In: Schizoaffective Disorders: New Research
Editor: William H. Murray, pp. 165-186
ISBN 1-60021-030-9

Chapter 7

VERBAL MEMORY DEFICIT IN SCHIZOPHRENIA AS A POSSIBLE ENDOPHENOTYPE OF THE DISEASE

V. E. Golimbet,* M. V. Alfimova, V. G. Kaleda, O. M. Lavrushina, G. I. Korovaitseva, T. V. Lezheiko and L. I. Abramova
Mental Health Research Center, Moscow, Russia.

ABSTRACT

Verbal memory deficit has been established as a central feature of neuropsychology of schizophrenia. There are certain lines of evidence that memory impairment is underpinned by genetic factors and might be considered as an endophenotype of schizophrenia. However, an endophenotypic character of different memory measures is less studied. Also, little is known about the contribution of any particular gene to the total variance in performance on memory tasks in schizophrenic patients. An aim of the present study was to evaluate a possible endophenotypic role of three different memory measures, namely long-term memory (LTM), short-term memory (STM) and verbal fluency (VF), in schizophrenia. This included the estimation of verbal memory heritability in schizophrenic families, relations of memory deficit with symptoms and personality changes and contribution of 5-HTR2A gene polymorphism to this deficit. We studied a sample including 352 patients with schizophrenia, 163 their first-degree non-psychotic relatives and 256 psychiatrically-well controls. Verbal memory was assessed using word lists recall and verbal fluency tasks. All variables were compared by genotypes of the serotonin receptor type 2A (5-HTR2A) gene, which had been earlier reported for association with short-term memory in healthy subjects. The T102C polymorphism, namely the A2A2 genotype, was repeatedly found to be associated with schizophrenia and clinical appearances of the disease. Both patients and relatives demonstrated significant impairment of verbal memory as compared to controls. Among all memory measures studied, the highest heritability was found for a delayed recall of deeply encoded verbal stimuli (LTM). Clinical symptoms were correlated with STM and VF in a larger extent than with LTM. Among personality features, schizotypal traits were the best predictors of LTM in relatives. An association was observed between the 5-

* Correspondence should be addressed to Vera Golimbet, PhD, e-mail: golimbet@mail.ru.

HTR2A polymorphism and STM in schizophrenic patients, with the A2A2 genotype patients recalling lesser words than those with the A1A1 and A1A2 genotypes. A complex pattern of association between VF, 5-HTR2A polymorphism, sex and schizophrenia was also observed. Males with chronic schizophrenia, who bear the A2A2 genotype, performed the worst on the VF task. Therefore, we can conclude that among all verbal memory measures LTM fulfils best the criteria of schizophrenia endophenotype. It is featured by the highest heritability and is likely to be independent of the influence of clinical symptoms in patients as well as correlated with schizotypal traits, which are thought to be another endophenotypic characteristic of schizophrenia, in relatives of schizophrenic patients.

INTRODUCTION

Along with impairment of attention and executive functions being established as center features of schizophrenia, verbal memory is thought to be an area vulnerable for the pathological process. It is recognized as one of the robust deficits of the disease that obviously has negative consequences for a patient's social functioning and may be regarded as a predictor or correlate of outcome (see Green 1996). Referring to the evidence of memory deficit impact on everyday life in schizophrenia patients, Toulopoulou and Murray (2004) argued that a better delineation of the nature of the deficit and of the molecular and neurobiological systems underlying it would have obvious therapeutic consequences.

Most research of memory in schizophrenia estimates verbal declarative memory, the ability to acquire, integrate, store and consciously and verbally recollect information about facts, objects, concepts and events. Verbal declarative memory may be subdivided into episodic and semantic memory. The former involves recollection of information associated with a distinct time and place whereas the latter relates to memory for information which has lost its contextual features to comprise general knowledge (Tulving, 1985; see also Cirillo and Seidman 2003). A schizophrenic performance deficit on verbal memory tasks has been observed across many kinds of material and testing conditions. Evidence from a review on verbal declarative memory dysfunction in schizophrenia has led Cirillo and Seidman (2003) to the conclusion that verbal declarative memory is among the most impaired domains of cognitive function in schizophrenia, its deficit being largely accounted for by deficits in the encoding stage. The authors have also noted that milder encoding deficits are present in high-risk subjects and non-psychotic relatives of individuals with schizophrenia suggesting that components of the memory deficit are associated with a genetic vulnerability to the illness and independent of the frank psychotic illness.

Indeed, several lines of evidence suggest that the verbal memory deficit in schizophrenia may be underpinned by genetic factors. Numerous studies demonstrated that relatives of schizophrenics exhibited episodic verbal memory impairments that were milder yet similar to those seen among patients (Kremen et al 1994, Cannon et al 1994, Faraone et al 1995, Lyons et al 1995, Toomey et al. 1998. Kremen et al 1998, Franke et al 1999, Laurent et al 1999, O'Driscoll et al 2001, Toulopoulou et al 2003, Appels et al 2003, Wittorf et al. 2004, Sponheim et al 2004, Hoff et al 2005, Schubert & McNeil 2005). The strongest evidence of impairment in relatives was found for logic memory (Faraone et al 1999, 2000, O'Driscoll et al 2001, Toulopoulou et al 2003) and verbal learning (Franke et al 1999, Laurent et al 2000, Toulopoulou et al 2003). A deficit in digit span immediate recall was reported by some

authors (Appels et al 2003), but not by others (Conklin et al 2000). Lyons et al (1995) observed a deficit in imposing semantic organizational strategy on unstructured material during word list recalling in adult relatives of schizophrenics. Impairment of information encoding was also found in adolescents and young adults at high risk for developing schizophrenia (Byrne et al 1999). As regard to semantic memory, reduction in verbal fluency was reported in patients and relatives (Kremen et al 1994, Keefe et al 1994, Laurent et al 1999, Appels et al 2003, Alfimova et al 2001). It should be noted that in schizophrenia studies word generation is commonly referred to as an executive function task. However, word generation requires the systematic retrieval of hierarchically organized information from semantic store and is often considered as a semantic memory test as well (e.g. Brucki and Rocha 2004). Moreover, schizophrenics were found to demonstrate disorganized semantic networks during word generation tasks (Aloia et al. 1996). A meta-analysis of cognitive impairments in relatives of schizophrenics indicated reliable relative-control differences on verbal memory recall (Sitskoorn et al. 2004), auditory verbal learning (Snitz et al. 2005) and verbal fluency (Snitz et al. 2005, Szoke et al. 2005). Whyte et al. (2005) conducted a systematic review and meta-analysis of the literature investigating declarative memory and found poorer performance in relatives compared to controls on all nine memory measures analyzed. Effect sizes were most significant on immediate list recall followed by immediate and delayed story recall. The authors concluded that there were greater deficits on tests of increasing memory load or those which placed demands on effective encoding processes.

Twin and family research demonstrated an influence of genetic factors on memory performance in the general population. Bouchard (1998) reviewed representative biometric studies that were used to generate estimates of genetic and environmental influences on special mental abilities and found the memory factor heritability averaged across studies of middle-aged twins to be 47%, with the common environment accounting for 23% of the variance. In contrast to other special abilities (e.g. verbal and special abilities), the heritability of memory remained the same (48%) late in life. A meta-analysis performed by the author showed that 48% of the variance in memory across different ages was due to genetic factors, with no influence of the common environment. However, Thapar et al. (1994) estimated heritability of eight memory measures drawn from different test batteries and demonstrated that memory heritability varied as a function of measure employed. They concluded that studies investigating heritability estimates of memory should use a multi-measure battery to investigate this construct. It should be mentioned that among memory measures, short-term memory was studied most often. According to Jensen and Marisi (1979) the heritability of performance on a digit span memory test, the most common method for short-term memory assessment, in a sample of teenage monozygotic and dizygotic twins was 44%, which, when corrected for attenuation, was increased to 52%. Similarly, Finkel et al. (1995) demonstrated the digit span heritability to be 55%. This was divided into genetic additive influences which were shared with general intelligence (16%) and those which were specific to the test (39%). The rest of the variance was accounted for by specific environmental factors. Ando et al. (2001) found the verbal short–term memory component of working memory to be 45% heritable.

There is less behavioral genetic evidence relating to verbal memory impairments in schizophrenic families. However, in several studies significant heritability estimates have been reported for a number of memory variables (Tuulio-Henriksson et al. 2002, Alfimova and Trubnikov 1994; Alfimova and Uvarova 2003). To assess upper limits of heritability of

cognitive impairments in schizophrenic families, Egan et al. (2001) used relative risk estimates. They found increased relative risk for word list learning and concluded that impairment in verbal memory in schizophrenia was familial and possibly heritable. Trends for increased relative risk were reported for logic memory and verbal (letter) fluency. Cannon et al. (2000) used a discordant-twin design to evaluate a number of cognitive measures as indicators of genetic risk for schizophrenia and found that among memory variables intrusions during a word list recall were the most sensitive to genetic loading for schizophrenia. Evidence of their genetic determination was provided by a higher intra-pair correlation in monozygotic compared with dizygotic pairs.

The data mentioned above suggest that, in genetic view, verbal memory fulfills the criteria for endophenotype definition. The term endophenotype was used by Gottesman and Shields (1972) for describing a trait that might be intermediate on the chain of causality from genes to disease. Later, the definition was clarified to distinguish endophenotypes reflecting genetic effects and criteria for endophenotype identification were suggested as follows: association with illness in the population, heritability and co-segregation within families, state-independence, emerging in relatives of the patients at a higher rate than in the general population (Gottesman and Gould 2003).

A concept of endophenotype tempts searching for genes responsible for the trait. However, the molecular genetic basis of cognitive functioning is poorly investigated so far. Recent studies have identified gene and chromosomal regions possibly involved in working memory. Gasperoni et al. (2003) found a linkage of the visual working memory performance with 1q chromosome markers. The results of another study (Hallmayer et al. 2003) indicated a suggestive linkage for the familial neurocognitive phenotype on chromosome 6. Also, attempts have been made towards a detection of molecular-genetic variants of certain candidate genes, which might be involved in neurocognitive functioning. A single nucleotide polymorphism Val158Met in the coding region of the catechol-*O*-methyltransferase (COMT) gene was repeatedly reported for association with brain activity in psychiatric and non-psychiatric populations, with the carriers of the low activity Met allele performing better on the working memory and attention tasks than those with the Val/Val genotype, which was implicated with more intensive dopamine degradation (Weinberger et al. 2001; Bilder et al. 2002; Goldberg et al. 2003; de Frias et al. 2004). An association between two candidate genes for major psychosis, namely DISC1 (Burdick et al. 2005) and BDNF (Egan et al. 2003), and neurocognition was observed as well.

Recently, Quervain et al. (2003) revealed an impact of serotonin receptor type 2a (5HTR2A) genetic variants (His/Tyr polymorphism) on word-lists recalling in psychiatrically well subjects. This finding is consistent with a concept of a role of serotonergic system in learning and memory functions. 5-HTR2A are widely presented in dorsolateral prefrontal cortex and hippocampus, i.e., in the areas thought to be involved in specific aspects of verbal memory (Luria 1976; Cohen and Eichenbaum 1993; Goldberg et al. 1989; Rolls 2000). There are certain lines of evidence suggesting that the administration of 5-HT2A receptor agonists prevents memory impairment (for review see Buhot et al. 2000). At the same time, the 5-HTR2A gene is regarded as a promising candidate for schizophrenia (Norton, Owen 2005). An association between a polymorphism caused by T102C nucleotide substitution in exon 1 and the disease has been reported in several studies (Williams et al. 1997; Joober et al. 1999; Golimbet et al. 2000; Abdolmaleky et al. 2004), with a frequency of the CC (A2A2) genotype being significantly higher in schizophrenics as compared to controls. Interestingly, when

personality characteristics and clinical symptoms of patients with schizophrenia were compared by 5-HTR2A genotype, the patients with the A2A2 genotype turned out to have lower scores on anxiety-related traits (Golimbet et al. 2002) and marked negative symptoms (Joober et al. 1999; Golimbet et al. 2002). This constellation of personality and clinical traits is characteristic of a specific phenotype of schizophrenia featured by more severe course and worse outcome.

It should be stressed that memory can be modulated by many factors. To assess the endophenotypic role of memory impairment in schizophrenia, the extent to which the deficit is a primary feature of the disease or a consequence of other influences should be established. So far intelligence, attention, symptoms and medication were intensively studied as possible confounds accounting for memory deficits in schizophrenia. A review of findings indicated the association of negative symptoms with memory test performance, the other factors appearing not to contribute substantially to memory deficit (Cirillo and Seidman 2003**).** Brébion et al (2001) found that recall of words relying on deep encoding was correlated with depression, while recall implied superficial encoding was linked with selective attention, and both were associated with slowing of processing speed. This finding suggests that different types of verbal memory impairments in schizophrenia may be consequences of different factors. Personality changes received little attention as possible confounds, although individual differences in personality traits of negative emotionality were shown to contribute to variability of memory test performance in the general population (Gabrys et al. 1987) and to episodic memory impairment in older persons without dementia (Meier et al. 2002) and with mild to moderate Alzheimer's disease (Wilson et al**.** 2004). Besides, correlations were found between personality traits and neurocognitive test scores in schizophrenics (Lysaker and Davis 2004). Apart from basic personality dimensions such as extraversion and neuroticism, schizotypal traits are the object of a growing body of research in schizophrenic families. It is well documented that neurocognitive deficits and symptoms of schizotypal personality disorder are both elevated in the first-degree relatives of schizophrenic patients and their relationship to each other has been investigated. However, it still remains unclear whether neurocognitive and schizotypal phenotypes are influenced by at least partially independent sets of genes. Associations between the two were observed in several studies suggesting common sources of variance. Relatives with a diagnosis of schizotypal personality disorder were found to be more impaired compared to those without schizophrenia-spectrum symptoms on a number of tests (Cannon et al. 1994; Keefe et al. 1994). Positive schizotypy was shown to co-vary with verbal long-term memory (Vollema and Postma 2002) and negative schizotypy with short-term memory (Squires-Wheeler et al. 1997). At the same time, Toulopoulou et al. (2003) demonstrated that relatives' deficit on a number of memory tests remained significant even after excluding those with schizotypal personality disorder. Also, Asarnow et al. (2002) observed that familial liability to schizophrenia can be transmitted across two generations, being independent of the presence of schizophrenia spectrum disorders in either the parent or proband and accounting for significant variance in proband's neurocognitive functioning. Two latter studies suggest that neurocognitive functioning and schizotypal traits may be relatively independent endophenotypes of schizophrenia.

In the present study we attempted to evaluate a possible endophenotypic role of three different measures of verbal memory in schizophrenia. This included the estimation of verbal memory heritability in schizophrenic families, relations of memory deficit to clinical symptoms and personality changes and contribution of 5-HTR2A gene polymorphism to this

deficit. We tested two hypotheses on a possible relation between the 5-HTR2A A2A2 genotype and verbal memory. In the frame of the first hypothesis, the A2A2 genotype contribution to the memory deficit may be accounted for its relation to the disease phenotype. According to the alternative assumption, the 5-HTR2A polymorphism would be associated with verbal memory independently of the disease presentations.

SUBJECTS AND METHODS

Sample

According to a study design, patients with schizophrenia, their first-degree relatives without any signs of schizophrenic psychosis and psychiatrically well subjects without a family history of schizophrenia were examined. After description of the goals and procedures of the study, all subjects gave a written consent for participation. Subjects with organic brain disorders or severe somatic diseases were withdrawn from the study. A sample comprised 352 patients (210 females, 142 males; mean age 36±14 years, age at onset 25±10 years, illness duration 11±10 years) with schizophrenia (broad definition) who were admitted to clinical departments of the Mental Health Research Center. A diagnosis was made according to diagnostic criteria of DSM-IV-R and was based on the semi-structured interviews and medical records. Once established by a psychiatrist, the diagnosis was confirmed by senior researchers. One hundred sixty-three unaffected relatives (116 parents and 33 siblings) of schizophrenic patients (83 men, 80 women, mean age 46±14 years) were included in the study. A control group comprised 256 subjects (189 men, 167 women, mean age 32±12 years). It was recruited randomly from the community and psychometrically screened before genotyping.

Methods

Clinical Assessment

The Positive and Negative Syndromes Scale (PANSS) (Kay et al. 1987) was used for measuring symptom severity in patients. The PANSS includes three subscales for assessing positive, negative and general psychopathological symptoms on 30 items: 7 for positive symptoms, 7 –for negative and 14 - for general psychopathological ones. Each symptom has 7 ratings (1 – symptom is absent, 2 – questionable, 3 – mild, 4 – moderate, 5 – severe, 6 – markedly severe, 7 –extremely severe). The rater performed clinical assessments blind to the results of neurocognitive tests and psychometric assessment.

Personality Questionnaires

Translated and adapted versions of the Eysenck personality inventory (EPI), MMPI, and the State Trait Anxiety Inventory (STAI) were administered to all subjects to measure personality traits. Besides, the Schizotypal Personality Questionnaire (SPQ) was used to test unaffected individuals (relatives and controls). EPI (57 items) encompasses personality traits on two scales: Extraversion and Neuroticism. MMPI (377 item version) consists of three

validity scales (L, F, K) and ten clinical diagnostic scales: Hypochondriasis, Depression, Hysteria, Psychopathic deviate, Masculinity-Femininity, Paranoia, Psychasthenia, Schizophrenia, Hypomania and Social introversion. STAI includes 20 items measuring trait anxiety. The patients completed the questionnaires themselves or with the assistance of a psychologist. Criteria for MMPI validity were: L < T 70, F <T 90 and K < T 80. Only valid profiles were used in the subsequent analysis. SPQ is a self-report measure that assesses the nine features of DSM-defined schizotypy (Ideas of reference, Excessive social anxiety, Odd beliefs or magical thinking, Unusual perceptual experiences, Odd or eccentric behavior, No close friends, Odd speech, Constricted affect, Suspiciousness) and its three higher-order dimensions (Cognitive-Perceptual, Interpersonal, and Disorganized). Total scores can range from 0 to 74.

Cognitive Assessment

An extensive battery of neuropsychological tests was performed as described in detail elsewhere (Alfimova, Uvarova 2003). For the present analysis, 3 tasks measuring different aspects of verbal memory were selected from the battery.

Episodic memory:

- An immediate 10-noun free recall test to measure short-term memory (STM). The subject listens to a set of 10 semantically unrelated nouns and is asked to recall immediately after presentation as many as possible, in any order. This procedure is performed twice. The STM score is the total number of words correctly recalled over two trials.
- "Pictograms" to measure long-term memory (LTM). The essence of the task is that 16 words are presented to the subject who is instructed to remember them. To facilitate recalling of words, the subject is asked to draw a picture or a sign (a pictogram) for every word that may help him/her later (40-60 min after the presentation) to recall the word. If a word was recalled correctly, it was evaluated as 1 score; in a case of using synonym, the score was 0.5. The method assesses delayed recall of deeply encoded verbal stimuli.

Semantic memory:

- A variant of the Controlled Oral Word Association Test to measure VF. The subject was asked to generate as many words belonging to a designated semantic category, as he/she could in one minute. Animals and fruits were used. The total number of correct instances was included in the analysis. The test involves retrieving words from long-term lexical storage (semantic memory) as well as generating retrieval strategies (executive function).

Clinical, personality and cognitive assessment was conducted after an improvement of patient clinical state being assessed as 1-3 with the Global Clinical Impression Scale. Before and during neuropsychological sessions patients were not withdrawn from the neuroleptics treatment.

Genotyping

The participants donated venous blood and DNA was extracted from the white cells using phenol-chloroform method. Genotyping for the T102C polymorphism was performed as described elsewhere (Warren et al. 1993). After Msp1 digestion and electrophoresis on a 2% agarose gel, DNA bands were assigned as allele A1 (T) - 342 bp and allele A2 (C) - 216 +126 bp.

Statistical Analysis

ANOVA with post hoc test and Student's t-test were used in analyses of neurocognitive traits by group and 5-HTR2A genotype. A quantitative genetic analysis included decomposing of phenotypic variance of each memory measure into genetic and environmental components. For the purpose of the analysis, correlation coefficients were calculated in pairs of relatives. Correlations were computed separately in groups according to type of relatives and sex. Parent-offspring correlation was an averaged coefficient of interclass correlations in four types of parent-offspring pairs (father-son, father-daughter, mother-son, mother-daughter). Sibling correlation was an average coefficient of intra- (brother-brother, sister-sister) and interclass (brother-sister) correlations. The components of the phenotypic variance were estimated by the least-squares method (Nance and Corey, 1976). For each measure, a full A (additive genetic), C (common environment), and E (non-shared environment) model was fitted to the data, followed by reduced models (AE, CE, and E only), which systematically removed one source of variance. The model that included neither negative values of components nor large standard errors of the values and comprised the maximum number of components was selected as the best model (Trubnikov and Gindilis, 1981). Relationships between the memory measures and clinical and personality variables were assessed by means of correlation and regression analyses. Nonparametric Spearmen rank order correlations were used for PANSS and SPQ scores, in all the other cases Pearson correlations were analyzed. A stepwise procedure of a multiple linear regression analysis was employed to predict memory performance from clinical and personality parameters.

Results

Performance on Memory Tests in Patients, Relatives and Controls

The groups were not equivalent in terms of age and gender. However, separately computed t-tests for each group failed to reveal any significant gender differences in either STM or LTM performance. There was a significant difference in verbal fluency (VF) between men and women in the schizophrenic group, the men generating fewer words than the women, 26(10) and 29(10), respectively ($t=2.63$ $df=307$ $p=0.009$). Age was correlated with performance on the STM test in all the groups, with LTM in the relatives and controls and with VF in the patients (Tables 3, 4). Each group demonstrated significant inter-correlations among the three memory measures ($p= 0.001$-0.000). As presented in Table 1, the groups differed significantly in all the three memory measures (ANOVA, $p=0.000$). The schizophrenic patients had lower memory scores than their first-degree relatives who, in turn, had lower memory scores than the non-psychiatric comparison participants. T-test indicated

that both the schizophrenic patients and their first-degree relatives performed significantly worse than comparison participants, while the difference between the patients and relatives reached the level of significance only for VF. When the analyses were repeated with age as a covariate (ANCOVA), the pattern of significant results was the same as without using covariates. When gender was considered as an additional factor in the analysis of VF performance, the main effect of the group remained, the effects of gender and gender×group interaction being non-significant.

Table 1. Memory measures (mean and standard deviation) in patients with schizophrenia, their relatives and control subjects

Memory measure	Mean (SD)			ANOVA	Post hoc t-tests
	Patients (P)	Relatives (R)	Controls (C)		
Short-term memory (number of words)	8.8 (2.7)	9.4 (2.5)	11.0 (2.3)	F(2, 653)=54.8 p=0.000	P vs.C (t=10.32; df=552; p=0.000) R vs. C (t=6.00; df=344; p=0.000)
Long-term memory (number of words)	8.2 (3.4)	8.8 (3.3)	12.4 (2.9)	F(2, 508)=96.3 p=0.000	P vs. C (t=12.15; df=358; p=0.000) R vs.C (t=11.28; df=387; p=0.000)
Verbal fluency (number of words)	28.5 (9.9)	35.1 (8.6)	41.3 (8.6)	F(2, 705) =141.9 p=0.000	P vs.C (t=16.6; df=600; p=0.000) R vs. C (t=6.27; df=354; p=0.000) P vs.R (t=6.21; df=456; p=0.000)

Table 2. Correlations in pairs of relatives and heritability models for memory measures in schizophrenic families

Memory measure	Correlations		Heritability models		
	Parent-Offspring	Sibs	Additive genetic	Common environment	Non-shared environment
Short-term memory	0.04 n=159	-0.25 n=46	-	-	100
Long-term memory	0.38 n=159	0.47 n=46	75(14)* 80(12)*	10(13) -	15(19) 20(12)
Verbal fluency	0.05 n=62	0.61 n=10	43(21) -	- 61(20)*	57(21) 39(20)

* $p < .05$.

Heritability

The additive genetic component was substantial for LTM (Table 2), impact of the common environment being non-significant. Non-shared environment was the only source of the STM variance. As regard to verbal fluency, both genetic and common environmental influences might affect similarities between family members. However, only the model including common environment influences yielded the statistically significant values of the components.

Table 3. Significant correlations between memory and clinical variables.

PANSS symptoms	STM (n=308)	LTM (n=116)	VF (n=309)
Positive symptoms	-0.16†		
Conceptual disorganization	-0.19‡		-0.12*
Suspiciousness/persecution	-0.17†		
Negative symptoms	-0.29‡	-0.20*	-0.32‡
Blunted affect	-0.26‡		-0.27‡
Emotional withdrawal	-0.22‡		-0.23‡
Poor rapport	-0.20‡		-0.22‡
Passive/apathetic social withdrawal	-0.26‡	-0.20*	-0.29‡
Difficulty in abstract thinking	-0.24‡		-0.32‡
Lack of spontaneity	-0.18†		-0.21‡
Stereotyped thinking	-0.30‡		-0.27‡
General psychopathology	-0.13*		-0.19‡
Mannerism and posturing			-0.13*
Uncooperativeness			-0.17†
Disorientation	-0.19†	-0.19*	-0.23‡
Poor attention	-0.15†		-0.12*
Lack of judgment and insight	-0.12*		
Disturbance of volition	-0.19‡	-0.24*	-0.21‡
Poor impulse control	-0.14*		-0.14*
Preoccupation	-0.13*		-0.16†
Active social avoidance	-0.23‡		-0.25‡
Age	-0.35‡		-0.18‡
Illness duration	-0.39‡		-0.23‡

* $p < .05$.
† $p < .01$.
‡ $p < .001$.

Associations between Clinical, Personality and Memory Variables

Means ± standard deviations of positive, negative and general psychopathological PANSS scores were 22.8 ± 7.7, 23.4 ± 7.7 and 48.2 ± 11.3, respectively. Significant correlations of clinical and personality scores with the memory measures are presented in Tables 3-4. STM and VF had similar patterns of correlations with PANSS scores. Associations were found for all of the negative symptoms and for majority of the general pathological ones. Only a few links between PANSS scores and LTM were statistically significant. There were no correlations between memory and personality in the patient group, while multiple personality scores were related to both episodic and semantic memory in unaffected individuals. As a number of correlations was large, a stepwise multiple regression analysis was conducted in order to identify the most important associations between symptoms, personality and memory. Clinical and personality variables which had significant univariate correlations with a particular memory measure were entered as predictors with controlling for age and sex when it was necessary. The results are presented in Table 5. The analysis revealed that illness duration was the most powerful predictor of STM performance in schizophrenia, accounting

for about 15% of the variance. VF and LTM were correlated with particular symptoms each accounting for no more than 10% of the variance of memory measures. With regard to personality traits, the strongest association was found between them and LTM performance in the group of relatives. About one half of the variance in LTM could be accounted for by personality variables, mainly schizotypal traits.

Table 4. Significant correlations between memory and personality in unaffected individuals

Personality traits	Relatives			Controls		
	STM	LTM	VF	STM	LTM	VF
Age	-0.24*	-0.21*		-0.27‡	-0.43‡	
TCI Self- Directedness	0.34* n=39					0.17* n=181
TCI Cooperativeness			0.39* n=39			
MMPI	n=93	n=113	n=94	n=227	n=221	n=234
Hypochondriasis	-0.26*	-0.29†	-0.24*			
Depression		-0.19*			-0.22‡	-0.16*
Hysteria				0.20†		0.13*
Masculunity-Femininity		0.24*	0.22*			
Paranoia					-0.15*	
Schizophrenia			-0.23*		-0.14*	
Mania			-0.21*			
SPQ	n=47	n=47	n=47	n=180		
Ideas of reference				0.17*		
Social Anxiety		-0.46‡				
Odd beliefs or magical thinking			0.29*			
Unusual perceptual experiences		-0.30*				
No close friends		-0.49‡				
Odd speech		-0.35*				
Constricted affect		-0.34*				
Suspiciousness		-0.34*				
Interpersonal Factor	-0.29*	-0.52‡				
Total SPQ		-0.41†				

* = $p < .05$.
† = $p < .01$.
‡ = $p < .001$.

Table 5. Multiple regression models for memory scores prediction from demographic variables, PANSS and personality test scores.

Memory measure	Contributing variables	Multiple Regression Summary		
		F (R^2_{adj})	Beta	Partial R^2
Schizophrenic patients				
Short-term memory	Illness duration	27.72‡ (0.16)	-0.27‡	0.15
	Age		-0.17*	0.01
Long-term memory	Disturbance of volition	8.20† (0.07)	-0.27†	0.06
Verbal fluency	Difficulty in abstract thinking	21.61‡ (0.17)	-0.31‡	0.10
	Sex		-0.19‡	0.05
	Disorientation		-0.19‡	0.03
Relatives				
Short-term memory	TCI Self-Directedness	4.95* (0.09)	0.34*	0.12
Long-term memory	SPQ Interpersonal factor	9.97‡ (0.50)	-1.71‡	0.25
	SPQ Total		2.03‡	0.13
	SPQ Odd speech		-0.65†	0.07
	MMPI Mf		0.27*	0.06
	SPQ Unusual perceptual experiences		-0.66‡	0.03
Verbal fluency	TCI Cooperativeness	6.15* (0.13)	0.39*	0.15
Controls				
Short-term memory	Age	12.10‡ (0.11)	-0.29‡	0.07
	MMPI Hysteria		0.22†	0.05
Long-term memory	Age	28.82‡ (0.20)	-0.44‡	0.18
	MMPI Schizophrenia		-0.16†	0.02
Verbal fluency	MMPI Depression	5.48† (0.05)	-0.21†	0.02
	MMPI Hysteria		0.19*	0.03

* = $p < .05$; † = $p < .01$; ‡ = $p < .001$, t-test, hypothesis: beta≠0; intercepts were included in the models but not shown; R^2- coefficient of determination.

Molecular-genetic Analysis

5-HTR2A genotypes were obtained for 269 patients, 141 relatives and 227 controls. The observed distribution of the genotypes in each group was consistent with Hardy-Weinberg equilibrium. Allele and genotype frequencies were similar in all the groups and did not differ from those reported for the European populations (Williams et al. 1997). Table 6 presents results of neurocognitive tasks in each group by 5-HTR2A genotype. An effect of genotype on verbal memory was observed only in the group of patients. An association was found between the 5-HTR2A polymorphism and STM (ANOVA F=4.4; df=2; p=0.008), with the A2A2 genotype carriers recalling lesser words than those with the A1A1 (post-hoc LSD test; p=0.04) and A1A2 (p=0.003) genotypes. The difference was highly significant when the A2A2 genotype was compared to combined A1A1 and A1A2 genotypes (t=3.1; df=267; p=0.002). We repeated the stepwise regression analysis to predict STM performance from

demographic and clinical characteristics with genotype as an additional independent variable. This yielded the statistically significant regression model (F=14.1; df=4.2; p=0.000) that included illness duration and genotype. The two predictors together explained 20% of the total STM variance, with genotype contribution estimated as 2.0%. Because sex was a significant predictor for VF, we performed two-way ANOVA with genotype and sex as between-group factors. The results showed a trend towards the main effect of genotype (p=0.08) and sex by genotype interaction (p=0.09). When the sample was stratified by gender, the lowest verbal fluency mean score, 23.5(9.9), was observed in male, but not female, patients with the A2A2 genotype. The score differed significantly (t=2.1; p=0.037) from that obtained for a group comprising patients with A1A2 and A1A1 genotypes (Table 7). Significant difference (t=2.4; df=53; p=0.02) between the A1A1 and A2A2 genotypes was found for male patients when only those with chronic schizophrenia (n=94), i.e., whose illness duration more than 10 years, were analyzed. However, inclusion of the genotype as a predictor in the regression model did not reveal its contribution to the VF variance.

Table 6. Emory measures (mean, standard deviation) by 5-HTR2A genotype in patients with schizophrenia, their first-degree relatives and controls.

	Patients (n=269)			**Relatives (n=141)**			**Controls (n=227)**		
Trait / 5HTR2A genotype	A1A1 (n=44)	A1A2 (n=114)	A2A2 (n=111)	A1A1 (n=17)	A1A2 (n=61)	A2A2 (n=63)	A1A1 (n=37)	A1A2 (n=91)	A2A2 (n=99)
Long-term memory (number of words)	7.8 (3.3)	7.7 (3.5)	7.9 (3.2)	9.6 (3.2)	8.9 (3.3)	8.7 (3.5)	12.9 (2.7)	12.6 (2.6)	12.2 (2.8)
Short-term memory (number of words)	8.9 (2.9)	9.1 (2.3)	7.9* (2.7)	10.0 (2.4)	9.2 (1.9)	9.8 (3.0)	11.0 (2.6)	11.2 (2.1)	10.8 (2.3)
Verbal fluency	26.7 (9.9)	28.5 (9.2)	25.5 (9.7)	34.9 (7.5)	34.5 (8.8)	37.6 (7.5)	40.7 (8.1)	42.4 (9.0)	41.0 (8.8)

* AVOVA F=4.4; df=2; p=0.008; t-test A1A1+A1A2 vs A2A2 (t=3.1 df=267; p=0,002)

Table 7. Verbal fluency (mean, standard deviation) by 5-HTR2A genotype in male and female patients with schizophrenia

Patients	**5-HTR2A genotypes**		
	A1A1 n=19	A1A2 n=53	A2A2 n=49
Female	25.7(10.6) n=22	29.6(9.2) n=46	26.6(10.1) n=43
Male	27.9 (9.6) n=20	27.4 (10.1) n=39	23.5 (9.9)* n=35
Male with chronic schizophrenia	26.05(10.8)	26.7(9.4)	21.8(9.)†

* A1A1 + A1A2 vs A2A2 (t=2.1; p=0,037).

† A1A1 vs A2A2 (t=2.4; p=0,02).

CONCLUSION

Therefore, the results obtained support the evidence for the memory deficit in schizophrenic patients and their relatives as compared to controls. Our data are compatible with the notion of sex and age influences on verbal memory and verbal fluency in different populations (Bäckman and Nilsson 1996; Herlitz et al. 1997; Kremen et al. 1997; Sitskoorn et al. 2004; Cirillo and Seidman 2003). However, controlling for these factors did not cancel differences between patients, relatives and control subjects, a finding consistent with that of Laurent et al. (1999).

In spite of the fact that the relatives performed worse on all the three memory tasks compared to the controls, only the LTM measure was found to be highly heritable in schizophrenic families. These results are similar to those from our previous study of another sample of schizophrenic families (Alfimova and Trubnikov, 1994) which showed high heritability for LTM (62%) and low heritability estimates for STM and VF (0-20%).

Results of the correlation analysis are in agreement with other findings indicating episodic memory and VF deficits to be associated mainly with negative symptoms (e.g. Basso et al. 1998; O'Leary et al. 2000). However, predicting patients' performance on the STM task from a wide range of clinical and demographic variables yielded illness duration as the sole clinical predictor. One intuitively appealing interpretation of these data is that illness duration represents the most general measure encompassing a number of factors associated with the disease course and outcome. Of note, this interpretation contradicts findings of Tuulio-Henriksson et al. (2004) showing that inclusion of illness duration in regression models did not eliminate effects of a number of other clinical characteristics on memory. Nevertheless, our data suggest that, when considering STM as an endophenotype, the disease-related factors should be controlled for. We found that most clinical symptoms did not contribute to the LTM variance. Disturbance of volition was sole predictor of the trait. An explanation of this association might lie in the nature of the LTM measure. In our study, the LTM task included deep encoding which was assumed to be an effortful process vulnerable to a motivational deficit. The most powerful predictor of verbal fluency was difficulty in abstract thinking. This might reflect a role of prefrontal lobe functioning underpinning executive mechanisms and abstraction in VF performance in patients. Besides, this finding is in agreement with the notion that thought disorder in schizophrenia is associated with and may result from semantic processing abnormalities seen during a word generation task (Goldberg et al. 1998). The magnitude of the observed relationship between symptoms and LTM and VF, however, was small suggesting the operation of a number of other sources of variance. In contrast to clinical variables, personality changes did not contribute to any of the memory measures in patients.

In relatives, there were no deterioration effects of personality changes on the STM performance and VF. On the contrary, these memory variables were positively related to the TCI items measuring character. High scores on character dimensions are thought to indicate coherence of personality, or, in other words, a state of wisdom and well-being (Cloninger, 2004). The Self-Directedness indicates how responsible, goal-oriented, realistic, and resourceful a person is, while the Cooperativeness quantifies the extent to which individuals conceive themselves as integral parts of human society being empathic, tolerant, and supportive. Therefore, our data suggest a link between some aspects of verbal memory and well-being in relatives of schizophrenics. This finding resembles those linking verbal memory

with a general outcome, including a sense of well-being and qualitative and quantitative aspects of interpersonal relationships, in schizophrenia (Green 1996, Lysaker and Davis 2004). There was a strong association between personality scores, mainly those on the SPQ scales, and LTM in relatives of schizophrenics. The SPQ Interpersonal factor was the most powerful predictor of the LTM deficit. This finding seems to be compatible with the evidence of the relationships between this memory measure and avolition in the schizophrenic group. The interpersonal factor is an overall measure of negative schizotypy tapping feelings associated with social isolation and anxiety, constricted affect and suspiciousness. It is important to note in the context of the endophenotype hypothesis that most investigations relying on diagnostic interviews as well as a study exploring the SPQ in a large sample of relatives found social-interpersonal features to differentiate best the first-degree biological relatives of schizophrenia patients from healthy comparison subjects, indicating that they may be the most important schizotypal features associated with genetic vulnerability for schizophrenia (Calkins et al. 2004). In our study, the controls had significantly higher scores on the SPQ scales with exception of the "No close friends" scale and the Interpersonal factor (the data are not presented). These data are in line with the hypothesis that schizophrenia relatives are more defensive in responding to schizotypy questionnaires than controls (e. g. Kendler et al. 1996). On the other hand, they support the observation that the interpersonal deficit is the most prominent schizotypal feature in relatives of schizophrenics (Calkins et al. 2004). Among the three experimental groups, the controls demonstrated the weakest correlations between memory and personality. Schizophrenic and depressive traits as measured by MMPI had small deteriorating effects on LTM and VF respectively, while correlations between the Hysteria scale scores and the memory measures were positive. It should be noted that the finding that the SPQ scores predict memory performance in relatives but not in controls is consistent with what has been observed by Johnson et al. (2003). The authors found that schizotypy symptoms influenced nearly all cognitive domains in unaffected co-twins of schizophrenic patients and were not related to impaired neurocognitive functioning in the absence of a family history of schizophrenia. In contrast to previous studies indicating relationships between memory performance and negative emotionality in different populations, we observed few correlations of the memory measures with anxiety-related traits (e.g. hypochondriasis and depression), which were mostly abolished when co-varying for the other personality scales.

The results of molecular-genetic study revealed that the A2A2 genotype contributed to STM and VF but not to LTM. Of note, the association between the 5-HTR2A polymorphism and STM was found only in patients with schizophrenia, though the relationship of this gene to STM had been reported earlier for non-clinical population (Quervain et al. 2003). The same, the A2A2 genotype was associated with lower VF scores only in patients, with the most striking difference observed in chronic male schizophrenics. The relationship between the 5-HTR2A T102C polymorphism and VF has been investigated in some studies. Chen et al. (2001) revealed a trend toward better performance on this test in patients with the A1A2 genotype comparing to the A2A2 genotype. In our previous study (Alfimova et al. 2003), an association between the A2A2 genotype and poorer performance on the VF test has been demonstrated for males with schizophrenia. Here we confirmed the association on the extended sample.

Thus, the 5-HTR2A polymorphism contributed to performance on memory tasks only in individuals with schizophrenia, its relations being observed with those memory measures

which were associated with symptoms and illness duration. Of importance, the A2A2 genotype was previously reported for associations with a chronic course of schizophrenia (Joober et al. 1999), poor response to atypical neuroleptics, e.g. clozapine, (Arranz et al 1998) and extrapyramidal effects (Segman et al 2001, Lerer et al 2005). Taken together, these and our data argue for the hypothesis that the 5-HTR2A A2A2 genotype impacts rather on some pathological appearances or complications of the disease in whole than on memory in particular. It should be stressed, however, that, according to our results, the A2A2 genotype had significant, though small, contribution to the STM variance even when illness duration was controlled for. In the context of the above hypothesis, it can be speculated that this contribution was mediated by a certain factor that was associated with the disease presentation but not correlated with illness duration.

Mechanisms of 5-HTR2A polymorphism relation to schizophrenia still remain unclear. Reduced 5-HTR2A binding in schizophrenic patients was supported by multiple studies (Pralong et al. 2000; Ngan et al. 2000; Dean et al. 1999). Polesskaya and Sokolov (2002) revealed that the expression of the A2 allele in the temporal cortex of normal postmortem brain evaluated by measuring of the total amounts of mRNA and receptor protein was lower than that of the A1 allele. The authors suggested that the presence of lower expressed allele A2, together with low overall reduction in 5-HTR2A expression in schizophrenic patients, might predispose to the disease. However the results were not confirmed in a replication study (Bray et al. 2004).

Therefore, we can conclude that among all the three verbal memory measures LTM best fulfils the criteria of schizophrenia endophenotype. It is featured by the highest heritability and, to a larger extent comparing to STM and VF, independent of the influence of clinical symptoms in patients. It is also correlated with schizotypal traits, which are thought to be other endophenotypic characteristics of schizophrenia, in relatives of schizophrenic patients. The fact that the A2A2 genotype, association of which with STM and VF proved to be under some influence of illness duration, did not contribute to the LTM variance may be regarded as an indirect evidence for our conclusion. The STM and VF deficit seems to be a part of the vulnerability as well as a consequence of the illness.

ACKNOWLEDGEMENTS

We wish to thank clinical psychiatrists Mrs. T.S. Kaidan, T.K. Ganisheva, A.A. Muratova, K.V. Chubabria, M.A. Streltsova, T.K. Shemyakina, L.F. Frolova for their assistance in providing patients for the study.

This work was partially supported by RFBR grant N 04-04-48588.

REFERENCES

Abdolmaleky, HM; Faraone, SV; Glatt, SJ; Tsuang, MT. Meta-analysis of association between the T102C polymorphism of the 5HT2a receptor gene and schizophrenia. *Schizophr Res* 2004, 67(1), 53-62.

Alfimova, MV; Trubnikov, VI. Psychological variables and genetic predisposition to schizophrenia. *J Rus East Psychology* 1994, 32, 53-66.

Alfimova, MV; Uvarova, LG; Trubnikov, VI. Psychological and brain mechanisms underlying verbal fluency impairments in schizophrenia. *Social and clinical psychiatry* 2001, 11(1), 67-74.

Alfimova, M; Uvarova, L. Cognitive peculiarities in relatives of schizophrenics: heritability and EEG-correlates. *Int J Psychophysiol* 2003, 49, 201-216.

Alfimova, MV; Golimbet, VE; Mitiushina, NG. Polymorphism of the serotonin receptor (5-HTR2A) gene and verbal fluency in normalcy and schizophrenia. *Mol Biol (Mosk)*. 2003, 37(1), 68-73. (Russian).

Aloia, MS; Gourovitch, ML; Weinberger, DR; Goldberg, TE. An investigation of semantic space in patients with schizophrenia. *J Int Neuropsychol Soc* 1996, 2(4), 267-273.

Ando, J; Ono, Y; Wright MJ. Genetic structure of spatial and verbal working memory. *Behav Genet*. 2001, 31(6), 615-624.

Appels, MC; Sitskoorn, MM; Westers, P; Lems, E; Kahn, RS. Cognitive dysfunctions in parents of schizophrenic patients parallel the deficits found in patients. *Schizophr Res*. 2003, 63(3), 285-293.

Arranz, MJ; Munro, J; Sham, P; Kirov, G; Murray, RM; Collier, DA; Kerwin, RW. Meta-analysis of studies on genetic variation in 5-HT2A receptors and clozapine response. *Schizophr Res*. 1998, 32(2), 93-99.

Asarnow, RF; Nuechterlein, KH; Asamen, J; Fogelson, D; Subotnik, KL; Zaucha, K; Guthrie, D. Neurocognitive functioning and schizophrenia spectrum disorders can be independent expressions of familial liability for schizophrenia in community and control children: the UCLA family study. *Schizophr Res*. 2002, 54(1-2), 111-120.

Bäckman, L; Nilsson, LG. Semantic memory functioning across the adult life span. *European Psychologist* 1996, 1, 27-33.

Basso, MR; Nasrallah, HA; Olson, SC; Bornstein, RA. Neuropsychological correlates of negative, disorganized and psychotic symptoms in schizophrenia. *Schizophr Res* 1998, 31, 99-111.

Bilder, RM; Volavka, J; Czobor, P; Malhotra, AK; Kennedy, JL; Ni, X; Goldman, RS; Hoptman, MJ; Sheitman, B; Lindenmayer, JP; Citrome, L; McEvoy, JP; Kunz, M; Chakos, M; Cooper, TB; Lieberman, JA. Neurocognitive correlates of the COMT Val(158)Met polymorphism in chronic schizophrenia. *Biol Psychiatry* 2002, 52(7), 701-707.

Bouchard, TJ Jr. Genetic and environmental influences on adult intelligence and special mental abilities. *Hum Biol* 1998, 70(2), 257-279.

Bray, NJ; Buckland, PR; Hall, H; Owen, MJ; O'Donovan, MC. The serotonin-2A receptor gene locus does not contain common polymorphism affecting mRNA levels in adult brain. *Mol Psychiatry* 2004, 9(1), 109-114.

Brebion, G; Gorman, JM; Malaspina, D; Sharif, Z; Amador, X. Clinical and cognitive factors associated with verbal memory task performance in patients with schizophrenia. *Am J Psychiatry* 2001; 158(5), 758-764.

Brucki, SM; Rocha, MS. Category fluency test: effects of age, gender and education on total scores,clustering and switching in Brazilian Portuguese-speaking subjects. Braz J *Med Biol Res* 2004, 37(12), 1771-1777.

Buhot, MC; Martin, S; Segu L. Role of serotonin in memory impairment. *Ann Med* 2000, 32(3), 210-221.

Burdick, KE; Hodgkinson, CA; Szeszko, PR; Lencz, T; Ekholm, JM; Kane, JM; Goldman, D; Malhotra, AK. DISC1 and neurocognitive function in schizophrenia. *Neuroreport* 2005, 16(12), 1399-1402.

Byrne, M; Hodges, A; Grant, E; Owens, DC; Johnstone, EC. Neuropsychological assessment of young people at high genetic risk for developing schizophrenia compared with controls: preliminary findings of the Edinburgh High Risk Study (EHRS). *Psychol Med* 1999, 29(5), 1161-1173.

Calkins, ME; Curtis, CE; Grove, WM; Iacono, WG. Multiple dimensions of schizotypy in first degree biological relatives of schizophrenia patients. *Schizophr Bull* 2004, 30(2), 317-325.

Cannon, TD; Zorrilla, LE; Shtasel, D; Gur, RE; Gur, RC; Marco, EJ; Moberg, P; Price, RA. Neuropsychological functioning in siblings discordant for schizophrenia and and healthy volunteers. *Arch Gen Psychiatry* 1994, 51(8), 651-661.

Cannon, TD; Huttunen, MO; Lonnqvist, J; Tuulio-Henriksson, A; Pirkola, T; Glahn, D; Finkelstein, J; Hietanen, M; Kaprio, J; Koskenvuo, M. The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. *Am J Hum Genet* 2000, 67(2), 369-382.

Chen, RY; Sham, P; Chen, EY; Li, T; Cheung, EF; Hui, TC; Kwok, CL; Lieh-Mak, F; Zhao, JH; Collier, D; Murray, R. No association between T102C polymorphism of serotonin-2A receptor gene and clinical phenotypes of Chinese schizophrenic patients. *Psychiatry Res* 2001, 105(3), 175-185.

Cloninger, C. R. Feeling Good: The Science of Well Being. New York, Oxford University Press 2004.

Cirillo, MA; Seidman, LJ. Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms. *Neuropsychol Rev* 2003, 13(2), 43-77.

Cohen, NJ; Eichenbaum, H. Memory, Amnesia, and the Hippocampal System. Cambridge, The MIT Press 1993.

Conklin, HM; Curtis, CE; Katsanis, J; Iacono, WG. Verbal working memory impairment in schizophrenia patients and their first-degree relatives: evidence from the digit span task. *Am J Psychiatry* 2000, 157(2), 275-277.

Dean, B; Hussain, T; Hayes, W; Scarr, E; Kitsoulis, S; Hill, C; Opeskin, K; Copolov, DL. Changes in serotonin 2A and GABA(A) receptors in schizophrenia: studies on the human dorsolateral prefrontal cortex. *J Neurochem* 1999, 72(4), 1593-1599.

De Frias, CM; Annerbrink, K; Westberg, L; Eriksson, E; Adolfsson, R; Nilsson, LG. COMT gene polymorphism is associated with declarative memory in adulthood and old age. *Behav Genet* 2004, 34(5), 533-539.

Egan, MF; Goldberg, TE; Gscheidle, T; Weirich, M; Rawlings, R; Hyde, TM; Bigelow, L; Weinberger, DR. Relative risk for cognitive impairments in siblings of patients with schizophrenia. *Biol Psychiatry* 2001, 50(2), 98-107.

Egan, MF; Kojima, M; Callicott, JH; Goldberg, TE; Kolachana, BS; Bertolino, A; Zaitsev, E; Gold, B; Goldman, D; Dean, M; Lu, B; Weinberger, DR. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 2003, 112(2), 257-269.

Faraone, SV; Seidman, LJ; Kremen, WS; Pepple, JR; Lyons, MJ; Tsuang, MT. Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a diagnostic efficiency analysis. *J Abnorm Psychol* 1995, 104(2), 286-304.

Faraone, SV; Seidman, LJ; Kremen, WS; Toomey, R; Pepple, JR; Tsuang, MT. Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a 4-year follow-up study. *J Abnorm Psychol* 1999, 108(1), 176-181.

Finkel, D; Pedersen, NL; McGue, M; McClearn, GE. Heritability of cognitive abilities in adult twins: comparison of Minnesota and Swedish data. *Behav Genet* 1995, 25(5), 421-431.

Franke, P; Gansicke, M; Schmitz, S; Falkai, P; Maier, W. Differential memory span-abnormal lateralization pattern in schizophrenic patients and their siblings? *Int J Psychophysiol* 1999, 34(3), 303-311.

Gabrys, JB; Schumph, D; Utendale, KA. Short-term memory for two meaningful stories and self-report on the Adult Eysenck Personality Questionnaire. *Psychological Reports* 1987, 61, 51-59.

Gasperoni, TL; Ekelund, J; Huttunen, M; Palmer, CG; Tuulio-Henriksson, A; Lonnqvist, J; Kaprio, J; Peltonen, L; Cannon, TD. Genetic linkage and association between chromosome 1q and working memory function in schizophrenia. *Am J Med Gen* 2003, 116(1suppl), 8-16.

Goldberg, TE; Weinberger, DR; Pliskin, NH; Berman, KF; Podd, MH. Recall memory defcit in schizophrenia. A possible manifestation of prefrontal dysfunction. *Schizophr Res* 1989, 2**,** 251–257.

Goldberg, TE; Aloia, MS; Gourovitch, ML; Missar, D; Pickar, D; Weinberger, DR. Cognitive substrates of thought disorder, I: the semantic system. *Am J Psychiatry* 1998, 155(12), 1671-1676.

Goldberg, TE; Egan, MF; Gscheidle, T; Coppola, R; Weickert, T; Kolachana, BS; Goldman, D; Weinberger, DR. Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. *Arch Gen Psychiatry* 2003, 60(9), 889-896.

Golimbet, VE; Manandian, KK; Abramova, LI; Orlova, VA; Kaleda, VG; Oleichik, IV; Iurov, IuB; Trubnikov, VI. Serotonin receptor gene allele polymorphism (5HTR2A) and clinical pathogenetic characteristics in patients with schizophrenia and schizophrenia spectrum disorders. *Zh Nevrol Psikhiatr Im S S Korsakova* 2000, 100(2), 36-39 (Russian).

Golimbet, VE; Alfimova, MV; Manandyan, KK; Mitushina, NG; Abramova, L; Kaleda, VG; Oleichik, IV; Yurov, Y; Trubnikov, VI. 5HTR2A gene polymorphism and personality traits in patients with major psychoses. *Eur Psychiatry* 2002, 17(1), 24-28.

Gottesman, II; Shields, J. Schizophrenia and genetics, Academic Press. New York&London; 1972.

Gottesman, II; Gould, TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 2003, 160, 636-646.

Green, MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 1996, 153(3), 321-330.

Hallmayer, JF; Jablensky, A; Michie, P; Woodbury, M; Salmon, B; Combrinck, J; Wichmann, H; Rock, D; D'Ercole, M; Howell, S; Dragovic, M; Kent, A. Linkage analysis of candidate regions using a composite neurocognitive phenotype correlated with schizophrenia. *Mol Psychiatry* 2003, 8(5), 511-523.

Herlitz, A; Nilsson, L.G; Bäckman, L. Gender differences in episodic memory. (Data from first test session). *Memory and Cognition* 1997, 25, 801-811.

Hoff, AL; Svetina, C; Maurizio, AM; Crow, TJ; Spokes, K; DeLisi, LE. Familial cognitive deficits in schizophrenia. *Am J Med Genet B Neuropsychiatr Genet*. 2005, 133(1), 43-49.

Jensen, AR; Marisi, DQ. A note on the heritability of memory span. *Behavior Genetics* 1979, 9(5), 379-387.

Johnson, JK; Tuulio-Henriksson, A; Pirkola, T; Huttunen, MO; Lonnqvist, J; Kaprio, J; Cannon, TD. Do schizotypal symptoms mediate the relationship between genetic risk for schizophrenia and impaired neuropsychological performance in co-twins of schizophrenic patients? *Biol Psychiatry* 2003, 54, 1200-1204.

Joober, R; Bendelfat, C; Brisebois, K; Toulouse, A; Turecki, G; Lal, S; Bloom, D; Labelle, A; Lalonde, P; Fortin, D; Alda, M; Palmour, R; Rouleau, GA. T102C polymorphism in the 5HTR2A gene and schizophrenia: relation to phenotype and drug response variability. *J Psychiatr Neurosci* 1999, 24, 141-146.

Kay, SR; Fizbein, A; Opler, LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987,13, 261-276.

Keefe, RS; Silverman, JM; Roitman, SE; Harvey, PD; Duncan, MA; Alroy, D; Siever, LJ; Davis, KL; Mohs, RC. Performance of nonpsychotic relatives of schizophrenic patients on cognitive tests. *Psychiatry Res* 1994, 53(1), 1-12.

Kendler, KS; Thacker, L; Walsh, D. Self-report measures of schizotypy as indices of familial vulnerability to schizophrenia. *Schizophr Bull* 1996, 22(3), 511-520.

Kremen, WS; Seidman, LJ; Pepple, JR; Lyons, MJ; Tsuang, MT; Faraone, SV. Neuropsychological risk indicators for schizophrenia: a review of family studies. *Schizophr Bull* 1994, 20(1), 103-119.

Kremen, WS; Goldstein, JM; Seidman, LJ; Toomey, R; Lyons, MJ; Tsuang, MT; Faraone, SV. Sex differences in neuropsychological function in non-psychotic relatives of schizophrenic probands. *Psychiatry Res* 1997, 66(2-3), 131-144.

Kremen, WS; Faraone, SV; Seidman, LJ; Pepple, JR; Tsuang, MT. Neuropsychological risk indicators for schizophrenia: a preliminary study of female relatives of schizophrenic and bipolar probands. *Psychiatry Res* 1998 79(3), 227-240.

Laurent, A; Moreaud, O; Bosson, JL; Naegele, B; Boucharlat, J; Saoud, M; Dalery, J; D'Amato, T. Neuropsychological functioning among non-psychotic siblings and parents of schizophrenic patients. *Psychiatry Res* 1999, 87(2-3), 147-157.

Laurent, A; d'Amato, T; Naegele, B; Murry, P; Baro, P; Foussard, N; Spitz, F; Dalery, J. Executive and amnestic functions of a group of first-degree relatives of schizophrenic patients. *Encephale* 2000, 26(5), 67-74.

Lerer, B; Segman, RH; Tan, EC; Basile, VS; Cavallaro, R; Aschauer, HN; Strous, R; Chong, SA; Heresco-Levy, U; Verga, M; Scharfetter, J; Meltzer, HY; Kennedy, JL; Macciardi, F. Combined analysis of 635 patients confirms an age-related association of the serotonin 2A receptor gene with tardive dyskinesia and specificity for the non-orofacial subtype. *Int J Neuropsychopharmacol* 2005, 8(3), 411-425.

Luria, AR. *Neuropsychology of Memory (Memory Disturbances in Deep Lesions of the Brain)*. Pedagogika. Moscow; 1976.

Lyons, MJ; Toomey, R; Seidman, LJ; Kremen, WS; Faraone, SV; Tsuang, MT. Verbal learning and memory in relatives of schizophrenics: preliminary findings. *Biol Psychiatry* 1995, 37(10), 750-753.

Lysaker, PH; Davis, LW. Social function in schizophrenia and schizoaffective disorder: Associations with personality, symptoms and neurocognition. *Health and Quality of Life Outcomes* 2004, 2, 15.

Meier, B; Perrig-Chiello, P; Perrig, W. Personality and memory in old age. *Aging Neuropsychol Cognit* 2002, 9, 135–144.

Nance, WE; Corey, LA. Genetic models for the analysis of data from the families of identical twins. *Genetics* 1976, 83(4), 811-826.

Ngan, ET; Yatham, LN; Ruth, TJ; Liddle, PF. Decreased serotonin 2A receptor densities in neuroleptic-naive patients with schizophrenia: A PET study using [(18)F]setoperone. *Am J Psychiatry* 2000, 157(6), 1016-1018.

Norton, N; Owen, MJ. HTR2A: association and expression studies in neuropsychiatric genetics. *Ann Med* 2005, 37(2), 121-129.

O'Driscoll, GA; Florencio, PS; Gagnon, D; Wolff, AV; Benkelfat, C; Mikula, L; Lal, S; Evans, AC. Amygdala-hippocampal volume and verbal memory in first-degree relatives of schizophrenic patients. *Psychiatry Res* 2001, 107(2), 75-85.

O'Leary, DS; Flaum, M; Kesler, ML; Flashman, LA; Arndt, S; Andreasen, NC. Cognitive correlates of the negative, disorganized, and psychotic symptom dimensions of schizophrenia. *J Neuropsychiatry Clin Neurosci* 2000, 12, 4-15.

Polesskaya, O; Sokolov, B. Differential expression of the "C" and "T" alleles of the 5-HTR2A receptor gene in the temporal cortex of normal individuals and schizophrenics. *L Neurosci Res* 2002, 67, 812-22.

Pralong, D; Tomaskovic-Crook, E; Opeskin, K; Copolov, D; Dean, B. Serotonin (2A) receptors are reduced in the planum temporale from subjects with schizophrenia. *Schizophr Res* 2000, 44(1), 35-45.

Quervain, DJF; Henke, K; Aerni, A; Coluccia, D; Wollmer, MA; Hock, C; Nitsch, RM; Papassotiropoulos, A. A functional genetic variation of 5-HT2a receptor affects human memory. *Nat Neurosci* 2003, 6(11), 1141-1142.

Rolls, ET. Memory Systems in the Brain. *Annu Rev Psychol* 2000, 51, 599-630.

Schubert, EW; McNeil, TF. Neuropsychological impairment and its neurological correlates in adult offspring with heightened risk for schizophrenia and affective psychosis. *Am J Psychiatry* 2005, 162(4), 758-766.

Segman, RH; Heresco-Levy, U; Finkel, B; Goltser, T; Shalem, R; Schlafman, M; Dorevitch, A; Yakir, A; Greenberg, D; Lerner, A; Lerer, B. Association between the serotonin 2A receptor gene and tardive dyskinesia in chronic schizophrenia. *Mol Psychiatry* 2001, 6(2), 225-229.

Sitskoorn, MM; Aleman, A; Ebisch, SJ; Appels, MC; Kahn, RS. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. *Schizophr Res* 2004, 71(2-3), 285-295.

Sitskoorn MM, Ebisch SJ, Appels M, Nuyen J, Kahn RS. Memory profiles in parents of patients with schizophrenia. *Psychiatry Res* 2004, 128(1), 27-37.

Snitz, BE; Macdonald, AW 3rd; Carter, CS. Cognitive Deficits in Unaffected First-Degree Relatives of Schizophrenia Patients: A Meta-analytic Review of Putative Endophenotypes. *Schizophr Bull* 2005 (in press).

Sponheim, SR; Steele, VR; McGuire, KA. Verbal memory processes in schizophrenia patients and biological relatives of schizophrenia patients: intact implicit memory, impaired explicit recollection. *Schizophr Res* 2004, 71(2-3), 339-348.

Squires-Wheeler, E; Friedman, D; Amminger, GP; Skodol, A; Looser-Ott, S; Roberts, S; Pape, K; Erlenmeyer-Kimling, L. Negative and positive dimensions of schizotypal personality disorder. *J Personal Disord* 1997, 11(3), 285-300.

Szoke, A; Schurhoff, F; Mathieu, F; Meary, A; Ionescu, S; Leboyer, M. Tests of executive functions in first-degree relatives of schizophrenic patients: a meta-analysis. *Psychol Med*. 2005, 35(6), 771-782.

Thapar, A; Petrill, SA; Thompson, LA. The heritability of memory in the Western Reserve Twin Project. *Behav Genet* 1994, 24(2), 155-160.

Toomey, R; Faraone, SV; Seidman, LJ; Kremen, WS; Pepple, JR; Tsuang, MT. Association of neuropsychological vulnerability markers in relatives of schizophrenic patients. *Schizophr Res* 1998, 31(2-3), 89-98.

Toulopoulou, T; Rabe-Hesketh, S; King, H; Murray, RM; Morris, RG. Episodic memory in schizophrenic patients and their relatives. *Schizophr Res*. 2003; 63(3):261-271.

Toulopoulou, T; Murray, RM. Verbal memory deficit in patients with schizophrenia: an important future target for treatment. *Expert Rev Neurother* 2004, 4(1), 43-52.

Trubnikov, VI; Gindilis, VM. A tabulated method of component partioning of phenotypic variance based on correlations between relatives. *Genetica 1981*, no. 11: 2034-2043.

Tulving, E. How many memory systems are there? *Am Psych* 1985, 40, 385-398.

Tuulio-Henriksson, A; Haukka, J; Partonen, T; Varilo, T; Paunio, T; Ekelund, J; Cannon, TD; Meyer, JM; Lonnqvist, J. Heritability and number of quantitative trait loci of neurocognitive functions in families with schizophrenia. *Am J Med Genet* 2002, 114(5), 483-490.

Tuulio-Henriksson, A; Partonen, T; Suvisaari, J; Haukka, J; Lonnqvist, J. Age at onset and cognitive functioning in schizophrenia. *The British Journal of Psychiatry* 2004, 185, 215-219.

Vollema, MG; Postma, B. Neurocognitive correlates of schizotypy in first degree relatives of schizophrenia patients. *Schizophr Bull* 2002, 28(3), 367-377.

Warren, JT; Peacock, ML; Rodrigues, LC; Fink, AG. An Msp1 polymorphism in the human serotonin receptor gene (5HTR2A): Detection by DGGE and FLP analysis. *Hum Mol Genet* 1993, 2, 338.

Whyte, MC; McIntosh, AM; Johnstone, EC; Lawrie, SM. Declarative memory in unaffected adult relatives of patients with schizophrenia: a systematic review and meta-analysis. *Schizophr Res* 2005, 78(1), 13-26.

Williams, J; Mc Guffin, P; Nothen, M.M; Owen M.J. Meta-analysis of association between the 5-HT2a receptor T102C polymorphism and schizophrenia. EMASS Collaborative group. European Multicenter Association Study of Schizophrenia. *Lancet* 1997, 349, 1221.

Wilson, RS; Fleischman, DA; Myers, RA; Bennett, DA; Bienias, JL; Gilley, DW; Evans, DA. *Premorbid proneness to distress and episodic memory impairment in Alzheimer's disease Journal of Neurology Neurosurgery and Psychiatry* 2004, 75, 191-195.

Wittorf, A; Klingberg, S; Wiedemann, G. Secondary verbal memory: a potential endophenotype of schizophrenia. *J Psychiatr Res*. 2004, 38(6), 601-612.