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Schizophrenia comorbid with panic disorder: Evidence for distinct cognitive profiles

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Abstract

Patients with comorbid schizophrenia and panic symptoms share a distinct clinical presentation and biological characteristics, prompting some to propose *panic psychosis* as a separate subtype of schizophrenia. Less is known about these patients' neuropsychological profiles, knowledge of which may facilitate target-specific treatments and research into the etiopathophysiology for such cases. A total of 255 schizophrenia patients with panic disorder (n=39), non-panic anxiety disorder (n=51), or no anxiety disorder (n=165) were assessed with the Wechsler Adult Intelligence Scale – Revised, the Wisconsin Card Sorting Test, the Trail Making Test, the Controlled Oral Word Association Test, the Animal Naming subtest of the Boston Diagnostic Aphasia Examination, and the Wechsler Memory Scale – Revised. Psychotic symptoms were assessed with the Positive and Negative Syndrome Scale. Patients with panic disorder demonstrated a higher verbal IQ and better problem solving, set switching, delayed recall, attention, and verbal fluency as compared to schizophrenia patients without comorbid anxiety. The schizophrenia-panic group reported a higher level of dysthymia on stable medication. Our findings suggest that patients with schizophrenia and comorbid panic disorder exhibit distinct cognitive functioning when compared to other schizophrenia patients. These data offer further support for a definable panic-psychosis subtype and suggest new etiological pathways for future research.

Keywords

schizophrenia; schizoaffective disorder; psychosis; panic disorder; anxiety disorder; neuropsychological profile; cognitive functioning

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1. Introduction

The heterogeneity of schizophrenia precludes efficiency in preventing and treating its effects (Tsuang et al., 1990). Reducing this heterogeneity has thus become an important goal, prompting researchers to look more closely at the experiences of patients with schizophrenia spectrum disorders and other comorbid diagnoses for differences in etiology and presentation (Tsuang et al., 1990). The occurrence of panic symptoms in psychosis is considered subordinate to a primary psychosis diagnosis in hierarchical diagnosis algorithms, but panic–related psychosis has received some attention for having a distinct etiopathophysiology. Unfortunately, despite the potential importance for treatment, cognitive symptoms and profiles in this subgroup have received limited attention from researchers.

Schizophrenia has long been known to be highly comorbid with myriad other disorders, including substance abuse (Buckley et al., 2009; Kamali et al., 2000) and major depression (Buckley et al., 2009; Fenton, 2001), as well as aggressive behavior (Rasanen et al., 1998; Volavka et al., 1997). Co-occurring anxiety disorders, particularly obsessive-compulsive disorder, post-traumatic stress disorder, and panic disorder, are now known to be exceptionally prevalent (Achim et al., 2009); although hierarchical diagnosis rules in previous versions of the *Diagnostic and Statistical Manual of Mental Disorders* may have obscured their presence until recently (Bermanzohn et al., 2000). Research into these comorbid anxiety disorders has illuminated not only high prevalence rates (Achim et al., 2009) but separate clinical features as well. Indeed, many patients diagnosed with schizophrenia and obsessive-compulsive disorder appear to have a distinct set of clinical symptoms, neuropsychological features, and treatment responses, prompting researchers to suggest the existence of a “schizo-obsessive disorder” (Reznik et al., 2001).

Researchers make a similar case with regard to schizophrenia and panic symptoms, with some arguing for the existence of a *panic psychosis* (Kahn, 2012; Kahn and Meyers, 2000). Rates of panic symptoms in schizophrenia vary widely due to the population surveyed and varying assessment techniques. Panic attacks have been found to occur in 7.1% (Goodwin et al., 2003) to 47.5% (Bayle et al., 2001) of schizophrenia patients, while 4.2% (Craig et al., 2002) to 35% (Bayle et al., 2001) meet criteria for panic disorder. A recent meta-analysis found a mean prevalence rate of 9.8% (95% CI, 4.3% to 15.4%) for co-occurring panic disorder in a schizophrenia population (Achim et al., 2009), compared to a worldwide lifetime prevalence rate of 1.2% (95% CI, 0.7% to 1.9%; Somers et al., 2006).

Schizophrenia patients with panic symptoms exhibit some differences in clinical presentation that set them apart from other schizophrenia patients. Data from multiple studies suggest that panic attacks are more common in patients with paranoid schizophrenia, compared to other schizophrenia subtypes (Bayle et al., 2001; Buckley et al., 2009; Labbate et al., 1999), and it has been proposed that panic may be directly related to delusional fears (Bayle et al., 2001; Bermanzohn et al., 1999) and to auditory hallucinations (Kahn and Meyers, 2000; Savitz et al., 2011) in some patients.

Patients with schizophrenia and panic attacks or panic disorder also exhibit higher rates of depression (Goodwin and Davidson, 2002; Ulas et al., 2007), suicidal ideation (Goodwin and Davidson, 2002; Goodwin et al., 2002), and lifetime substance use (Goodwin et al., 2003). Data on positive and negative symptoms are mixed, with some studies showing no differences from other schizophrenia patients (Higuchi et al., 1999; Ulas et al., 2010), while other studies report elevations for positive symptoms (Lysaker and Salyers, 2007; Ulas et al., 2007).

Many patients with schizophrenia report having experienced panic prior to the onset of psychosis, which points to the possible role panic may play in the schizophrenia prodrome for panic psychosis (Kahn and Meyers, 2000; Tien and Eaton, 1992). These patients seem to possess better insight into their illness (Cosoff and Hafner, 1998; Lysaker and Salyers, 2007), and they are seven times more likely to seek mental health treatment than are schizophrenia patients without panic (Goodwin et al., 2002).

Biological evidence for a panic psychosis also exists, though it is limited (Buckley et al., 2009). Heun and Maier (1995) found an increased risk for panic among first-degree relatives of patients with schizophrenia, suggesting a heritable component for the combination. Lyons et al. (2000) provided further support for this notion by showing that the nonaffected, monozygotic twin of an individual with schizophrenia has a 7.5-fold increased odds of a panic disorder diagnosis, though this finding was not statistically significant. Data from pharmaceutical treatment trials are also indicative of the biological etiology of schizophrenia and panic. For example, traditional antipsychotics may worsen panic symptoms in patients with schizophrenia and comorbid panic disorder (Kahn and Meyers, 2000), whereas adjunctive alprazolam or clonazepam may reduce both panic symptoms and psychosis symptoms (Kahn et al., 1988). More recently, researchers have noted the positive effects of atypical antipsychotics as well (Takahashi et al., 2001; Takahashi et al., 2004).

Despite this mounting evidence, the case for a panic-psychosis subtype is still nominal. Buckley et al. (2009) noted a particular lack of investigation into the neurobiological factors of these comorbid disorders. Our study was designed to help address this gap in the literature by examining and comparing cognitive and neuropsychological functioning and symptomatology in schizophrenia patients with panic disorder, non-panic anxiety disorder, or no comorbid anxiety disorder.

2. Method

2.1 Participants

Participants were inpatients on the Schizophrenia Research Unit (SRU) at the New York State Psychiatric Institute (NYSPI) between 1995 and 2004. The SRU recruits patients from emergency rooms, private practices, and public clinics, as well as through word of mouth, for treatment of schizophrenia and participation in a variety of potential research studies. Only participants diagnosed with schizophrenia or schizoaffective disorders and deemed medically healthy by physical examination and laboratory evaluation were permitted to engage in the present protocol. All participants gave informed consent and all research procedures were approved by the NYSPI Institutional Review Board.

2.2 Assessments

All diagnoses were assessed with the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994), and final diagnoses were given according to DSM-III-R criteria and by the consensus of staff members. For the purposes of this study, all schizophrenia or schizoaffective participants were also classified as having (1) no comorbid anxiety disorders, (2) comorbid panic disorder, or (3) comorbid non-panic anxiety disorders. The DIGS was also used to obtain demographic information about gender, age, education, duration of illness, and current and past Global Assessment of Symptoms (GAS).

Clinical symptoms were assessed using the 30-item Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). Five symptom factors were derived from the PANSS using the pentagonal model (White et al., 1997), which uses 25 of the 30 PANSS items to group symptoms into five categories: (1) positive symptoms, such as delusions and hallucinations; (2) negative symptoms, such as loss of interest and emotional withdrawal; (3) dysthymic

mood symptoms, such as anxiety, guilt, and depression; (4) activation symptoms, such as hostility and excitement; and (5) autistic preoccupation symptoms, such as avolition, poor attention, and stereotyped thinking. We used this approach over the standard three-factor model because of its greater ability to disentangle mood symptoms from other psychopathology and its more finely delineated classification of negative symptoms. We examined PANSS ratings at two specific points in time: (1) at baseline/admission (i.e., Time 1) and (2) at one week prior to discharge or at "fixed dose" treatment (i.e., on a stable dose of antipsychotic medication for more than 3–4 weeks; Time 2). The amount of time between Time 1 and Time 2 PANSS assessments was 5–10 weeks for most patients.

In addition to the PANSS assessment, a battery of tests to assess cognitive and neuropsychological performance was also given at Time 2. Intelligence was measured with the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1981), generating full scale, verbal, and performance IQ scores. The following neuropsychological abilities were also evaluated: (1) problem solving and set switching via the Wisconsin Card Sorting Test (WCST; Heaton, 1993); (2) visual attention and task switching via the Trail Making Test A & B (Reitan and Wolfson, 1985); (3) verbal fluency (semantic and categorical) via the Controlled Oral Word Association Test (COWAT/FAS; Benton and Hamsher, 1989) and the Animal Naming subtest of the Boston Diagnostic Aphasia Examination (Goodglass and Kaplan, 1983); and (4) attention and verbal, visual, delayed recall, and general memory via the Wechsler Memory Scale – Revised (WMS-R; Wechsler, 1987).

All assessments were administered by trained clinical or research staff. DIGS and PANSS assessments were performed by at least Master's-level psychologists. Clinical raters achieved high inter-rater reliability (i.e., Kappa > 0.80 for individual symptom ratings and 95% agreement on diagnosis) before conducting evaluations, and all diagnoses were determined by consensus of all research staff members (Malaspina et al., 2000).

2.3 Data analysis

Statistical analysis was conducted using SPSS (version 17.0). The data were cleaned and evaluated for normality, heterogeneity of variance, and outliers. We examined the three patient groups for demographics effects using the chi-square statistic to examine categorical data and analysis of covariance (ANCOVA) for the continuous data. Schizophrenia diagnosis (schizophrenia or schizoaffective disorder) was entered as the covariate for all univariate and multivariate analyses of covariance. For our primary analyses, we used multivariate analysis of covariance (MANCOVA) to analyze the five-factor symptom scales of the PANSS at Time 1 and Time 2. We also conducted MANCOVAs on the data from the cognitive and neuropsychological tests. Patient group and gender served as the main factors for MANCOVA analyses. If multivariate analyses were found to be not significant, we examined between-subjects analyses (ANOVA) on individual indices and subtests, as each conveys important information in its own right. Overall measures, such as the WAIS-R Full Scale IQ and the WMS-R General memory index, were examined using separate ANCOVAs. When analyses of variance or covariance indicated group differences, a least significant difference (LSD) post-hoc *t* test was used to identify the significantly different pairwise groups.

3. Results

3.1 Demographics

A total of 255 inpatients met our inclusion criteria. Of these, 165 patients were diagnosed with schizophrenia or schizoaffective disorder but no accompanying anxiety disorder (schizophrenia-only group), 39 were diagnosed with comorbid panic disorder (panic-schizophrenia group), and 51 were diagnosed with a non-panic anxiety disorder (anxiety-

schizophrenia group). Significantly more men than women comprised the schizophrenia-only group, while more women than men were found in the anxiety-schizophrenia group (chi-square = 7.16, $df = 2$, $P = 0.028$). The panic-schizophrenia group had roughly equal numbers of men and women. As such, gender was used as a factor in our primary analyses. Some main effects for gender are reported below, but no significant diagnosis by gender interactions were found. There were no significant effects of age, duration of illness, education, current Global Assessment of Symptoms (GAS), or past month GAS on diagnosis group or gender (Table 1). Women generally experienced a later first onset of psychotic symptoms, $F(1, 246) = 8.22$, $P = 0.032$. Patient diagnosis of schizophrenia or schizoaffective disorder had no effect on the data.

Because of reports indicating higher rates of paranoid schizophrenia among those with comorbid panic symptoms (Bayle et al., 2001; Buckley et al., 2009; Labbate et al., 1999), we also examined the prevalence of this subtype in the three study groups. We found no difference among the groups: 33.9% of patients were diagnosed with paranoid schizophrenia in the schizophrenia-only group, 27.5% in the anxiety-schizophrenia group, and 33.3% in the panic-schizophrenia group, chi-square = 0.76, $df = 2$, $P = 0.684$.

3.2 Clinical symptoms

Table 2 displays all findings regarding symptomatology. In this sample of schizophrenia and schizoaffective patients, 118 cases had PANSS assessments at both admission (Time 1) and at fixed dose treatment (Time 2). Across all three patient groups combined, symptomatology improved from Time 1 to Time 2 for the positive ($P = 0.002$), dysthymic ($P = 0.016$), and autistic preoccupation ($P = 0.041$) symptom factors, but no significant improvement was seen for the negative or activation symptom factors. Looking at each diagnostic patient group, the schizophrenia-only group showed improvements at Time 2 in the positive ($P = 0.020$), dysthymia ($P = 0.054$), and autistic ($P = 0.008$) factors; only the positive factor improved over time for the anxiety-schizophrenia group ($P = 0.014$), while no factors showed significant improvement in the panic-schizophrenia group.

Only one significant difference in symptomatology was found between diagnostic groups: At Time 2, the panic-schizophrenia group reported more dysthymia ($F[2, 201] = 7.36$, $P = 0.001$) than the other two patient groups (post-hoc Ps < 0.001). Otherwise, there were no significant differences between diagnostic groups at Time 1 or Time 2 for any PANSS factor on the five-factored model.

To further explore this finding, we examined the PANSS lack of insight/judgment item (G12) at Time 1 and Time 2. At Time 1, there was a significant main effect for diagnostic group ($F[2, 118] = 3.12$, $P = 0.048$), where the panic-schizophrenia group exhibited better insight/judgment than the schizophrenia-only group ($P = 0.011$) and the anxiety-schizophrenia group ($P = 0.031$). The panic-schizophrenia group continued to show marginally better insight at Time 2 ($F[2, 203] = 2.92$, $P = 0.056$), though this difference was only significant when compared to the schizophrenia-only group ($P = 0.007$).

We additionally found a gender effect in PANSS symptomatology, with men reporting more negative symptoms at Time 1, $F(1, 117) = 4.82$, $P = 0.030$; this disparity was not present at Time 2. Although the men's negative symptoms were higher across diagnostic groups, only the gender differences in the schizophrenia-only group reached statistical significance in post-hoc analyses ($P = 0.006$).

3.3 Cognitive and neuropsychological performance

Cognitive and neuropsychological findings are shown in Table 3. The panic-schizophrenia group exhibited the highest Verbal and Full Scale IQ scores, showing significant differences

over the schizophrenia-only group (post-hoc *P*s < 0.011). The higher Full Scale IQ scores were driven primarily by this group's Verbal IQ scores ($F[2, 180] = 3.73$, $P = 0.026$). No other significant IQ differences were found in other diagnostic group comparisons, and no gender effects were found.

Multivariate analysis of the WMS-R memory indices showed both diagnostic (Wilks' Lambda = 2.75, $P = 0.006$) and gender (Wilks' Lambda = 2.75, $P = 0.001$) effects. Performance on the attention index primarily drove the main effect for diagnosis, $F(2, 133) = 4.80$, $P = 0.010$, with the panic-schizophrenia group performing significantly better than the schizophrenia-only group ($P = 0.004$). Across all diagnostic groups, men exhibited better attention than women, $F(1, 133) = 4.55$, $P = 0.035$. However, for the delayed recall index, women outperformed men, $F(1, 133) = 6.70$, $P = 0.011$, predominantly due to the better performance of the women in the panic-schizophrenia group, compared to their male counterparts, (post-hoc $P = 0.044$). Women also performed marginally better than men on the verbal memory index, $F(1, 133) = 3.68$, $P = 0.057$.

The panic-schizophrenia group also distinguished itself in executive function tasks. Though the groups performed similarly on most WCST scores (Wilks' Lambda = 1.21, P = ns), there was a significant difference in diagnostic groups on WCST error percentage ($F[2, 190] = 3.24$, $P = 0.042$). Post-hoc analyses showed that the panic-schizophrenia group had significantly fewer errors than the anxiety-schizophrenia group ($P = 0.013$) and marginally fewer errors than the schizophrenia-only group ($P = 0.073$). Moreover, they were significantly faster than the schizophrenia-only group on Trails A, $F(2, 176) = 4.29$, $P = 0.015$, post-hoc $P = 0.035$, with a multivariate trending significance for both Trails A & B (Wilks' Lambda = 2.21, $P = 0.068$). Finally, data also showed a main effect for diagnosis on verbal fluency (Wilks' Lambda = 2.75, $P = 0.028$), with the panic-schizophrenia group showing better fluency than the schizophrenia-only group on the Animal Naming test, $F(2, 183) = 5.38$, $P = 0.005$, post-hoc $P = 0.018$. The panic-schizophrenia group also scored higher on Trails and Verbal Fluency tests than the anxiety-schizophrenia group, but these differences did not reach statistical significance. No significant main effects or interaction effects for gender were found.

4. Discussion

The panic-schizophrenia group differed significantly from schizophrenia-only group on several measures. They demonstrated a higher verbal IQ and better recall following a delay, though the latter finding pertained to the women in this group only. They furthermore exhibited more efficient problem solving and set switching abilities and had better attentional and verbal fluency skills than the schizophrenia-only group. The panic-schizophrenia group also made significantly fewer errors on problem-solving tasks than the anxiety-schizophrenia group and performed better on measures of attention and verbal fluency, though these latter differences did not reach statistical significance. On measures of symptomatology, the panic-schizophrenia group reported more dysthymia when on stable medication than did the other two patient groups. For all other symptom subscales, the panic-schizophrenia patients reported similar levels of symptomatology as patients from the other diagnostic groups.

These findings lend support to the distinctiveness of patients with schizophrenia and panic disorder, as well as to panic psychosis as a potential subtype of schizophrenia with a unique cognitive profile. Moreover, these results suggest that patients with panic and schizophrenia may be more cognitively intact than schizophrenia patients without comorbid anxiety and are less likely to exhibit the same level of deficits in executive functioning and overall intelligence that are often considered to be a core feature of schizophrenia (Aylward et al.,

1984; Kremen et al., 2001). Because our patient groups had equal numbers of paranoid schizophrenia patients, who often score higher on intelligence and neuropsychological tests than do other schizophrenia patients (Goldstein et al., 2005; Potter and Nestor, 2010), the better neuropsychological performance of our panic-schizophrenia group suggests that the presence of panic symptoms may be particularly important in this relationship.

It is likely that both the presence of panic symptoms and the better neuropsychological performance are precipitated by an underlying neurobiological factor. One promising element to consider is the role of dopamine and its ability to impact executive functioning, positive symptoms in schizophrenia, and panic symptoms. Researchers have hypothesized that mesolimbic dopaminergic systems may be responsible for fear conditioning, the dysfunction of which may lead to panic attack (Pezze and Feldon, 2004). Dopamine has also long been implicated in schizophrenia syndromes, including theories that a hyperdopaminergic state is associated with increased positive schizophrenia symptoms (Zierhut et al., 2010), while a hypodopaminergic mesocortical and/or striatal state is associated with negative schizophrenia symptoms and cognitive deficits (Simpson et al., 2010; Toda and Abi-Dargham, 2007). Therefore, one possible explanation for our findings is that an individual in an overly hyperdopaminergic state, absent the accompanying hypodopaminergia, might be expected to display panic attacks and positive schizophrenia symptoms while being protected against the typical cognitive deficits that characterize many schizophrenia patients. More work is needed to evaluate the strength of this theory.

We found only one symptomalogical difference related to diagnosis: Patients in the panic-schizophrenia group experienced more dysthymia when they reached a stable state. Previous researchers have noted that schizophrenia patients with panic show better insight into their illness than other schizophrenia patients (Cosoff and Hafner, 1998; Lysaker and Salyers, 2007); we also found significantly more insight among the panic-schizophrenia group as compared to the other diagnostic groups using the Insight/Judgment item on the PANSS (G12). These data, combined with our findings of relatively intact executive functioning, might indicate a better capacity for meta-cognition and self-reflection for these patients. It may be that once their acute psychoses had resolved, they were more dysphoric about their experiences and prognosis.

Though some studies have reported that patients with schizophrenia and panic symptoms have more severe positive symptoms than other schizophrenia patients (Lysaker and Salyers, 2007; Ulas et al., 2007), our findings were in accordance with Higuchi et al. (1999) and Ulas et al. (2010), who found no differences in positive or negative symptoms among various diagnostic groups. This may be due to participant sample bias. If paranoid schizophrenia patients are the most likely to experience comorbid panic (Bayle et al., 2001; Labbate et al., 1999), we would expect the panic-schizophrenia group to exhibit more severe positive and paranoid symptomatology. Yet for this study, each diagnostic group had similar numbers of patients with the paranoid subtype, with similar levels of positive and negative symptomatology. This may suggest that elevation in positive symptoms is due to the framework of the paranoid subtype, and not to panic, *per se*. More research is needed to disentangle these concepts and to elucidate why patients with paranoid schizophrenia are more likely to have panic attacks and panic disorder.

Our study group included a total of 255 patients, making it one of the largest studies on panic and schizophrenia to date. Approximately 15% of our schizophrenia sample had comorbid panic disorder, a prevalence rate that roughly corresponds to findings in other studies. Despite this, there are several limitations to this study that bear discussion. Unfortunately, cognitive testing results were not available for all tasks for all patients, and, in some cases, sample sizes were small, especially in the panic-schizophrenia group.

Additionally, due to the large number of analyses conducted, our results may also be prone to Type I error, and thus caution should be used in interpreting our findings. We included both patients with schizophrenia and schizoaffective disorder in the study, which we attempted to control for in our analyses. However, as both disorders are heterogeneous, future studies should examine panic symptoms in more homogeneous schizophrenia groups.

Finally, two alternative interpretations of our data should be considered. First, the diagnosis of panic disorder in schizophrenia is a documented difficulty, often stemming from patients' cognitive limitations and confusion of panic with psychotic symptoms. As such, it is possible that subjects with higher levels of cognitive functioning may be better at recognizing and reporting panic symptoms. This scenario underscores the importance of a careful and methodical patient interview (Bayle et al., 2001; Kahn and Meyers, 2000). Carbon dioxide challenge, recently piloted with schizophrenia patients, may also be a safe and effective method for detecting a vulnerability to panic attacks (Savitz et al., 2011) and may reveal a high prevalence in subgroups such as those with auditory hallucinations. Furthermore, it is possible that a fair amount of undiagnosed panic disorder existed within the anxiety-schizophrenia group, which would account for the lack of significant differences between the panic-schizophrenia and anxiety-schizophrenia groups on several neurocognitive measures. A second alternative hypothesis concerns treatment of psychosis. In some patients, treatment with antipsychotics improves cognitive function (Harvey and Keefe, 2001; Keefe et al., 1999), and the alleviation of psychotic symptoms and improvement of cognition might reveal previously masked symptoms of panic. Future research should further investigate these possibilities, specifically examining the moderating effects of different medications.

In conclusion, our findings contribute to the theory that patients with panic psychosis may constitute a distinct group within those with schizophrenia. These patients experience a unique clinical presentation, prognosis, biology, and neuropsychological profile, possibly influenced by a hyperdopaminergic state. Further research into this subgroup is vital, in order to facilitate the identification and treatment of comorbid panic, as well as to better understand how comorbidity influences an individual's experience of schizophrenia.

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Table 1

Demographics by Comorbid Diagnosis and Gender.

	Schizophrenia Only		Schizophrenia + Non-Panic Anxiety		Schizophrenia + Panic					
	Males (*n* = 117)	Females (*n* = 48)	Males (*n* = 26)	Females (*n* = 25)	Males (*n* = 24)	Females (*n* = 15)	Comorbid Diagnosis		Gender	
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	F	P	F	P
Current Age	32.3 (11.1)	36.6 (9.6)	32.9 (10.0)	33.5 (9.2)	33.4 (12.1)	35.1 (9.5)	0.33	0.721	1.57	0.211
Age at Onset of Psychotic Symptoms	20.1 (5.5)	23.3 (8.3)	19.0 (4.0)	22.4 (7.8)	20.8 (4.8)	22.9 (7.9)	0.54	0.582	8.22	0.032 *
Duration of Illness	12.1 (9.9)	13.3 (9.8)	13.8 (9.6)	11.1 (8.8)	12.6 (11.5)	12.2 (10.2)	0.04	0.965	0.23	0.634
Education (grade)	12.5 (2.8)	12.8 (3.4)	12.9 (2.7)	13.1 (2.5)	12.9 (3.0)	14.1 (2.7)	1.19	0.306	1.07	0.302
GAS Current[a]	29.5 (9.3)	29.8 (6.8)	31.6 (8.6)	31.7 (8.4)	30.4 (7.6)	30.7 (6.3)	1.07	0.346	0.05	0.824
GAS Past Month[a]	36.9 (8.8)	36.4 (8.2)	37.7 (7.7)	38.3 (8.1)	35.6 (7.7)	36.2 (9.6)	0.65	0.525	0.03	0.874

Note. Schizophrenia diagnosis of participant (i.e., schizophrenia or schizoaffective disorder) was entered as a covariate but was insignificant in all analyses. There were no significant interactions between the Comorbid Diagnosis and Gender factors. GAS = Global Assessment of Symptoms.

[a]Some GAS scores were missing: Schizophrenia only group, $n = 151$; Schizophrenia + non-panic anxiety group, $n = 45$; Schizophrenia + panic group, $n = 36$.

*$P < 0.05$.

Table 2

Positive and Negative Syndrome Scale (PANSS) Symptoms at Time 1 and Time 2 by Comorbid Diagnosis and Gender.

	Schizophrenia Only		Schizophrenia + Non-Panic Anxiety		Schizophrenia + Panic					
	Males	Females	Males	Females	Males	Females	Comorbid Diagnosis		Gender	
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	F	P	F	P
	Time 1 (At Admission)									
Positive Factor	11.6 (5.0)	13.0 (4.5)	11.4 (4.5)	14.2 (4.9)	12.1 (4.6)	11.9 (3.0)	0.25	0.783	2.40	0.124
Negative Factor	20.0 (6.6)	15.3 (5.6)	21.2 (9.0)	18.8 (7.2)	19.1 (7.6)	16.5 (4.5)	1.54	0.218	4.82	0.030 *
Activation Factor	9.8 (4.2)	9.6 (5.0)	10.3 (4.4)	11.2 (5.1)	9.9 (3.9)	10.9 (4.6)	0.80	0.453	0.57	0.451
Dysthymi a Factor	9.6 (4.7)^a	10.0 (2.9)^a	9.3 (3.4)^a	10.5 (4.2)^a	12.3 (2.5)^b	10.7 (4.1)^b	1.68	0.190	0.00	0.955
Autism Factor	13.0 (4.6)	13.0 (5.1)	13.4 (5.2)	13.8 (3.6)	12.1 (4.5)	11.3 (3.5)	1.43	0.244	0.01	0.929
	n = 45	*n* = 21	*n* = 16	*n* = 17	*n* = 15	*n* = 10				
	Time 2 (At Fixed Dose Treatment)									
Positive Factor	10.8 (5.1)	12.2 (4.8)	10.5 (5.0)	11.0 (5.4)	11.0 (4.8)	10.5 (4.1)	0.47	0.624	0.55	0.581
Negative Factor	18.6 (7.3)	16.3 (6.2)	20.0 (6.0)	20.0 (7.5)	19.2 (7.0)	18.8 (6.7)	2.36	0.097	0.46	0.630
Activation Factor	8.7 (4.1)	9.7 (4.4)	9.9 (3.2)	11.1 (5.7)	8.9 (2.9)	10.7 (5.2)	1.53	0.219	0.08	0.925
Dysthymia Factor	8.1 (3.5)^a	8.7 (3.5)^a	8.2 (3.4)^a	9.6 (4.2)^a	11.4 (5.2)^b	11.4 (4.2)^b	7.36	0.001 ***	0.43	0.650
Autism Factor	11.8 (4.3)	12.6 (5.0)	12.0 (4.1)	13.1 (4.5)	11.9 (4.9)	11.3 (5.6)	0.46	0.632	0.34	0.714
	n = 93	*n* = 37	*n* = 24	*n* = 22	*n* = 21	*n* = 12				

Note. Schizophrenia diagnosis of participant (i.e., schizophrenia or schizoaffective disorder) was entered as a covariate but was insignificant in all analyses. There were no significant interactions between the Comorbid Diagnosis and Gender factors.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

[a] and [b] superscripts are used to denote statistically different diagnostic groups ($P < 0.05$), where applicable, as confirmed by LSD post-hoc analysis.

Table 3

Neuropsychological Test Results by Comorbid Diagnosis and Gender.

	Schizophrenia Only		Schizophrenia + Non-Panic Anxiety		Schizophrenia + Panic					
	Males	Females	Males	Females	Males	Females	Comorbid Diagnosis		Gender	
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	F	P	F	P
WAIS-R										
Performance IQ	81.0 (12.6)	80.1 (12.6)	85.0 (16.2)	81.4 (10.8)	86.7 (9.9)	85.5 (11.3)	2.22	0.112	0.55	0.459
Verbal IQ	87.1 (13.0)[a]	85.3 (14.2)[a]	91.5 (11.6)	86.5 (10.8)	93.2 (12.3)[b]	95.5 (15.7)[b]	3.73	0.026*	0.58	0.447
Full Scale IQ	83.6 (12.4)[a]	82.1 (13.1)[a]	87.3 (12.2)	83.5 (9.8)	89.3 (10.2)[b]	91.0 (14.2)[b]	3.53	0.031*	0.35	0.557
	n = 87	*n* = 37	*n* = 19	*n* = 18	*n* = 15	*n* = 11				
WMS-R										
Verbal	77.7 (16.6)	85.5 (16.0)	80.7 (9.8)	84.9 (16.4)	84.6 (11.7)	92.8 (16.4)	1.46	0.236	3.68	0.057
Visual	88.5 (21.5)	90.6 (19.8)	93.1 (14.8)	94.5 (18.8)	82.7 (26.3)	98.1 (19.5)	0.37	0.693	1.88	0.173
Attention	82.8 (17.6)[a]	78.8 (17.4)[a]	97.6 (15.1)	81.6 (19.2)	96.1 (13.4)[b]	93.6 (20.5)[b]	4.80		4.55	0.035*
Delayed Recall	80.5 (19.1)	86.5 (14.4)	83.1 (12.3)	87.0 (18.9)	72.1 (17.0)[a]	94.4 (26.1)[b]	0.07	0.929	6.70	0.011*
	n = 72	*n* = 26	*n* = 10	*n* = 13	*n* = 9	*n* = 10				
WCST										
Error % Perseverative	41.7 (21.2)	39.8 (18.8)	45.7 (20.5)[a]	45.7 (21.4)[a]	37.2 (18.6)[b]	29.5 (16.7)[b]	3.24	0.042*	0.74	0.355
Response % Perseverative	33.8 (29.1)	27.6 (17.6)	30.1 (16.0)	30.2 (24.3)	27.0 (26.6)	20.2 (15.2)	1.04	0.355	1.10	0.296
Error % Non-perseverative	26.0 (20.3)	23.9 (13.8)	27.7 (15.1)	24.9 (17.7)	22.5 (19.3)	17.9 (11.8)	1.12	0.328	1.11	0.294
Errors	14.1 (12.3)	15.4 (10.6)	16.8 (15.6)	17.1 (12.2)	14.0 (10.2)	10.6 (5.3)	1.36	0.259	0.01	0.916
	n = 91	*n* = 34	*n* = 21	*n* = 18	*n* = 20	*n* = 13				
Trail Making Test										

	Schizophrenia Only		Schizophrenia + Non-Panic Anxiety		Schizophrenia + Panic		Comorbid Diagnosis		Gender	
	Males	Females	Males	Females	Males	Females				
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	F	P	F	P
Trails A	51.1 (26.9)[a]	54.1 (21.8)[a]	44.6 (14.3)	49.2 (18.8)	40.8 (13.4)[b]	39.9 (11.3)[b]	4.29	0.015 *	0.05	0.823
Trails B	130.0 (69.0)	156.0 (75.0)	127.0 (56.0)	130.0 (63.0)	118.0 (68.0)	105.0 (41.0)	2.66	0.073	0.11	0.746
	n = 84	*n* = 32	*n* = 18	*n* = 19	*n* = 19	*n* = 11				
Verbal Fluency										
Animal Naming	15.8 (5.7)[a]	14.1 (5.4)[a]	16.0 (5.2)	16.6 (5.7)	17.4 (4.8)[b]	19.8 (5.3)[b]	5.38	0.005 **	0.46	0.499
COWAT/FAS	30.6 (13.8)	29.2 (11.2)	31.5 (12.1)	29.7 (11.8)	34.3 (11.8)	36.2 (9.9)	2.26	0.108	0.00	0.991
	n = 85	*n* = 34	*n* = 19	*n* = 21	*n* = 20	*n* = 11				

Note. Schizophrenia diagnosis of participant (i.e., schizophrenia or schizoaffective disorder) was entered as a covariate but was insignificant in all analyses. There were no significant interactions between the Comorbid Diagnosis and Gender factors. WAIS-R = Wechsler Adult Intelligence Scale – Revised. WMS-R = Wechsler Memory Scale – Revised. WCST = Wisconsin Card Sorting Test. COWAT/FAS = Controlled Oral Word Association Test.

* $P < 0.05$.

** $P < 0.01$.

[a] and [b] superscripts are used to denote statistically different diagnostic groups ($P < 0.05$), where applicable, as confirmed by LSD post-hoc analysis.