equilibrium (P>0.05).

The results of WCST in AN patients and HC with different SNAP-25 polymorphisms are shown in Tab. 4 – *next page*. Comparison of the results of cognitive tests within genotypes of all three SNAP-25 polymorphisms did not reveal significant differences either in the whole group of patients or in healthy controls. Also, no differences of cognitive tests were found in the group of patients and controls with genotypes of three SNAP-25 polymorphisms as to age, mean onset of illness and duration of illness (only in patients group), education level, and intensity of depression symptoms (data not presented).

DISCUSSION

Previously performed neuropsychological studies have indicated that patients with eating disorders obtained significantly worse results in cognitive performance tests than healthy controls [27]. In patients with AN, various deficits in executive functioning have been identified such as: problems with working memory [28], response inhibition [29] or set shifting ability [11, 30, 31]. Set-shifting is the ability to move back and forth between multiple tasks, operations or mental sets [32]. Several authors have suggested that the problem with set shifting may be a risk factor [33] for development of eating disorder and also maintenance factor [11]. Furthermore, set shifting deficits has been implicated as a promising endophenotype for eating disorders especially for anorexia nervosa because such deficits seems to be heritable and have been found in unaffected first degree relatives [16, 27, 29]. Moreover, difficulties set shifting have been found in current ill and recovered patients witch diagnosis AN [11, 31, 34]. Friederich and Herzog recapitulated according to neuropsychological studies addressing flexibility that an impaired cognitive set-shifting (i.e., concrete and rigid behaviors to changing rules) as well as an impaired behavioral response shifting (i.e., stereotyped or perseverative behaviors) occurs in AN patients independent of nutritional status and body weight [35]. Thus of particular importance are domains of WCST as they can indicate problems with set shifting [11]. Particularly, the perseverative errors are indicative for an impairment of set-shifting abilities while the high rate of perse and nonperseverative errors are indicative for low motivation or an impairment of abstraction, working memory, learning abilities, problem solving or poor inhibition [36-37]. Recent studies confirmed that AN patients had overall worse performance in all domain of WCST in comparison to healthy controls. Especially a higher number of both perseverative and nonperseverative errors were observed [14, 38]. Results obtained in this study do not support disturbances in executive functioning in AN patients in comparison to healthy controls.

Table 4. Results of WCST in relation to polymorphisms of SNAP25 gene in AN patients and healthy controls

	AN N=61				HC N=49			
rs362552 SNAP25	1 (GG)	2 (GA)	3 (AA)	p	1 (GG)	2 (GA)	3 (AA)	p
WCST-P	14.00 ± 13.50	12.15 ± 13.50	18.91 ± 21.39	0.213	9.75 ± 4.27	13.64 ± 10.07	13.92 ± 6.77	0.502
WCST-NP.	7.80 ± 2.28	10.78 ± 5.64	13.86 ± 7.72	0.072	19.25 ± 21.86	1196 ± 6.32	12.85 ± 8.60	0.999
WCST%CONC	74.00 ± 19.22	72.84 ± 14.20	64.17 ± 19.81	0.151	65.75 ± 30.90	67.80 ± 18.64	67.28 ± 16.67	0.873
WCST-CC	5.60 ± 0.89	5.75 ± 0.87	5.00 ± 1.97	0.231	5.00 ± 2.00	5.20 ± 1.44	5.07 ± 1.85	0.993
WCST 1st CAT	12.00 ± 1.22	14.71 ± 7.15	29.95 ± 37.44	0.197	14.50 ± 6.40	18.28 ± 17.21	21.85 ± 31.03	0.801
rs8636 SNAP25	1 (CC)	2 (CT)	3 (TT)	p	1 (CC)	2 (CT)	3 (TT)	p
WCST-P	19.18 ± 22.45	13.03 ±7.19	10.16 ± 4.16	0.509	12.58 ± 7.80	15.04 ± 11.04	17.00 ± 6.63	0.423
WCST-NP.	11.63 ± 6.75	12.22 ± 6.92	8.83 ± 3.71	0.475	13.79 ± 11.25	12.66 ± 6.58	10.75 ± 2.75	0.923
WCST%CONC	68.00 ± 20.35	69.12 ± 16.09	77.66 ± 8.86	0.440	67.41 ± 21.28	65.66 ± 19.31	66.00 ± 7.70	0.490
WCST-CC	5.36 ±1.55	5.38 ± 1.49	6.00 ± 0.00	0.513	5.16 ± 1.73	5.00 ± 1.54	5.75 ± 0.50	0.651
WCST 1st CAT	19.77 ± 25.08	22.19 ± 27.20	12.5 ± 2.88	0.640	17.16 ± 23.99	20.95 ± 18.49	15.00 ±5.41	0.126
rs363050 SNAP25	1 (AA)	2 (AG)	3 (GG)	p	1 (AA)	2 (AG)	3 (GG)	p
WCST-P	13.38 ± 8.31	15.14 ± 19.42	16.33 ± 11.55	0.960	14.47 ± 8.52	13.58 ± 10.47	13.72 ± 9.28	0.807
WCST-NP.	13.61 ± 8.93	10.48 ± 4.08	11.26 ± 6.76	0.715	14.09 ± 7.94	10.52 ± 5.16	15.00 ± 14.07	0.368
WCST%CONC	66.33 ± 21.96	73.29 ± 9.79	67.06 ± 20.96	0.899	64.47 ± 19.44	70.70 ± 15.43	64.09 ± 25.02	0.723
WCST-CC	5.16 ± 1.82	5.88 ± 0.42	5.00 ± 1.88	0.163	5.00 ±1.76	5.47 ± 1.28	4.90 ± 1.70	0.653
WCST 1st CAT	25.94 ± 34.56	16.03 ± 8.54	20.60 ± 30.16	0.875	18.66 ± 25.58	18.11 ± 10.95	19.27 ± 23.18	0.811

WCST-P: the percentage of perseverative errors; WCST-NP: the percentage of nonperseverative errors; WCST-CC: the number of correctly completed categories; WCST-%conc: the percentage of conceptual level responses; WCST-1st CAT: the set to the first category.

Our findings are in concordance to the findings of two previous research groups [39, 40], but in contrast to others [41]. It may be a result in different mean age of patients in various studies. Usually, mean age of subjects was >20 years [12, 27] and was higher in comparison to mean age of patients and controls in our research (<16 years). The myelinization process of neurons which connects prefrontal cortex with other brain structures runs around 20 years old. It may explain why results of cognitive tests in group of AN and HC were similar. The second reason may be connected with fact that individuals with broader range of set shifting difficulties had heightened depression and longer illness duration [27]. In our sample, we had mostly first hospitalized adolescent patients now then with short illness duration. It is possible that the cognitive deficits become more apparent with time as the illness progress so the neuropsychological tests are sufficiently sensitive to detect them. Roberts et al. 2007 have presented a systematic review of set shifting ability measured by six different neuropsychological tests including Wisconsin Card Sorting Test [27]. Authors pointed out that the size of the pooled effect size varied between tasks, from small (TMT B), medium (WCST and CatBat task), to large (Haptic task). The authors also pointed out that weak set shifting is an endophenotype that broadly increases the risk of many forms of psychiatric illnesses. All mentioned causes may be also reasons of lack of differences across genotypes of all three polymorphisms of SNAP-25 gene and performing of cognitive test in AN patients and HC presented in this paper.

So far, molecular-genetic studies on prefrontal cognition in psychiatric disorders especially in schizophrenia have mostly focused on dopaminergic (DA) system. In AN patience set shifting is impaired, but biochemical process is still unknown. Nakazato et al. noted that in animal model glutaminergic pathway in the prefrontal cortex play important role in set shifting ability. Authors try to determine whether glutaminergic neurotransmission is associated witch set shifting in AN. The results showed that serum glutamine concentration were significantly higher in AN patients then in HC and may be a biomarker of illness severity. However, directly association between serum glutamine concentra-

tion and changes in executive function measured by WCST was not found. Studies of genetic association between glutaminergic pathway genes and set shifting ability could be interesting. According to neurodevelopmental model of AN, Brain-derived neurotrophic factor (BDNF) gene seems to be promising candidate in studies investigating the relationship between the polymorphisms and WCST performance in AN. Several authors reported association between a polymorphism in BDNF (Val66Met; rs6265) and AN [42, 43, 44] and with changes in cognitive function [45, 46, 47]. Nakazato et al. demonstrated that serum BNDF concentrations in female patients currently ill with AN were significantly lower than in a healthy control group and also compared to women recovered from AN, however they found no evidence that serum BDNF concentrations are directly related to set-shifting difficulties as measured by the WCST. Authors pointed out that because any genetic studies was not performed, they could not establish whether serum BDNF concentrations are associated with AN-related polymorphisms in the BDNF gene and set shifting impairment [48].

In this paper, we have selected SNAP-25 gene as a novel candidate gene in psychiatric disorders which may be involved in brain neurodevelopment and synaptic plasticity [review in [9, 49]]. We also hypothesized that the synaptosomal associated protein of 25 kD (SNAP-25), as one of the core proteins involved in the regulation of neurotransmitter release, may influence on cognitive function. Furthermore, the SNAP-25 gene lies in an area of previous suggestive linkage to intelligence [50] and is highly expressed by neurons in the hippocampus [51] which plays a central role in learning and memory [52]. Moreover recent studies provided in animal model and human brain indicate changed expression of SNAP-25 in prefrontal cortex linked with set shifting ability [19, 20, 21]. In recent research Gray et al. assessed the levels of SNAP-25 in three cortical regions (BA10, 40 and 46) obtained post-mortem from subjects with bipolar disorder, schizophrenia and healthy controls. In bipolar disorder cortex (parietal; BA40), a significant increase in the expression of SNAP-25 was found [53]. In addition, the association of several single nucleotide polymorphisms of this gene has been demonstrated in psychiatric illnesses with cog-

nitive deficits. Gosso et al. showed an association of four variants of SNAP-25 gene (rs363043, rs353016, rs363039 and rs363050) with variation in IQ phenotypes across two Dutch cohorts of 371 children and 391 adults [7, 54]. The association of ADHD has been demonstrated with different polymorphisms of SNAP-25 in different populations [review in [55]]. Genotype at rs363039 of SNAP-25 was associated to working memory capacity and with measures of other cognitive functions in ADHD patients. In addition, this polymorphism affected the gray matter and brain activity in the posterior cingulate cortex, an area included in the so-called default mode network previously correlated to regulation of attention and hypothesized to be implicated in ADHD [56]. Spillmann et al. observed a significant association between rs1051312 of SNAP-25 gene and cognitive dysfunctions in patients with schizophrenia. Carriers of TT genotype showed better results in such cognitive domains as verbal memory and executive functions than others genotypes [57]. In contrast, Golimbet et al. showed that carriers of the TT genotype of MnlI polymorphism (rs3746544) had worse measures of verbal memory and executive functions than carriers of other genotypes [58].

In our recent study, we were the first to demonstrate the lack of association between the polymorphisms of SNAP-25 gene and a performance on WCST in AN patients and HC in Polish adolescents.

The limitation of our study may be: firstly, small group and young age of patients and control subjects; secondly, using only the WCST test for estimation executive function in adolescents. Thirdly, broader range of SNAP-25 gene polymorphisms should be taken in to account. Thus, the results obtained should be considered as preliminary and require confirmation by other researchers.

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Submission to EuroCogSci 2011 is now closed. **Reviews be available by March 15th, 2011.**

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