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Working memory and attention deficits in adolescent offspring of schizophrenia or bipolar patients: Comparing vulnerability markers

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ABSTRACT

Background: Working memory deficits abound in schizophrenia and attention deficits have been documented in schizophrenia and bipolar disorder. Adolescent offspring of patients may inherit vulnerabilities in brain circuits that subserve these cognitive domains. Here we assess impairments in offspring of schizophrenia (SCZ-Offspring) or bipolar (BP-Offspring) patients compared to controls (HC) with no family history of mood or psychotic disorders to the second degree.

Methods: Three groups (n = 100 subjects; range: 10–20 yrs) of HC, SCZ-Offspring and BP-Offspring gave informed consent. Working memory was assessed using a delayed spatial memory paradigm with two levels of delay (2 s & 12 s); sustained attention processing was assessed using the Continuous Performance Task—Identical Pairs version.

Results: SCZ-Offspring (but not BP-Offspring) showed impairments in working memory (relative to HC) at the longer memory delay indicating a unique deficit. Both groups showed reduced sensitivity during attention but only BP-Offspring significantly differed from controls.

Conclusions: These results suggest unique (working memory/dorsal frontal cortex) and potentially overlapping (attention/fronto-striatal cortex) vulnerability pathways in adolescent offspring of patients with schizophrenia and bipolar disorder. Working memory and attention assessments in these offspring may assist in the clinical characterization of the adolescents vulnerable to SCZ or BP.

1. Introduction

The distinction between schizophrenia and bipolar disorder appears unclear from the perspective of neurobiology. For example, studies in molecular genetics suggest significant overlap in genetic vulnerability for each (Craddock and Owen, 2005) thereby implying a common etiological basis. If the genetic etiology is overlapping across phenotypes, it is plausible that neurodevelopment plays a critical role in the pathways toward each disorder. The idea that neurodevelopmental trends may distinguish between these disorders has been advanced (Murray et al., 2004), as has the general idea that complementary developmental trajectories contribute to distinct phenotypes post-adolescence (Keshavan et al., 2005a; Paus, 2005; Paus et al., 2008). In this view, complex interactions between programmed genetic development and environmental factors combine to alter or derail neurodevelopmental pathways during critical periods such as adolescence. This is now the modal view for all developmental hypotheses in schizophrenia (Lewis and Levitt, 2002), though its relevance for bipolar disorder is not yet established. These pathways may be realized through the disordered development of specific cortical systems in the brain, and therefore of cognitive domains that are closely tied to these cortical systems. Because both schizophrenia and bipolar disorder aggregate in families (Pavuluri et al., 2005), adolescent offspring of schizophrenia and bipolar patients are at increased risk for impaired cognition and psychopathology (Birmaher et al., 2009; Birmaher et al., 2010; Keshavan et al., 2005b) and are increasingly vulnerable to the disorders themselves. Estimates indicate that nearly 10%–15% of offspring of schizophrenia patients

Abbreviations: SCZ-Offspring, offspring of patient with schizophrenia; BP-Offspring, offspring of patient with bipolar disorder; HC, healthy control; FSIQ, Full Scale Intelligence Quotient; SCID, Structured Clinical Interview for Diagnostic Statistical Manual for Mental Disorders-IV; K-SADS, Schedule for Affective Disorders and Schizophrenia -Child Version; CPT-IP, Continuous Performance Task—Identical Pairs; ADHD, Attention Deficit Hyperactivity Disorder.

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will be diagnosed with schizophrenia (Erlenmeyer-Kimling et al., 1997), and that 5%–15% of offspring of bipolar patients will develop a mood disorder in their lifetimes (Lapalme et al., 1997). Furthermore, increasing evidence suggests alterations in cortical systems in these subjects (Diwadkar et al., 2006), supporting the idea of neurodevelopmental derailment during adolescence. Therefore, understanding unique or non-specific patterns of cognitive impairment in these groups may prove informative.

1.1. Working memory and sustained attention: distinct and overlapping components

Working memory and sustained attention have been closely mapped to prefrontal and striatal circuitry (Cohen et al., 1997; Corbetta et al., 1998). Working memory in particular is heavily dependent on sustained activity in prefrontal circuitry that is necessary for the temporary maintenance of information (Braver et al., 1997; Fuster, 1989). Sustained attention or vigilance is tied to interactions between cortico-striatal circuitry (Buchel and Friston, 1997; Luna et al., 2001). In general, the development of frontal and striatal circuitry is particularly dynamic during adolescence (Booth et al., 2003; Rubia et al., 2006), marked by both increased coordination during attention and working memory in particular (Edin et al., 2007), and increased frontal engagement with age (Rubia et al., 2000). Developmental deviations in regional function in SCZ- and/or BP-Offspring may affect working memory and sustained attention.

Prefrontal dysfunction is a central correlate of schizophrenia pathophysiology (Lewis, 1997) and delayed working memory paradigms elegantly elucidate the bases of disordered prefrontal function in the diathesis (Goldman-Rakic, 1994). Electrophysiological studies in primates indicate that when memoranda must be maintained in memory over a delay, maintenance is sub-served by tonic activity of prefrontal neurons that persists over the duration of the memory interval (Goldman-Rakic, 1988). Furthermore, the duration of this activity scales with the duration of the memory interval indicating a direct parametric effect on the demands of the prefrontal cortex. SCZ-offspring are in fact characterized by disordered fronto-striatal function during working memory that scales with increased memory demand (Bakshi et al., 2011), and errors in memory in offspring are most apparent at increased memory delays (Diwadkar et al., 2001). Thus, parametric effects of working memory load are a useful metric for distinguishing between SCZ-Offspring and controls. By comparison, the relationship of working memory deficits to bipolar disorder is less well established. Early studies indicated that bipolar patients performing similarly to controls (Park and Holzman, 1992), though recent data present a more heterogeneous pattern. Working memory deficits in bipolar subjects may be mediated by the presence of psychosis (Glahn et al., 2006) or manic symptoms (Sweeney et al., 2000). fMRI studies suggest that working memory in bipolar disorder is characterized by aberrant increases in engagement of the frontal cortex (Adler et al., 2004; Chang et al., 2004; Monks et al., 2004), though the value of working memory as a vulnerability marker in the mood spectrum is not established. Also, the relationship of working memory to neurophysiological processes such as dopaminergic neurotransmission (Vijayraghavan et al., 2007) or reduced synchrony between GABA-ergic neurons (Lewis et al., 2005) is hypothesized as central in schizophrenia, though this translational angle appears absent in bipolar disorder. Thus, it is plausible that working memory deficits may reflect essential aspects of altered prefrontal circuitry in schizophrenia that may be inherited in, and unique to SCZ-Offspring.

Attentional processes are not dependent on sustained maintenance by prefrontal neurons but may depend on cortico-striatal structural and functional connectivity (Graham et al., 2009; Haber and Calzavara, 2009). Other studies indicate that neural activity in key striatal regions such as the caudate are central to attention, and translating attention into motor outputs (Hikosaka and Sakamoto, 1986), suggesting that the striatum and its constituents are more central in the brain's attention pathway. Sustained attention has in fact emerged as a common marker of deficit in both adult schizophrenia and bipolar populations (Cornblatt and Erlenmeyer-Kimling, 1989; Strakowski et al., 2004). Attention deficits appear to be stable and enduring, have been documented in adolescent offspring of schizophrenia patients (Michie et al., 2000), and may result from disordered fronto-striatal function (Diwadkar et al., 2011), suggesting that such deficits may be markers of genetic vulnerability for schizophrenia. Young bipolar offspring (age<25) endorse attention deficits but objective measures of attention deficits have provided mixed results (Klimes-Dougan et al., 2006). Nevertheless, several reasons motivate the idea that attention deficits would reflect neurodevelopmental vulnerability in both groups. For example, striatal abnormalities are noted in the earliest phases of the illness in both schizophrenia (Lawrie et al., 2001) and bipolar disorder (Strakowski et al., 2005), and have been associated with deficits in attention.

Here we investigated working memory and sustained attention deficits in age-matched HC, SCZ-Offspring and BP-Offspring using established measures of working memory (Diwadkar et al., 2001) and sustained attention (Salgado-Pineda et al., 2004). Based on the emerging literature, we expected that SCZ-Offspring (but not BP-Offspring) would show unique impairments in working memory reflected in greater error in a delayed match to sample spatial working memory task as a function of increased memory delay. By comparison, we expected offspring of both schizophrenia and bipolar patients to demonstrate non-specific impairments in sustained attention reflected in lower sensitivity to detect targets in a sustained attention task.

2. Methods

2.1. Subjects

One hundred subjects ($10 \leq \text{Age} \leq 20$ yrs) gave informed consent or assent to participate. All protocols were cleared by the Institutional Review Boards at the University of Pittsburgh and Wayne State University. Groups did not differ in age overall ($F_{2,97} = .95$, $p > .35$) or Full Scale IQ ($F_{2,97} = .40$, $p > .65$). Table 1 provides a characterization of subjects, with age, gender and Full Scale IQ scores. All subjects were free from medications at the time of assessments.

2.2. Clinical characterization

SCZ-Offspring and BP-Offspring were recruited through contacts in in-patient and out-patient services at the Western Psychiatric Institute and Clinic (WPIC) of the Dept. of Psychiatry at the University of Pittsburgh, from the greater Detroit area through advertisements, and patient services at the Wayne State University School of Medicine. HC were recruited from the same communities as the SCZ- and BP-Offspring through community based advertisements. Rule outs were achieved through telephone and personal interview, and screening questionnaires, to ascertain if subjects had a history of psychotic illness in first-degree relatives. Diagnoses for parents of offspring were reached using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). Subjects younger than 15 years were clinically evaluated using the Schedule for Affective Disorders and Schizophrenia—Child Version (K-SADS) (Kaufman et al., 1997); those

Table 1
Age, full scale IQ (± sd) and gender information for the samples.

	SCZ-Offspring (n = 36)	BP-Offspring (n = 23)	HC (n = 41)
Age (yrs) ± sd	14.5 ± 2.7	14.0 ± 2.4	14.9 ± 2.7
M/F	22/14	13/10	25/16
FSIQ	98.7 ± 14.9	101.5 ± 12.9	101.8 ± 18.2