



Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Memory systems in schizophrenia: Modularity is preserved but deficits are generalized

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ARTICLE INFO

Article history:

Received 2 July 2015

Received in revised form 6 August 2015

Accepted 10 August 2015

Available online xxxx

Keywords:

Psychosis

Working memory

Episodic memory

Cognition

Bipolar disorder

ABSTRACT

Objective: Schizophrenia patients exhibit impaired working and episodic memory, but this may represent generalized impairment across memory modalities or performance deficits restricted to particular memory systems in subgroups of patients. Furthermore, it is unclear whether deficits are unique from those associated with other disorders.

Method: Healthy controls ($n = 1101$) and patients with schizophrenia ($n = 58$), bipolar disorder ($n = 49$) and attention-deficit-hyperactivity-disorder ($n = 46$) performed 18 tasks addressing primarily verbal and spatial episodic and working memory. Effect sizes for group contrasts were compared across tasks and the consistency of subjects' distributional positions across memory domains was measured.

Results: Schizophrenia patients performed poorly relative to the other groups on every test. While low to moderate correlation was found between memory domains ($r = .320$), supporting modularity of these systems, there was limited agreement between measures regarding each individual's task performance ($ICC = .292$) and in identifying those individuals falling into the lowest quintile ($\kappa = 0.259$). A general ability factor accounted for nearly all of the group differences in performance and agreement across measures in classifying low performers.

Conclusions: Pathophysiological processes involved in schizophrenia appear to act primarily on general abilities required in all tasks rather than on specific abilities within different memory domains and modalities. These effects represent a general shift in the overall distribution of general ability (i.e., each case functioning at a lower level than they would have if not for the illness), rather than presence of a generally low-performing subgroup of patients. There is little evidence that memory impairments in schizophrenia are shared with bipolar disorder and ADHD.

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1. Introduction

Memory impairment is a core feature of schizophrenia (Kahn and Keefe, 2013) related to functioning and prognosis (Green et al., 2004). Patients with schizophrenia and their first-degree relatives demonstrate impairment in working and episodic memory (Agnew-Blais and Seidman, 2012; Aleman et al., 1999; Forbes et al., 2009; Snitz et al., 2006; Trandafir et al., 2006) and both working memory (Glahn et al., 2003) and episodic

memory are moderately heritable (Finkel and McGue, 1993; Owens et al., 2011). Thus, memory impairments may represent a biomarker of schizophrenia; however, questions about the generality of these deficits remain to be addressed.

First, despite group level memory impairment in schizophrenia, measures of memory performance are limited as individualized diagnostic classifiers (Glahn et al., 2007; Kern et al., 2011). It is unclear whether deficits across memory domains and modalities (e.g., working vs. episodic, verbal vs. visuospatial) reflect generalized impairment (Gold and Dickinson, 2013), a specific subgroup of patients exhibiting neurocognitive deficits in multiple domains (McDermid Vaz and Heinrichs, 2002), or different subsets of patients displaying deficits in different domains (Karlsgodt et al., 2011). Previous research in a

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large schizophrenia sample found that cognitive impairment was best explained by a single deficit factor (Keefe et al., 2006); however, this study did not include controls and so could not directly assess how patterns found in patients compare to typical cognitive structure. A model including executive functioning, memory and processing speed best discriminates schizophrenia from controls (Lam et al., 2014), which supports the theory that patients with schizophrenia are broadly cognitively impaired, but this study included relatively independent cognitive tasks and the structure within multiple memory-related tasks has not been measured. Additionally, more refined, cognitive neuroscience-based tasks might better identify discrete neurocognitive subsystems that are impaired in patient groups (Carter and Barch, 2007).

Second, it is unclear whether memory deficits associated with schizophrenia represent biomarkers of risk processes shared with other diagnostic syndromes, such as bipolar disorder (Kurtz and Gerraty, 2009) or attention-deficit-hyperactivity-disorder (ADHD) (Martinussen et al., 2005). While memory impairments in ADHD are likely more circumscribed (Castel et al., 2011), impairments in bipolar disorder may be closer to those found in schizophrenia, particularly among cases with psychotic symptoms (Glahn et al., 2006; Hill et al., 2013). Thus, it is important to assess the structure of cognitive dysfunction across diagnostic boundaries (Cuthbert and Insel, 2010).

This study sought to clarify the distribution and covariation of impairments across domains of memory in patients with schizophrenia and to determine to the extent to which these impairments are shared with bipolar disorder and ADHD. The psychiatric comparison groups allow us to examine memory impairment in schizophrenia in the context of individuals who are hypothesized to share genetic risk architecture with schizophrenia. A large reference sample of community volunteers ($n = 1101$) was collected to provide robust estimation of the normative distributions of performance on all measures, which included both established neuropsychological tasks and experimental tasks designed to isolate theoretically separable aspects of working and episodic memory functioning (Carter et al., 2008).

We hypothesized that among patients with schizophrenia, distributions on all measures of memory performance would be shifted downward compared with those of the reference population and that there would be consistency in terms of where particular patients scored in the distributions across domains and modalities. We further hypothesized that there would be a similar distributional shift and cross-distributional consistency among bipolar cases with psychotic features, but not among non-psychotic bipolar patients or subjects with ADHD.

2. Methods

2.1. Subjects

The study was approved by the Institutional Review Boards of UCLA and Yale University and participants provided written informed consent. Subjects were recruited via the UCLA Consortium for Neuropsychiatric Phenomics (www.phenomics.ucla.edu). 1101 healthy controls (CON) without history of psychosis or ADHD and no current mood or anxiety disorders were studied, as well as 58 schizophrenia (SCZ) patients, 49 bipolar (BP) patients, and 46 ADHD patients. Participants, aged 21–50, were recruited by community advertisements from the Los Angeles area, identified as “White, Not of Hispanic or Latino Origin” or “Hispanic or Latino, of Any Race” and completed at least 8 years of education. (Other racial and ethnic groups were not recruited to minimize confounding planned genetic analyses in the broader study.) Participants were screened for neurological disease, head injury with loss of consciousness or cognitive sequelae, or substance dependence within the past 6 months. Subjects were excluded if urinalysis results were positive for drugs of abuse on the day of testing.

2.2. Clinical and cognitive assessment

Participants were interviewed using the SCID-IV (First et al., 1995) and patient groups were rated on the Hamilton Psychiatric Rating Scale for Depression (HAM-D) (Hamilton, 1960), the Scale for the Assessment of Positive and Negative Symptoms (SAPS and SANS) (Andreasen, 1983a,b) and the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). Participants in the BP group were also differentiated into those with history of psychosis, determined by report of positive psychotic symptoms during the SCID interview, and those without history of psychosis. Interviewers were trained to criterion levels of reliability, which for the SCID involved meeting kappa scores of .85 or greater on diagnosis and .75 or greater on symptom and algorithm decisions (Ventura et al., 1998). For symptom assessment scales interviewers were trained to a criterion ICC = .80 or greater (Ventura et al., 1995).

The neuropsychological testing battery consisted of multiple measures related to memory functioning including the California Verbal Learning Test (CVLT) (Delis et al., 2000), Visual Reproduction, Symbol Span, Digit Span and Letter–Number Sequencing from the Wechsler Memory Scale-IV (Wechsler, 2009). In addition, Vocabulary and Matrix Reasoning from the Wechsler Adult Intelligence Scale-IV (Wechsler, 2008), and the Color Trails Test (D’Elia et al., 1996) were included as estimates of verbal intelligence, nonverbal reasoning and processing speed/cognitive switching, respectively.

During the cognitive testing session subjects also performed computer-based tasks, programmed and presented in E-prime®, designed to probe working and episodic memory functioning. Remember–Know and Scene Recognition tasks were designed to test verbal and visual episodic memory, respectively. Verbal and spatial working memory capacity, maintenance and manipulation were also tested. Detailed task descriptions are available in the appendix (SA1).

2.3. Statistical analysis

Statistical analyses were conducted using R (R Core Team, 2015). Group differences on cognitive performance were tested using MANOVA followed by univariate ANOVA and Tukey’s HSD to clarify patterns of performance in each domain. Effect size (Hedges’ g) was calculated to compare the relative size of group effects and linear discriminant analysis with leave-one-out cross validation was used to determine how well tasks differentiated between groups.

To evaluate whether the same subjects showed impairment across memory domains, we examined correlations between the primary performance measures for each task, both in terms of their original continuous scaling and in terms of consistency interclass correlations of measures transformed into quintile rankings based on the full sample distribution. The consistency with which an individual falls in the lowest performance range is of particular interest as they are more likely to suffer associated functional impediments. Kappa coefficient of agreement was to measure the consistency of individuals in this lowest quintile of performance, where each measure was included as a separate ‘rater’ of performance. These measures of consistency were conducted across all tasks as well as within a priori defined domains of memory (i.e. working vs. episodic memory and verbal vs. spatial memory. See SA2 for a list of tasks in each domain).

Principal component analysis (PCA) was then used to further examine the data. The first principal component was determined to represent a general cognitive factor and tested for group differences. The residual variance was then tested using the above methods to determine how the structure of memory impairments among the subject groups is affected by generalized versus task specific effects.

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