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Memory generalization is selectively altered in the psychosis dimension

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ABSTRACT

Global deficits in declarative memory are commonly reported in individuals with schizophrenia and psychotic bipolar disorder, and in their biological relatives. However, it remains unclear whether there are specific components within the global declarative memory dysfunction that are unique to schizophrenia and bipolar disorder, or whether these impairments overlap the two psychoses. This study sought to characterize differential components of learning and memory in individuals within the psychosis dimension: probands with schizophrenia (SZP, n = 33), probands with psychotic bipolar I disorder (BDP, n = 20), and biological relatives of SZP (SZR, n = 21), contrasted with healthy controls (HC, n = 26). A computerized cognitive paradigm, the Acquired Equivalence test, with probes for associative learning, memory for learned associations, and memory generalization was administered, along with standardized neuropsychological measures of declarative memory. All study groups were able to learn and remember the associations, although SZP were slower than HC in the initial learning stages. Both SZP (significantly) and BDP (at a trend level) showed altered memory generalization compared to HC (SZP vs. HC, $p = .038$, $d = .8$; BDP vs. HC, $p = .069$, $d = .95$). SZR showed memory generalization intermediate between SZP and HC, although their performance did not differ significantly from either group. These findings indicate that probands with schizophrenia and bipolar psychoses have similar alteration in the ability to flexibly generalize learned knowledge when probed with novel stimuli, despite overall sufficient associative learning and memory for what they learned. These results suggest that the two disorders present a clinical continuum with overlapping hippocampus-mediated memory generalization dysfunction underlying the psychosis phenotype.

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1. Introduction

Deficits in declarative memory (DM) are one of the broadly studied cognitive phenotypes of schizophrenia (SZ) and bipolar disorder (BD) commonly observed in both probands (Glahn et al., 2004; Schretlen et al., 2007; Arts et al., 2008; Hill et al., 2008; Stefanopoulou et al., 2009) and their biological relatives (Toomey et al., 1998; Sitskoorn et al., 2004; Glahn et al., 2010). Novel cognitive paradigms translated from animal and computational models have allowed the dissection of memory function (Myers et al., 2003; Titone et al., 2004; Preston et al., 2005; Shohamy and Wagner, 2008) and provided evidence that a 'global' DM phenotype presents a complex array of cognitive processes including memory encoding and consolidation, retrieval and subsequent generalization of past memories to novel environments (Heckers et al., 1998; Myers et al., 2003; Titone et al., 2004; Preston et al., 2005; Shohamy and Wagner, 2008). Deficits in generalizing learned information to novel choices, thought to be mediated by hippocampus (Heckers et al., 1998; Myers et al., 2003; Heckers et al., 2004; Shohamy and Wagner, 2008; Shohamy et al., 2010; Eichenbaum et al., 2011), have been reported in SZ probands (SZP). Notably, these deficits are found despite intact associative learning and memory retention (Heckers et al., 2004; Keri et al., 2005; Ongur et al., 2006; Shohamy et al., 2010). Furthermore, we have recently contrasted memory-based generalization performance in SZP on- and off-antipsychotic medication, and demonstrated a positive, yet not normalizing, effect of antipsychotics on memory generalization (Shohamy et al., 2010).

Growing evidence from translational and genetic studies suggests that psychosis, a clinical dimension overlapping empirically defined diagnostic categories (e.g., SZ and BD), may be associated with unique neurophysiological and molecular markers independent of the categorical diagnoses (see Ivleva et al., 2010 for review). Although 'SZ-like' DM alterations measured by neuropsychological tests have been reported in probands with psychotic BD (BDP) (Hill et al., 2008; Glahn et al., 2010), specific phenotypes within DM have not been tested. Similarly, no previous studies have examined familial association of memory generalization. Therefore, building on prior work in SZ (Heckers et al., 1998; Titone et al., 2004; Shohamy et al., 2010),

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here we extend the testing of memory-based generalization to BDP, as well as to biological relatives of SZP (SZR). We applied a version of the Acquired Equivalence (AE) paradigm (Myers et al., 2003) that allows a selective assessment of memory-based generalization. We hypothesized that 1) SZP and BDP would both show intact feedback-driven associative learning and subsequent memory for learned associations, but would be impaired at generalization of what they learned, with both groups performing similarly to each other and worse than healthy controls (HC); and, 2) SZR would show learning, memory for learned associations and generalization performance intermediate between SZP and HC. The study groups were matched on age and had equivalent levels of education and IQ, providing a similar baseline of cognition-relevant features for the DM phenotype characterization.

2. Experimental materials and methods

2.1. Subjects

Probands who met the DSM-IV (American Psychiatric Association, 1994) criteria for SZ or BD, type I, with lifetime history of psychotic symptoms, eligible first-degree relatives of SZP with and without lifetime psychiatric diagnoses, and community HC were recruited. Initially, 37 SZP, 22 BDP, 24 SZR and 28 HC were tested; however 4 SZP, 2 BDP, 3 SZR and 2 HC were defined as outliers based on their cognitive performance (described in 2.4 Statistical analyses) and excluded from all analyses. The study did not allow enrollment of individuals with a history of major neurological or decompensated medical illness, mental retardation, traumatic brain injury, substance abuse within the last month or substance dependence within the last 3 months. The study was approved by the institutional review board of the UT Southwestern Medical Center. All volunteers provided written informed consent.

Demographic, clinical and neuropsychological characteristics of the study sample and pertinent statistical results are presented in Table 1. The groups did not differ in age, handedness, race, or years of education; SZP had a higher proportion of males compared to HC. The Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996) was used to determine Axis I diagnoses in probands and SZR; the Structured Interview for DSM-IV Personality Disorders (Zanarini et al., 1996) was used for Axis II diagnoses in SZR. The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) was used to evaluate active symptom severity; BPRS psychosis and affective subscale scores, as well as total BPRS scores were calculated. The Global Assessment of Functioning/DSM-IV Axis V (GAF) ratings were also collected in probands and relatives. The probands were clinically stable medicated out-patients with active psychosis and/or mood symptom severity varying from remission/euthymic state to mild symptoms. SZR who had lifetime psychiatric diagnoses were clinically stable and asymptomatic while active in the study. No relatives with a proband-like psychosis diagnosis (SZ or BD) were included here. Five/21 SZR had no identifiable DSM-IV Axis I/II diagnoses, 5/21 SZR reported a lifetime history of psychotic symptoms (4 with psychotic depression and 1 with unspecified psychosis), the rest of relatives met criteria for other lifetime Axis I and/or II diagnoses. Thirty one/33 SZP, 14/20 BDP and 3/21 SZR reported past psychiatric hospitalizations. SZP and BDP did not differ on age of psychosis onset or age of the first psychiatric hospitalization. SZP reported a higher number of lifetime hospitalizations compared to either BDP or SZR. The probands did not differ in GAF or total BPRS scores, although SZP had higher psychosis scores and lower affective scores compared to BDP. The probands had higher total, psychosis and affective BPRS scores and lower GAF scores than SZR.

Most probands (16/33 SZP, 16/20 BDP) and 3/21 SZR were treated with a combination of psychotropic agents while active in this study, including antipsychotics (all SZP, 12/20 BDP), mood stabilizers (3/33 SZP, 16/20 BDP, and 3/21 SZR), and other agents among which antidepressants and anxiolytics were most common. Since the proband groups were comparable with respect to active medication status, cognitive outcomes were not adjusted for medication use.

2.2. Neuropsychological tests

In addition to the clinical assessments, probands and relatives completed three standardized tests of DM [Logical Memory II/delayed story recall (LM-II) from the Wechsler Memory Scale — Third edition (Wechsler, 1997), the Word Recognition (WARR-W) and the Face Recognition (WARR-F) subtests from the Warrington Recognition Memory Test (Warrington, 1984)], as well as the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001) general intelligence estimates. Individual DM test scores and the DM composite score were calculated. No differences emerged between SZP and BDP on any of the DM tests. Probands scored lower than relatives on WARR-W and on the DM composite, but not on the LM-II or WARR-F. The study groups did not differ on WTAR IQ estimates.

2.3. Acquired Equivalence task

A modified version of the AE paradigm (Myers et al., 2003) was used to examine three cognitive measures: associative learning, memory for learned associations, and memory generalization. A detailed description of the task is provided elsewhere (Myers et al., 2003; Shohamy et al., 2010). In brief, the task consists of two phases: learning and test (Fig. 1). During the learning phase, participants used feedback to learn associations between cartoon faces of people and differently colored fish. Feedback-based learning proceeded in three stages to an accuracy of 95%. Each of the stages consisted of eight blocks, with one block containing two instances of each trial type, with a total of 192 learning trials. Learning performance was assessed based on the number of errors made prior to reaching an accuracy of 95% in each stage of learning (number of 'errors to criterion', ETC).

During the test phase, memory for previously learned associations and memory generalization were tested. Participants were presented with interleaved trials consisting of probes for the six previously learned ('trained') associations as well as probes for the two critical instances of generalization to untrained associations ('generalized'), each presented six times. No feedback was provided. During this phase, accuracy on memory for trained associations and memory generalization was assessed as percentage of correct responses for 'trained' and 'generalized' trials, respectively.

2.4. Statistical analyses

A one-way analysis of variance (ANOVA) with a subsequent post hoc Tukey HSD test, two-tailed *t*-test, and Yates corrected chi-square test were used as appropriate for socio-demographic, clinical and neuropsychological outcomes. To test the a priori hypotheses, learning, trained and generalization accuracy performance were compared between 1) the psychosis probands and controls (SZP vs. BDP vs. HC), and 2) SZ probands, relatives and controls (SZP vs. SZR vs. HC). Because some individuals have exceptional difficulty navigating the basic task demands, we defined outliers as individuals whose learning performance fell above 3 standard deviations from the mean ETC over all stages of learning in each of the groups. These outliers were excluded from all analyses (4 SZP, 2 BDP, 3 SZR, and 2 HC).

Learning and generalization outcomes were analyzed using a mixed-effects repeated measures analysis (PROC MIXED, SAS). For the *learning* outcome, the groups were compared over three stages of learning (ETC 1–3). The log of ETC scores was used because the log transformation produced a model which satisfied the assumption of normally distributed errors. The model contained terms for group,