SCHIZOAFFECTIVE PSYCHOSIS AND SCHIZOPHRENIA
WITH- OR WITHOUT AFFECTIVE SYNDROME: A
COMPARATIVE CLINICAL, NEUROPSYCHOLOGICAL
AND MOLECULAR-GENETIC STUDY

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INTRODUCTION

Schizoaffective disorder (SA) is a nosological category included in many classifications of diseases, i.e. ICD-10 and DSM-IV. Main diagnostic features of the disorder are combination of schizophrenic and affective symptoms and favorable outcome. However an overlap of these criteria with both affective disorders and schizophrenia challenges the diagnostic validity of SA (Welner 1977; Tsuang & Simpson 1984). Multiple studies have been devoted to elucidation whether SA was a separate clinical entity or it should be considered as schizoaffective syndrome in clinical presentation of the above mentioned illnesses. Several hypotheses on the nature of schizoaffective psychosis have been delineated (Brockington & Meltzer 1983; Marneros 2003), according to which the disorder was supposed (1) to be a variant or an expression of either schizophrenia or affective psychosis; (2) to occur as a result of comorbidity of schizophrenia with mood disorders and (3) to be a piece of the spectrum of clinical states from “pure” schizophrenia to “pure affective psychosis”.

To test these hypotheses, different designs were explored. Most often, researchers compared schizoaffective psychosis with schizophrenia and bipolar disorder with or without psychotic symptoms (Evans 1999; Benabarre 2001; Marneros 2004; Averill 2004). More detailed models analyzed a broader range of states, in particular those comprising various

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subtypes of schizoaffective psychosis, e.g. (1) mainly affective (affective dominant) and mainly schizophrenic (schizodominant) ones (Meltzer 1984); (2) “concurrent” or “sequential” subtypes (Marneros 2003-a); (3) a subtype with non-progressive phase dynamics and a schizoaffective subtype of attack-like progressive schizophrenia (Panteleeva & Bologov 2002).

At the same time, the differences between SA and schizophrenia with affective syndrome (SPA) are understudied though the latter is recognized as a common and rather frequent feature of schizophrenia, ranging from 6% to 50% (Sands & Harrow 1999). Its existence and relevance were confirmed by a number of factor analytic studies of clinical symptoms (Kay, Sevy 1990; Lindenmayer 1994; Wolthaus et al 2000; Lykouras et al 2000; Lancon et al 2000; El Yazaji et al 2002) and it was suggested as a possible endophenotype of schizophrenia (McGrath et al 2004).

In the present study, we compared clinical, personality, cognitive, and molecular-genetic characteristics of patients with SA, SPA and schizophrenia without affective syndrome (SP) and attempted to mark out the main features that may be specific for SA.

To date, a number of studies have been conducted to differentiate SA and schizophrenia on the base of clinical variables and personality or neurocognitive characteristics. In contrast, in psychiatric genetics SA did not gain much attention as a categorical definition. A vast body of research in the field operates with so called “broad definition” of schizophrenia, which comprises SA and spectrum disorders. Due to epidemiological data, a proportion of SA cases in such investigations may vary from 10 to 30% (Meltzer et al 1984; Levinson et al 1999). To our knowledge, no studies, except that of Kaiser et al (2001), have been carried out so far to compare allele and genotype distribution of any candidate gene between schizophrenia and SA.

To investigate molecular genetic characteristics of SA, SP and SPA, we selected a set of genes, which have been previously reported to play a role in etiology and pathogenesis of major psychoses. These were genes for serotonin transporter (5-HTT), serotonin receptor type 2A (5-HTR2A) and brain-derived neurotrophic factor (BDNF).

5-HTT is implicated in the regulation of serotonin neurotransmission by removing serotonin from the synaptic cleft thus modulating serotonergic signaling. The 5-HTT gene bears a polymorphism in the 5-HTT gene-linked polymorphic region (5-HTTLPR) located approximately 1 kb upstream of the transcription initiation site in chromosome 17. The polymorphism is represented by two alleles distinguished by different number of repeats and assigned the long (l) and the short (s) alleles. The alleles have been reported to determine differences in 5-HTT expression, with a higher rate of expression in case of the ll genotype comparing to the ls and ss variants (Lesch et al 1996). A number of studies demonstrated a role of the s allele in etiology of mood disorders, preferably major depressive disorder (Steffens et al 2002; Nellisery et al 2003; Nobile et al 2004; Hoefgen et al 2005) but not schizophrenia (Tsai et al 2000; Serretti et al 2002; Pae et al 2005; Dubertret et al 2005).

BDNF, a neurotrophin found primarily in the neocortex, hippocampus, and amygdale, is thought to affect the mechanisms involved in cell formation, cell death, and/or neuroplasticity. In animal studies, BDNF was shown to promote the function and growth of serotonin (5-HT) neurons in the brain (Mamounas et al 1995). The gene is localized on the short arm of chromosome 11. The Val66Met single nucleotide polymorphism (SNP) that determines a valine-to-methionine substitution at position 66 has been described in the coding region and tested for association with various mental disorders. It was shown that this
polymorphism was associated with bipolar affective disorder (Sklar et al 2002; Neves-Pereira et al 2002), with the Val allele contributing to susceptibility to the disease. The Met allele was found to be protective against depression (Strauss et al 2005) and obsessive-compulsive disorder (Hall et al 2003). However in some populations, the association between Val66Met polymorphism and affective disorders was not observed (Tsai et al 2003; Oswald et al 2004; Kunugi et al 2004). The results on relation of the Val66Met polymorphism to schizophrenia are even less persuasive. In some studies, the association between this gene and the disorder was found (Neves-Pereira et al 2005) but was not confirmed in the others (Virgos et al 2001; Skibinska et al 2004).

5-HTR2A is thought to be involved in the pathology of schizophrenia and the effects of some antipsychotic drugs as well (Dean 2003). A decrease in the number of these receptors and alterations of mRNA expression were found in the prefrontal cortex of postmortem brains of schizophrenic patients (Harrison et al 1997; Hernandez & Sokolov 2000; Matsumoto et al 2005) and in patients with depression (Mintun et al 2004). At the same time, the results of other studies revealed an increase of the 5-HTR2A in affective and schizoaffective patients (Hrdina et al 1997; Pandey et al 2003). The T102C polymorphism in exon 1 of the 5-HTR2A gene yielded the most promising results in associative studies of schizophrenia, with higher frequency of the CC genotype being observed in schizophrenic populations as compared to controls (see meta-analysis Williams et al 1997; Abdolmaleky et al 2004). Some studies, including our own, reported that the CC genotype frequency was higher in schizophrenic patients with severer negative symptoms and chronic course of the disease (Joober et al 1999; Golimbet et al 2002).

**Subjects and Methods**

**Patients**

A sample included 877 patients (507 females, 370 males; age 39±14 years, age at onset 26±10.6 years) with schizophrenia and 185 patients with SA (demographic and clinical characteristics are presented in Table 1) who were admitted to clinical departments of Mental Health Research Center. Patients with organic brain disorders or severe somatic diseases were withdrawn from the study. 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 the senior researchers (Kaleda VG & Abramova LI).

When criteria for SA were met, a classification was made into manic (51 (27.6%) patients), depressed (90 (48.6%)), or bipolar (34 (18.4%)) subtypes. For 10 patients (5.4%) the subtype was not specified. The group of schizophrenic patients was stratified according to the presence or absence of affective syndrome. Out of the total sample, 170 patients had affective syndrome and 702 had not. Five patients were excluded from the study because of ambiguous data on the presence of affective syndrome. Clinical and demographic characteristics of patients are presented in Table 1. Most of schizophrenic patients (601 or 85.6%) in the SP group were diagnosed with paranoid schizophrenia; the other had a diagnosis of catatonic, hebephrenic, residual, simple and not otherwise specified subtypes. Fifty four patients (7.7%) met the diagnosis of schizotypal personality disorder and 8 (1.1%)
of acute psychotic disorder. In the SPA group, there were 129 (75.9%) patients with paranoid subtype of schizophrenia, 16 (9.4%) patients with other subtypes and 25 (14.7%) with schizotypal personality disorder. Thirty-two patients (18.8%) had a syndrome of mania and 138 (81.2%) a depressive syndrome.

Controls

A control group was recruited randomly from community and psychometrically screened before genotyping. The exclusion criteria were the presence of familial history of major psychosis and scores above 40 on Schizotypal Personality inventory (SPQ-74) and above 90 on the F scale of the Minnesota Multiphasic Personality Inventory (MMPI), which the participants have been suggested to complete. In total, 338 subjects (138 men, 250 women, mean age 32.7 (13.8) years) have been included in the analysis.

Clinical Variables

Age at the initial stage of the disease was established as the time of first signs of illness that could be noticed by the relatives and significant others before patient’s referring to a psychiatrist. Age at the disease onset was registered by the time of establishing a diagnosis. Clinical symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS). The PANSS (Kay et al 1987) is a widespread instrument proven to be valid and suitable for quantitative clinical studies. It includes three subscales measuring 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 PANSS interviews completed by a trained researcher were conducted one week before the patient’s discharge from the hospital.

Table 1. Clinical and demographic characteristics of patients with schizophrenia with (SPA) and without (SP) affective syndrome and schizoaffective psychosis (SA)

<table>
<thead>
<tr>
<th>Clinical and demographic characteristics</th>
<th>SP (n=702)</th>
<th>SPA (n=170)</th>
<th>SA (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>295</td>
<td>74</td>
<td>81</td>
</tr>
<tr>
<td>Females</td>
<td>407</td>
<td>96</td>
<td>104</td>
</tr>
<tr>
<td>Age, years</td>
<td>39.3 (14.0)</td>
<td>37.7 (14.4)</td>
<td>30.7 (11.6)</td>
</tr>
<tr>
<td>Age at initial stage of the disease, years</td>
<td>21.5 (9.8)</td>
<td>23.0 (11.5)</td>
<td>20.4 (8.3)</td>
</tr>
<tr>
<td>Age at the disease onset, years</td>
<td>25.8 (10.5)</td>
<td>26.7 (11.4)</td>
<td>24.9 (8.5)</td>
</tr>
<tr>
<td>Illness duration, years</td>
<td>13.5 (3.7)</td>
<td>11.0 (3.1)</td>
<td>5.8 (3.4)</td>
</tr>
<tr>
<td>Cases with illness duration less than one year</td>
<td>46 (6.7%)</td>
<td>11 (8.5%)</td>
<td>59 (31.9%)</td>
</tr>
</tbody>
</table>

1 mean, standard deviation (SD);
2 SP vs SA (t=7.6; df=885; p<0.0001);
3 SP vs SA (t=25.6; df=885; p<0.0001); SPA vs SA (t=15.0; df=353; p<0.0001); SP vs SPA (t=8.1; df=870; p<0.0001);
4 number of patients (%).
Personality Questionnaires

Translated and adapted versions of the Eysenck Personality Inventory (EPI), MMPI, and the State Trait Anxiety Inventory (STAI) were administered to measure personality traits. 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 (1), Depression (2), Hysteria (3), Psychopathic deviate (4), Masculinity-Femininity (5), Paranoia (6), Psychasthenia (7), Schizophrenia (8), Hypomania (9) and Social introversion (0). STAI includes 20 items measuring trait anxiety. To reduce an influence of affected status on evaluation of personality traits, the patients were administered to psychometric assessment after an improvement of their clinical state being assessed as 1 or 2 or 3 with Global Clinical Impression scale. The patients completed the questionnaires themselves or with the assistance of a psychologist. Criteria for MMPI validity were: L < 70 T-scores, F < 90 T-scores and K < 80 T-scores. Only valid profiles were used in the subsequent analysis.

Cognitive Assessment

An extensive battery of neuropsychological tests was performed as described in detail elsewhere (Alfimova, Uvarova 2003). For the present analysis, 4 tasks, measuring verbal memory and executive functions, have been selected from the battery.

Verbal memory tasks:

- An immediate 10-noun free recall test to measure short-term memory. 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 short-term memory score is the total number of words correctly recalled over two trials.
- The “Pictograms” Test to measure long-term memory. 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 a delayed recall of deeply encoded verbal stimuli.

Executive function tasks:

- A variant of the Controlled Oral Word Association Test to measure verbal fluency. 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.
- A serial subtraction test to measure working memory, i.e. the capacity to hold and manipulate information in mind while performing a cognitive task. Mental serial
subtraction by seven has been utilized by psychiatrists for many years to assess the patient's attention. Herzog and Wallace (1997) have argued that this is a measure of working memory. We used a difficult, hard-load version of the task, in which subjects were instructed to subtract successively 5 and 2, by turns, from a previous result, beginning with 200. The number of correct operations, produced within one minute, was used as a measure of sustained attention and working memory.

**Ethical Requirements**

After being informed about the goals of the investigation, each subject gave a written informed consent to participate in the study and donated venous blood for DNA extraction. The study was approved by the Ethics Committee of Mental Health Research Center.

**Genotyping**

To avoid ethnical stratification biases, only Russians were included in the study. DNA was extracted using phenol-chloroform method. Primers for 5-HTTLPR, 5-HTR2A and BDNF genotyping and PCR performance were as described in Lesch et al 1996, Warren et al 1993, Neves-Pereira et al 2002, respectively.

To detect the 5-HTTLPR polymorphism, amplification products were resolved by electrophoresis on 5% polyacrilamide gel (PAAG). Alleles of interest were designated the “s” for 484 base pairs (bp) and the “l” for 528 bp. For the 5-HTR2A T102C polymorphism, MspI digestion was used with subsequent electrophoretic separation on the 2% agarose gel. The intact DNA fragment (342 bp) was assigned the A1 (T) allele and the fragment with the MspI restriction site presented by 2 bands (216 and 126 bp) - the A2 (C) allele. BDNF polymorphism was determined using PspC I digestion and 5% PAAG electrophoresis. The A or Met allele was represented by a 113 bp DNA fragment and the G or Val allele comprised the bands of 78 and 35 bp.

**Statistical Procedures**

Personality and cognitive measures were compared using Student t-test. Because of rank characteristics of the PANSS ratings, Mann-Whitney (U) test was applied for between-group comparisons by the PANSS scores. Allele and genotype frequencies were compared using $\chi^2$ criterion. Odds ratio (OR) was estimated in case of significant differences between categorical variables. All statistical analyses were performed using the Graph Pad Prism 4.0 statistical package.
RESULTS

As presented in Table 1, patients’ ages at initial stage and at onset of the disease were similar in the groups studied. All the groups differed significantly (p<0.0001) in illness duration, which was the longest in SP patients and the shortest in SA ones. Also the SP group was featured by the older mean age comparing to the SA group. The number of patients with the illness duration less than one year was the highest in the SA group (31.9%) and of similar values for the SP (6.7%) and SPA (8.5%) groups.

Clinical symptoms in patients measured by the PANSS are presented in Table 2. All groups differed by clinical presentations. Positive symptoms were mostly pronounced in patients with SP, while the SPA and SA groups had similar scores. Negative symptoms tended to gradual decreasing as SP>SPA>SA, with statistically significant differences between all the groups. As concerns general psychopathological symptoms, patients both with SPA and SA had higher scores on anxiety and depressive-related items as compared to the SP group. The latter was featured by the highest scores on the items related to cognitive and volition symptoms which, analogous to negative symptoms, decreased gradually in the SPA and SA groups. When compared by scores on the PANSS subscales, the SA group had the lowest ratings as on each of subscales as well in total (Table 3).

All the groups differed in personality traits from the controls demonstrating higher levels of neuroticism and anxiety, lower levels of extraversion and variants of MMPI schizophrenic-type profiles (Table 4, Fig.1). However there were a number of differences between the clinical groups. SA patients had better personality functioning than SP and SPA patients. Extraversion and Neuroticism scores in patients with SA did not differ significantly from controls’ values. On the STAI and MMPI scales, SA patients scored higher comparing to the controls; however none of their MMPI mean scores would be considered elevated outside of normal limits. SA had an 89 (Schizophrenia-Hypomania) profile code (Fig.1), which reflected a combination of moderately pronounced schizoid and hypomanic traits, i.e. alienation, inappropriate behavior, hyperactivity and positive affect, and indicated a relatively good psychological adjustment.

Subjects with SPA showed the most deviated scores on all the personality scales that suggested they were much more compromised on the personality dimensions than subjects with SA and SP. They had a high ranging MMPI profile with marked elevations on scales 8 (Schizophrenia), 7 (Psychasthenia) and 6 (Paranoia) and secondary elevations on scales 2 (Depression) and 1 (Hypochondriasis ) that reflected significant psychological maladjustment and psychiatric symptoms, in particular confused and disorganized thinking, alienation, worrying and a great deal of paranoid traits coupled with anxiety and depression. However, the profiles of the clinical groups differed mainly in level of mean scores, while the patterns were not remarkably different from each other with the exception of the Depression/Hypomania ratio.

Assessment of cognitive functions (Table 5) did not reveal any significant between-group differences although there was a weak trend to better performance on the executive and short-term memory tasks in patients with SA as compared to SP and SPA patients. It should be mentioned that all clinical groups scored significantly lower (p<0.001) on the tests than did the control group.
### Table 2. Means and standard deviations for PANSS items in patients with schizoaffective psychosis (SA) and schizophrenia with- (SPA) or without (SP) affective syndrome

<table>
<thead>
<tr>
<th>PANSS items</th>
<th>SP</th>
<th>SPA</th>
<th>SA</th>
<th>SP vs SPA U (Mann-Whitney)</th>
<th>SPA vs SA U</th>
<th>SP vs SA U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>4.5 (1.6)</td>
<td>3.6 (1.7)</td>
<td>3.8 (1.8)</td>
<td>27770*</td>
<td>ns</td>
<td>27690*</td>
</tr>
<tr>
<td>Conceptual disorganization</td>
<td>4.3 (1.3)</td>
<td>.4 (1.4)</td>
<td>3.3 (1.5)</td>
<td>25670*</td>
<td>ns</td>
<td>21380*</td>
</tr>
<tr>
<td>Hallucinatory behavior</td>
<td>3.6 (1.8)</td>
<td>2.4 (1.6)</td>
<td>2.2 (1.6)</td>
<td>24770*</td>
<td>ns</td>
<td>20260*</td>
</tr>
<tr>
<td>Excitement</td>
<td>3.1 (1.5)</td>
<td>2.3 (1.5)</td>
<td>3.0 (1.9)</td>
<td>28890*</td>
<td>7132**</td>
<td>ns</td>
</tr>
<tr>
<td>Grandiosity</td>
<td>2.4 (1.6)</td>
<td>1.8 (1.3)</td>
<td>2.1 (1.7)</td>
<td>31340*</td>
<td>ns</td>
<td>30460**</td>
</tr>
<tr>
<td>Suspiciousness/ persecution</td>
<td>3.9 (1.5)</td>
<td>3.2 (1.6)</td>
<td>3.0 (1.9)</td>
<td>31080*</td>
<td>ns</td>
<td>25970*</td>
</tr>
<tr>
<td>Hostility</td>
<td>3.0 (1.6)</td>
<td>2.3 (1.4)</td>
<td>2.3 (1.6)</td>
<td>30450*</td>
<td>ns</td>
<td>26640*</td>
</tr>
<tr>
<td>Blunted affect</td>
<td>4.0 (1.3)</td>
<td>3.5 (1.2)</td>
<td>2.5 (1.2)</td>
<td>31240*</td>
<td>5205*</td>
<td>14600*</td>
</tr>
<tr>
<td>Emotional withdrawal</td>
<td>3.8 (1.3)</td>
<td>3.4 (1.3)</td>
<td>2.1 (1.2)</td>
<td>33750**</td>
<td>4418*</td>
<td>12980*</td>
</tr>
<tr>
<td>Poor rapport</td>
<td>3.9 (1.3)</td>
<td>3.3 (1.3)</td>
<td>2.3 (1.3)</td>
<td>29170*</td>
<td>5365*</td>
<td>14050*</td>
</tr>
<tr>
<td>Passive/apathetic social withdrawal</td>
<td>3.9 (1.5)</td>
<td>3.3 (1.3)</td>
<td>2.0 (1.1)</td>
<td>32010*</td>
<td>4215*</td>
<td>11980*</td>
</tr>
<tr>
<td>Difficulty in abstract thinking</td>
<td>3.7 (1.6)</td>
<td>2.6 (1.3)</td>
<td>2.0 (1.0)</td>
<td>25370*</td>
<td>6300*</td>
<td>13790*</td>
</tr>
<tr>
<td>Lack of spontaneity</td>
<td>3.5 (1.5)</td>
<td>2.8 (1.4)</td>
<td>2.1 (1.1)</td>
<td>31380*</td>
<td>6155*</td>
<td>16980*</td>
</tr>
<tr>
<td>Sterotyped thinking</td>
<td>3.9 (1.4)</td>
<td>3.1 (1.3)</td>
<td>1.9 (1.1)</td>
<td>27500*</td>
<td>4609*</td>
<td>10560*</td>
</tr>
<tr>
<td>Somatic concern</td>
<td>2.2 (1.4)</td>
<td>2.9 (1.6)</td>
<td>1.9 (1.3)</td>
<td>29890*</td>
<td>5801*</td>
<td>31120***</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2.7 (1.4)</td>
<td>3.4 (1.4)</td>
<td>3.1 (1.4)</td>
<td>29850*</td>
<td>ns</td>
<td>30530***</td>
</tr>
<tr>
<td>Guilt feelings</td>
<td>1.5 (1.1)</td>
<td>2.5 (1.6)</td>
<td>2.1 (1.5)</td>
<td>26750*</td>
<td>7479***</td>
<td>30160**</td>
</tr>
<tr>
<td>Tension</td>
<td>3.6 (1.4)</td>
<td>3.1 (1.3)</td>
<td>3.1 (1.3)</td>
<td>32730**</td>
<td>ns</td>
<td>28340**</td>
</tr>
<tr>
<td>Mannerism and posturing</td>
<td>3.4 (1.4)</td>
<td>2.8 (1.4)</td>
<td>2.4 (1.2)</td>
<td>30830*</td>
<td>7523***</td>
<td>21600*</td>
</tr>
<tr>
<td>Depression</td>
<td>2.0 (1.3)</td>
<td>3.9 (1.8)</td>
<td>3.4 (1.8)</td>
<td>17880*</td>
<td>ns</td>
<td>19990*</td>
</tr>
</tbody>
</table>
Motor retardation  2.7 (1.4)  3.1 (1.5)  2.4 (1.4)  34920***  6914**  31600***

Uncooperativeness  3.3 (1.6)  2.5 (1.4)  2.1 (1.4)  29860*  7311**  20960*

Unusual thought content  3.9 (1.7)  2.9 (1.6)  2.6 (1.8)  28180*  ns  22870*

Disorientation  1.8 (1.2)  1.4 (0.9)  1.3 (0.9)  33560**  ns  26540*

Poor attention  3.8 (1.3)  3.3 (1.2)  3.3 (1.1)  33010**  ns  26790*

Lack of judgment and insight  5.1 (1.3)  4.2 (1.4)  4.2 (1.7)  26540*  ns  24480*

Disturbance of volition  3.8 (1.3)  3.3 (1.2)  3.0 (1.1)  30770*  7583***  21920*

Poor impulse control  2.6 (1.6)  2.0 (1.3)  2.0 (1.3)  30490*  ns  26760*

Preoccupation  4.2 (1.4)  3.8 (1.2)  3.4 (1.4)  33000**  7376***  24160*

Active social avoidance  4.0 (1.4)  3.5 (1.3)  3.0 (1.4)  30460*  7429***  1300*

p<0.0001; ** p<0.001; *** p=<0.01; ns – non-significant.

MMPI scales: L, F, K (validity scales), Hypochondriasis (HS), Depression (D), Hysteria (Hy), Psychopathic deviate (Pd), Masculinity-Femininity (Mf), Paranoia (Pa), Psychasthenia (Pt), Schizophrenia (Sc), Hypomania (Ma) and Social introversion (Si).

Subjects with SPA showed the most deviated scores on all the scales that suggested that they were much more compromised on the personality dimensions than subjects with SA and SP.

Figure 1. MMPI profiles of the SP, SPA and SA groups.
Table 3. Means and standard deviations for PANSS subscales in patients with schizoaffective psychosis (SA) and schizophrenia with (SPA) - or without (SP) affective syndrome

<table>
<thead>
<tr>
<th>PANSS subscales</th>
<th>SP (n=567)</th>
<th>SPA (n=143)</th>
<th>SA (n=126)</th>
<th>SP vs SPA U (Mann-Whitney)</th>
<th>SPA vs SA U</th>
<th>SP vs SA U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>24.7 (7.8)</td>
<td>19.0 (7.6)</td>
<td>19.3 (9.1)</td>
<td>27090* ns</td>
<td>28760*</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>26.3 (7.8)</td>
<td>22.2 (6.7)</td>
<td>14.5 (6.1)</td>
<td>30250* 4667* 10510*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>50.2 (12.0)</td>
<td>48.5 (11.5)</td>
<td>42.0 (13.0)</td>
<td>ns 7839* 27080*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>101.2 (27.5)</td>
<td>89.7 (25.8)</td>
<td>75.8 (28.1)</td>
<td>28890* 7132* 28060*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p<0.0001; ns – non-significant.

Table 4. Means and standard deviations for the personality traits in patients with schizoaffective psychosis (SA) and schizophrenia with- (SPA) or without (SP) affective syndrome

<table>
<thead>
<tr>
<th>Personality traits Mean (SD)</th>
<th>SP (n=282)</th>
<th>SPA (n=93)</th>
<th>SA (n=118)</th>
<th>controls (n=292)</th>
<th>SP vs SPA t=2.8; df=373; p=0.005;</th>
<th>SP vs SA t=4; df=209; p&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPI</td>
<td>10.3 (3.7)</td>
<td>9.1 (3.2)</td>
<td>11.1 (3.9)</td>
<td>11.6 (3.8)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Neuroticism</td>
<td>12.9 (5.3)</td>
<td>15.0 (4.9)</td>
<td>13.4 (4.9)</td>
<td>12.7 (4.8)</td>
<td>t=3.4; df=373; p=0.001</td>
<td>t=2.4; df=209; p&lt;0.0001</td>
</tr>
<tr>
<td>MMPI</td>
<td>60.8 (13.8)</td>
<td>66.7 (12.7)</td>
<td>57.0 (13.2)</td>
<td>53.3 (11.3)</td>
<td>t=3.1; df=238; p=0.002</td>
<td>t=4.9; df=179; p&lt;0.0001</td>
</tr>
<tr>
<td>Hypochondriasis</td>
<td>60.6 (13.9)</td>
<td>70.2 (14.2)</td>
<td>56.2 (13.4)</td>
<td>50.4 (11.9)</td>
<td>t=4.852; df=238; p&lt;0.0001</td>
<td>t=6.704; df=179; p&lt;0.0001</td>
</tr>
<tr>
<td>Depression</td>
<td>58.6 (11.9)</td>
<td>62.8 (11.7)</td>
<td>56.4 (11.0)</td>
<td>53.5 (10.7)</td>
<td>t=2.5; df=238; p=0.01</td>
<td>t=3.7; df=179; p&lt;0.0003</td>
</tr>
<tr>
<td>Hysteria</td>
<td>59.6 (11.3)</td>
<td>65.3 (9.7)</td>
<td>56.4 (11.7)</td>
<td>53.8 (10.7)</td>
<td>t=3.7; df=238; p=0.0003</td>
<td>t=5.3; df=179; p&lt;0.0001</td>
</tr>
<tr>
<td>Psychopathic deviate</td>
<td>54.8 (11.6)</td>
<td>52.8 (10.9)</td>
<td>52.8 (12.6)</td>
<td>51.5 (11.6)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Masculinity-Femininity</td>
<td>64.3 (11.5)</td>
<td>69.1 (19.2)</td>
<td>60.4 (15.9)</td>
<td>53.7 (12.6)</td>
<td>t=2.4; df=238; p=0.02</td>
<td>t=3.3; df=179; p&lt;0.0001</td>
</tr>
</tbody>
</table>
Schizoaffective Psychosis and Schizophrenia with- or without Affective Syndrome

<table>
<thead>
<tr>
<th>Cognitive variables</th>
<th>SP</th>
<th>SPA</th>
<th>SA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term memory</td>
<td>8.5 (2.7)</td>
<td>9.3 (2.3)</td>
<td>9.7 (1.8)</td>
<td>11.0 (2.3)</td>
</tr>
<tr>
<td>Long-term memory</td>
<td>8.3 (3.6)</td>
<td>8.7 (2.3)</td>
<td>7.9 (2.9)</td>
<td>12.5 (2.8)</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>27.0 (9.5)</td>
<td>29.4 (10.2)</td>
<td>29.6 (9.1)</td>
<td>41.3 (8.6)</td>
</tr>
<tr>
<td>Sustained attention</td>
<td>9.9 (6.5)</td>
<td>7.9 (6.5)</td>
<td>11.2 (5.4)</td>
<td>17.2 (6.9)</td>
</tr>
</tbody>
</table>

All clinical groups differed significantly (p<0.001) from the controls in the cognitive traits measured.

The distribution of 5-HTTLPR, 5-HTR2A and BDNF genotypes was in accordance to Hardy-Weinberg equilibrium, that is, it did not differ from the one expected. Alleles and genotypes frequency of the polymorphisms studied was similar to those of European populations. The results on allele and genotype distribution are presented in Tables 6 and 7.

There were no significant differences in the distribution of 5-HTTLPR alleles and genotypes between the SP, SPA and control groups though the ss genotype frequency tended to be higher in the SPA group (p=0.14). However, in patients with SA, frequency of the s allele and the ss genotype was significantly higher (p=0.02) comparing to SP patients and controls (p=0.01) but did not differ from that in SPA patients. When the SA and SPA groups have been combined, the ss genotype prevalence still remained significantly higher (p=0.02) as compared to either the SP or control groups.

Table 5. Means and standard deviations for the cognitive variables in patients with schizoaffective psychosis (SA) and schizophrenia with- (SPA) or without (SP) affective syndrome
Table 6. The 5-HTTLPR, 5-HTR2A and BDNF genotypes distribution (frequency and number of cases) in the clinical groups and controls

<table>
<thead>
<tr>
<th>Genotype</th>
<th>5-HTTLPR</th>
<th>5-HTR2A</th>
<th>BDNF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LL</td>
<td>LS</td>
<td>SS</td>
</tr>
<tr>
<td>SP</td>
<td>36.6 (98)</td>
<td>47.0 (126)</td>
<td>16.4 (44)</td>
</tr>
<tr>
<td>SPA</td>
<td>29.3 (27)</td>
<td>48.9 (45)</td>
<td>21.7 (20)</td>
</tr>
<tr>
<td>SA</td>
<td>31.6 (24)</td>
<td>36.8 (28)</td>
<td>31.6 (24)</td>
</tr>
<tr>
<td>Controls</td>
<td>36.6 (142)</td>
<td>46.6 (181)</td>
<td>16.8 (65)</td>
</tr>
</tbody>
</table>

Between-group differences in the ll and the ss genotypes frequency:
- SA vs controls - $\chi^2 = 5.9$; df= 1; p=0.01. OR 2.2 (CI 95% 1.2-4.1);
- SA vs SP - $\chi^2 = 5.6$; df= 1; p=0.02. OR 2.2 (CI 95% 1.4-4.3);
- SA vs SPA - $\chi^2 = 5.7$; df= 1; p=0.02. OR 1.8 (CI 95% 1.1-3.0).

Between-group differences in the A1A1 and the A2A2 genotypes frequency:
- SP vs controls - $\chi^2 = 6.3$; df= 1; p=0.01. OR 1.7 (CI 95% 1.1-2.5);
- SA vs controls - $\chi^2 = 8.5$; df= 1; p=0.003. OR 2.4 (CI 95% 1.3-4.3);
- SA vs SPA - $\chi^2 = 5.1$; df= 1; p=0.02. OR 2.3 (CI 95% 1.1-4.6).

For the 5-HTR2A polymorphism, the genotype distribution was similar for SP and SA patients. Comparing to the control group, higher frequency of the A2 allele and the A2A2 genotype (p=0.01) was observed in the SP and SA groups but not in the SPA group. Also, there was significant difference in the frequency of the A1A1 and A2A2 genotypes between the SA and SPA groups.

Table 7. The 5-HTTLPR, 5-HTR2A and BDNF allele distribution (frequency and number of cases) in the clinical groups and controls

<table>
<thead>
<tr>
<th>Genotype</th>
<th>5-HTTLPR</th>
<th>5-HTR2A</th>
<th>BDNF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L</td>
<td>S</td>
<td>n</td>
</tr>
<tr>
<td>SP</td>
<td>60.1 (322)</td>
<td>39.9 (214)</td>
<td>536</td>
</tr>
<tr>
<td>SPA</td>
<td>53.8 (99)</td>
<td>46.2 (85)</td>
<td>184</td>
</tr>
<tr>
<td>SA</td>
<td>50 (76)</td>
<td>50 (76)</td>
<td>152</td>
</tr>
<tr>
<td>Controls</td>
<td>59.9 (465)</td>
<td>40.1 (311)</td>
<td>776</td>
</tr>
</tbody>
</table>

Between-group differences in the l and the s alleles frequency:
- SA vs controls - $\chi^2 = 5.2$; df= 1; p=0.02. OR 1.5 (CI 95% 1.1-2.1);
- SA vs SP - $\chi^2 = 4.9$; df= 1; p=0.03. OR 1.5 (CI 95% 1.1-2.2).

Between-group differences in the A1 and the A2 genotypes frequency:
- SP vs controls - $\chi^2 = 7.0$; df= 1; p=0.008. OR 1.3 (CI 95% 1.1-1.6);
- SA vs controls - $\chi^2 = 8.6$; df= 1; p=0.003. OR 1.5 (CI 95% 1.1-2.0).
The distribution of the BDNF alleles and genotypes did not differ in all the groups studied. A trend to higher frequency of the Met allele-contained genotypes (Met/Met + Val/Met) that failed to reach a level of significance was found in the combined group of SA and SPA patients as compared to SP patients (p=0.08) and control group (p=0.12). The distribution of combined genotypes for 5-HTTLPR and BDNF genes has been also studied. We assumed that these genes might have an additive or interactive effect on the phenotype, especially in case of SA, because BDNF was reported to modulate serotonin transporter function in cells depending on a 5-HTTLPR genotype (Mossner et al 2000). The combinations of interest were as follows: (1) the BDNF Met allele and the 5-HTTLPR ll genotype due to their plausible protection effect against affective disorders and (2) the BDNF GG and 5-HTTLPR ss genotypes, which may predispose to affective disorders. As expected, we found a higher frequency of combined genotypes (Met/Met + Met/Val + ll) versus a genetic variant, comprising Val/Val + ss genotypes, in the control group (49 versus 37 cases respectively). In contrast, an opposite ratio was observed for the above mentioned combinations in the SA group (5 versus 15 cases). This between-group difference in genotype ratio was significant (Chi2=6.0; df=1; p=0.01; OR 4.2; CI 95% 1.3-13.6).

CONCLUSION

Therefore, we demonstrated that patients with SP, SPA and SA had significant differences in clinical, personality, and molecular genetic, but not cognitive, characteristics. Patients with SA were featured by the lowest ratings of negative symptoms, milder psychotic and affective symptoms and less pronounced personality changes. Notably, the dramatic gap was detected between SP and SA whereas the difference between SPA and SA was less striking, especially with regard to positive, affective and disorganization (e.g. conceptual disorganization, unusual thought content) symptoms. Clinical symptoms tended to descend from SP to SA, with SPA taking an interim position, thus suggesting an existence of a certain kind of continuum between these groups. Indirect evidence for the lack of the transparent differentiation is provided by the finding of the younger age at the time of examination, shorter illness duration and a higher percent of the cases with the disease duration less than one year in patients with SA. This fact can be explained by the possibility of changing the diagnosis of SA for SP during the disease progression. A possibility of such changes has been argued earlier (Avrill et al 2004). Interestingly, a study of Fenton & McGlashan (1989) on diagnostic efficiency of schizophrenia revealed that the most valid definition of the disease is based on characteristic symptoms plus absence of affective symptoms plus 6-months duration. It should be mentioned that our study is in line with some previous investigations into clinical symptoms of schizophrenia and SA. The absence of the differences in age at onset between SP and SA was reported by a number of researches (Evans et al 1999; Benabarre et al 2001). There are controversial findings as well, for example, Ricca et al (1997) reported the same levels of perception and thought disturbances in SP as well as in SA patients. However, the results have been obtained in a relatively small sample, which in total included 58 patients with schizophrenia and SA.

With regard to personality, each group showed a pattern of traits reflecting schizophrenia-type personality changes as measured by MMPI. Besides, higher levels of neuroticism and anxiety and lower level of extraversion were found in all clinical groups that
was in accordance with the results reported by other authors, who studied combined samples of schizophrenic and schizoaffective patients (Lysaker & Davis 2004; Camisa et al 2005). It should be noted that self-ratings of SPA patients were severest though they were rated by clinicians mainly as intermediate between SP and SA patients. This may be due to their high levels of depression and anxiety and reflects significant amount of subjective distress. The SA group demonstrated the mildest personality changes, the finding being mainly consistent with the PANSS results. Notably, in this group, there was a discrepancy between clinically and subjectively rated levels of depression. In particular, given established links between personality and general outcome, including sense of well being in schizophrenia spectrum disorders (e.g. Lysaker & Davis 2004), one might suggest different prognoses for SPA and SA patients despite their resemblance on symptom ratings.

In contrast to symptoms and personality traits, cognitive functioning was similar in all clinical groups that was consistent with other studies (Miller et al 1996; Manschreck et al 1997; Beatty et al 1993; Evans et al 1999; Gooding & Tallent 2002; Goldstein et al 2005), which have reported the same level of cognitive deficits both in schizophrenia and SA. Interestingly, the fact that schizoaffective patients did not differ from schizophrenics in cognitive functioning even prompted some researchers to challenge a validation of SA as a diagnostic category (Gooding & Tallent 2002).

The results of molecular genetic study revealed that all clinical groups had both the differences and similarities by genotype distribution. The SA group was closer to the SP group by the prevalence of the A2A2 5-HTR2A genotype and to the SPA group by higher frequency of the ss 5-HTTLPR genotype and the BDNF Met allele. However, only the SA group had a specific genotype combination, namely higher frequencies of the 5-HTTLPR s allele and ss genotype, the A2 5-HTR2A allele and A2A2 genotype and the genetic variant the ss and the Met allele, which differentiated it distinctly from the control group. Notably, in accordance to OR estimation, possession of these variants raised liability to SA by 2 to 4 times. A contribution of the 5-HTTLPR, 5-HTR2A and BDNF polymorphisms to SP and SPA was less obvious. There were no genetic variants associated with SPA, 5-HTR2A polymorphism only being found to contribute to schizophrenia with OR 1.7. The results of our molecular genetic study, to a certain extent, replicated the earlier reports on the relation of 5-HTTLPR and 5-HTR2A polymorphisms to schizophrenia and SA. For example Kaiser and associates (2001) have found higher frequency of the ss genotype in patients with SA as compared to patients with schizoparanoid or residual subtypes of schizophrenia. The samples used in positive association studies of the 5-HTR2A polymorphism in schizophrenic populations (Williams et al 1997) comprised a portion of SA cases with higher frequency of the A2A2 genotype comparing to the A1A1 genotype.

As it has been mentioned earlier, genetics of SA is poorly understood. Family studies (for review see Abrams 1984) seem to reveal both a schizophrenic and affective genetic contribution to schizoaffective disorder, which differentiates it from either schizophrenia or affective disorder. Our molecular genetic findings support this observation. In compliance with literature, the 5-HTTLPR polymorphism is related to depression and anxiety (Mossner et al 2001; Mueller & Kranzler 2003; Golimbet et al 2004) while the 5-HTR2A polymorphism is associated with schizophrenia symptoms (Joober et al 1999; Golimbet et al 2002). In our study, both the “depression prone” ss 5-HTTLPR genotype and the schizophrenia-related 5-HTR2A A2A2 genotype were associated with schizoaffective psychosis.
Based on the results of the study, the following conclusions may be drawn out: (1) the presence of affective syndrome in the course of psychotic episode in schizophrenia is correlated with particular clinical presentations and personality changes of schizophrenic patients; (2) SA is more similar to SPA than to SP with regard to clinical symptoms and molecular-genetic characteristics; (3) SA is characterized by some specific features, namely, by the lowest ratings for negative symptoms, one of the most stable characteristic of schizophrenia, which is thought to be underpinned by genetic factors, and by a combination of genotypes of the candidate genes for major psychosis. Taken together, these factors discriminate SA distinctly from SP and SPA in genetic view.

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