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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.

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 (Kamali et al., 2000; Buckley et al., 2009) and major depression (Fenton, 2001; Buckley et al., 2009), as well as aggressive behavior (Volavka et al., 1997; Rasanen et al., 1998). 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 and Meyers, 2000; Kahn, 2012). 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% (Baylé et al., 2001) of schizophrenia patients, while 4.2% (Craig et al., 2002) to 35% (Baylé 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).

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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 (Labbate et al., 1999; Baylé et al., 2001; Buckley et al., 2009), and it has been proposed that panic may be directly related to delusional fears (Bermanzohn et al., 1999; Baylé et al., 2001) 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 (Tien and Eaton, 1992; Kahn and Meyers, 2000). 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 1 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, d.f. = 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