



## Verbal and visual–spatial memory impairment in youth at familial risk for schizophrenia or affective psychosis: A pilot study

Silvia Scala<sup>a,b</sup>, Andrea Pousada<sup>b</sup>, William S. Stone<sup>b</sup>, Heidi W. Thermenos<sup>b,c</sup>, Theo C. Manschreck<sup>d</sup>, Ming T. Tsuang<sup>b,e</sup>, Stephen V. Faraone<sup>f</sup>, Larry J. Seidman<sup>b,c,\*</sup>

<sup>a</sup> Department of Public Health and Community Medicine, Section of Psychiatry and Clinical Psychology, University of Verona, P.le L.A. Scuro, 10-37134, Italy

<sup>b</sup> Harvard Medical School, Department of Psychiatry, Massachusetts Mental Health Center Division of Public Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA 02115, USA

<sup>c</sup> Athinoula A. Martinos Center for Biomedical Imaging (Massachusetts Institute of Technology, Harvard Medical School and Massachusetts General Hospital), Charlestown, MA 02129, USA

<sup>d</sup> Commonwealth of Massachusetts Research Center, Department of Psychiatry, Harvard Medical School, John C. Corrigan Mental Health Center, Fall River, MA 02720, USA

<sup>e</sup> University of California, San Diego, Department of Psychiatry, Center for Behavior Genomics and Institute of Genomic Medicine, La Jolla, CA 92093, USA

<sup>f</sup> Departments of Psychiatry, Neuroscience and Physiology, SUNY, Upstate Medical University, Syracuse, NY 13210, USA

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### ABSTRACT

**Background:** Schizophrenia and affective psychoses share several common biological origins, particularly genetic susceptibility. Kraepelin posited that differing clinical expressions in these disorders reflect different etiopathologies. We tested a neuropsychological component of this hypothesis by evaluating verbal memory and visual memory performance in nonpsychotic youth at familial risk for psychosis, taking into account contributions to memory dysfunction including executive processing and psychopathology.

**Methods:** Teenage and young adults (ages 13–25) at familial high-risk (FHR) for schizophrenia (HR-SCZ,  $n = 41$ ) or affective psychosis (HR-AFF,  $n = 24$ ) were compared to community controls (CC,  $n = 54$ ) on verbal (Miller–Selfridge Context Memory) and visual (Rey–Osterrieth Complex Figure) memory tests in which the roles of strategy and contextual processing on distinct recall domains could be assessed. Effects of psychopathology, vigilance and working memory were investigated to determine their influence on memory performance.

**Results:** HR-AFF and HR-SCZ exhibited similarly impaired memory profiles and elevated levels of psychopathology compared to CC. HR-SCZ were significantly impaired on both verbal memory and visual–spatial memory, while HR-AFF in verbal memory only. However, effect sizes, in the medium range, were largely comparable between the two HR groups. Deficits in verbal recall and in visual memory organization remained significant after adjustment for confounders.

**Conclusions:** Youth at FHR for psychosis present relatively common memory deficits across both visual–spatial and verbal modalities that are not explained by current psychopathology, vigilance or working memory deficits. Deficits in organizing information to be recalled represent a promising trait of psychosis vulnerability.

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## 1. Introduction

The degree of overlap between schizophrenia and affective psychosis is a recurring question, with differences in diagnostic symptoms and clinical outcomes conceptualized both categorically and dimensionally (Kraepelin, 1974) and with increasing evidence of some shared genetic susceptibility (Craddock et al., 2005). Neurocognitive compromise, while not part of the diagnostic criteria for schizophrenia or psychotic

mood disorders, is a key part of the schizophrenia syndrome, beginning with the concept, “dementia praecox”. This observation has overwhelming support in chronic (Heinrichs and Zakzanis, 1998) and first-episode cases (Mesholam-Gately et al., 2009) with schizophrenia. On the other hand, neurocognitive impairment in affective psychosis has traditionally been considered a relatively mild component of the illness (Goodwin and Jamison, 1990) because deficits were not commonly observed before onset, pointing to the possibility of subsequent deterioration of neuropsychological functions associated with the disorder. Nevertheless, although studies of neurocognition in bipolar disorder (BD) and major depressive disorder (MDD) are not as exhaustive as for schizophrenia, both BD and MDD patients have been increasingly observed to present neurocognitive impairments that intensify with the degree of psychosis (Rubinsztein et al., 2000; Dittmann

\* Corresponding author at: Massachusetts Mental Health Center, Commonwealth Research Center, 5th Floor, 75 Fenwood Road, Boston, MA 02115, USA. Tel.: +1 617 754 1238; fax: +1 617 754 1240.

E-mail address: [lseidman@bidmc.harvard.edu](mailto:lseidman@bidmc.harvard.edu) (L.J. Seidman).

et al., 2008). Moreover, in direct comparisons, patients with schizophrenia (SCZ) or affective psychosis (AFF) present similar neurocognitive impairments (Goldberg et al., 1993; Schretlen et al., 2007), although the level of severity is greater in SCZ (Seidman et al., 2002; Lewandowski et al., 2011; Zilles et al., in press).

Determining whether neurocognitive dysfunctions are specific to type of psychosis is confounded by the effects of psychosis and by various medications these patients receive. An alternative strategy is to test nonpsychotic, unmedicated, first-degree relatives of psychotic individuals who share approximately 50% of genes with their ill relatives, but are typically free of psychosis confounds that could affect neurocognition (Glahn et al., 2010; Jabben et al., 2010). The genetic or familial high-risk (FHR) approach of evaluating relatives of patients builds upon the knowledge that the best-known risk factors for the psychoses are susceptibility genes (Gottesman and Gould, 2003) and one expression is by neurocognitive dysfunctions (Faraone et al., 1995). Some studies have assessed neurocognition in first-degree relatives of individuals with SCZ and AFF directly in the same study, but these vary in the neurocognitive functions assessed and the literature is still relatively limited, especially in FHR youth (Kremen et al., 1998; Erlenmeyer-Kimling et al., 2000; McIntosh et al., 2005; Pirkola et al., 2005; Seidman et al., 2006, 2013).

Declarative memory in psychotic disorders and in HR individuals is one of the most promising functions to study because it has been studied extensively in patients and there are few direct comparisons in relatives of SCZ vs. AFF. Verbal declarative memory is prominently impaired in SCZ and AFF psychosis (Aleman et al., 1999; Fossati et al., 2004). Moderate size memory impairments are also consistently reported in both nonpsychotic adult relatives of patients with SCZ (Kremen et al., 1994; Snitz et al., 2006; Trandafir et al., 2006) and AFF psychosis (Kieseppä et al., 2005; Robinson et al., 2006; Arts et al., 2008). Difficulties in spontaneously organizing information during the encoding stage are considered to be one of the primary dysfunctional cognitive mechanisms of verbal memory in individuals with SCZ and in their relatives (Cirillo and Seidman, 2003).

However, visual memory has been relatively under-explored and, therefore, the mechanisms that are responsible for these deficits are poorly understood (Tracy et al., 2001; Kalinowski et al., 2003; Seidman et al., 2003). As in schizophrenia patients, adult first-degree relatives demonstrate impaired visual memory (Tuulio-Henriksson et al., 2003; Skelley et al., 2008). In affective psychosis, deficits in visual patterns and spatial memory support evidence of impaired visual memory (Sweeney et al., 2000; Bearden et al., 2006). Because prefrontal cortex is strongly implicated in the activation of deep categorizing and semantic memory strategies, and in organization and planning (Cirillo and Seidman, 2003), we assume that organizational processing is impaired in both verbal memory and visual-spatial memory in both disorders. Thus, a deficit in strategic and organizational processing could play a significant role in verbal and visual memory impairments in HR youth.

The study of youth at FHR enhances the important goal of identifying neurocognitive vulnerability indicators for later disability or illness. There are far more studies of neurocognition in youth at FHR for schizophrenia (HR-SCZ) than for affective psychoses. A recent quantitative literature review of neurocognition yielded 28 studies of HR-SCZ (aged <30 years) appropriate for quantitative analysis and far fewer in HR-AFF subjects (Agnew-Blais and Seidman, 2012). The largest average effect sizes (ESs) using Cohen (1988) were for full-scale IQ ( $d = -0.777$ ), vocabulary ( $d = -0.749$ ), single word reading ( $d = -0.698$ ) (often used as IQ estimates), and verbal declarative memory ( $d = -0.541$ ) in HR-SCZ. Schubert and McNeil (2005) suggested that verbal memory is a specific trait marker for schizophrenia liability since impairments were present in offspring of mothers with schizophrenia and not in offspring of affective patients. Thus far, however, the few studies that compared youth at HR for different psychoses are inconclusive as to specificity of memory dysfunction

(e.g. Maziade et al., 2009) and none have focused on memory tasks highlighting spontaneous organization.

The goal of this study was to identify whether there are distinct or common memory impairments in HR-SCZ and HR-AFF. To investigate verbal memory and visual memory, and to assess the role of strategic and organizational processes in memory we used a visual memory and perceptual organization test (Rey-Osterrieth Complex Figure [ROCF], Rey, 1941; Osterrieth, 1944) and a context-aided verbal memory test (Miller-Selfridge [MS], Miller and Selfridge, 1950; Manschreck et al., 1997). Our first hypothesis was that both high-risk groups would be impaired on verbal and visual memory measures compared to controls as tested by the MS Total score and the organizational memory scores on the ROCF. Secondly, we expected to find a linear trend such that the HR-SCZ group would perform worse than the HR-AFF group. In particular, we expected that HR-SCZ would present more problems on the organization of the ROCF (cf. Jones et al., 2003). Thirdly, we expected HR-SCZ to show greater vulnerability to low semantic context on the MS word lists, reflecting their hypothesized weakness in self-organizing words. Finally, we sought to assess whether the hypothesized memory deficits could be explained by concurrent psychopathology or by high load auditory attention-executive processing.

## 2. Methods

### 2.1. Subjects

Study data were collected as part of the Harvard Adolescent Family HR Study between 1998 and 2007. This sample and its ascertainment procedures and some neurocognitive analyses were described previously (Seidman et al., 2006, 2012); the ROCF data has not been published previously in these samples and the MS data has not been published in HR-AFF or in most of the HR-SCZ participants. In a functional neuroimaging study, we briefly reported the MS Total score for 26 controls and 21 HR-SCZ, roughly 50% of those samples reported here (Thermenos et al., 2007). The present study comprises nonpsychotic first-degree relatives of patients with a DSM-IV (A.P. Association, 1994) diagnosis of schizophrenia or schizoaffective disorder, depressed type (HR-SCZ), bipolar psychotic disorder or Major Depressive Disorder with psychotic features (HR-AFF) and a community control group (CC). Probands were diagnosed using the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994) and the Family Interview for Genetic Studies (FIGS; Maxwell, 1992). Nonpsychotic relatives were ascertained through adult probands.

The HR-SCZ group consisted of 41 relatives (40% offspring, 60% siblings) of SCZ probands, whereas the HR-AFF group consisted of 24 relatives (62.5% offspring, 37.5% siblings) of patients with AFF psychosis. The CCs consisted of 54 children of parents diagnosed according to DSM-IV criteria with no mental illness ( $n = 25$ ), major depressive disorder ( $n = 8$ ), mood disorder due to a general medical condition ( $n = 1$ ), or cannabis abuse ( $n = 1$ ) using the DIGS and FIGS. The adult control probands were drawn from respondents to local newspaper advertisements and announcements posted in the sites from which HR probands were recruited (e.g., local hospital and clinics). All HR youth assessed were between 13 and 25 years old.

### 2.2. Exclusion criteria

HR and CC participants were excluded if they had: a lifetime diagnosis of psychotic illness, substance dependence, neurological disease, head injury or medical illness with documented cognitive sequelae, sensory impairments, current psychotropic medication use, or a full-scale IQ less than 70 based on eight sub-tests of the WISC-III or WAIS-III (Wechsler, 1991, 1997). CCs had an additional exclusion criterion of any first- or second-degree biological relatives

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