Memory generalization is selectively altered in the psychosis dimension

Elena I. Ivleva a,⁎, Daphna Shohamy b, Perry Mihalakos a, David W. Morris a, Thomas Carmody a, Carol A. Tamminga a

a Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX 75390, United States
b Department of Psychology, Columbia University, New York, NY 10025, United States

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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),
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 stabilized 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,
learning stage, and group × learning stage interaction. Stage of learning (ETC 1–3) was the repeated effect. Group was a fixed between-subjects effect while intercepts and stage of learning were random effects. For the analysis involving SZR, correlations between members effect while intercepts and stage of learning were random effects. Stage of learning stage, and group×learning stage interaction. Stage of learning (ETC 1–3) was the repeated effect. Group was a fixed between-subjects effect while intercepts and stage of learning were random effects. For the analysis involving SZR, correlations between members effect while intercepts and stage of learning were random effects. Stage of learning stage, and group×learning stage interaction. Stage of learning (ETC 1–3) was the repeated effect. Group was a fixed between-subjects effect while intercepts and stage of learning were random effects. For the analysis involving SZR, correlations between members effect while intercepts and stage of learning were random effects. Stage of learning stage, and group×learning stage interaction. Stage of learning (ETC 1–3) was the repeated effect. Group was a fixed between-subjects effect while intercepts and stage of learning were random effects. For the analysis involving SZR, correlations between members effect while intercepts and stage of learning were random effects. Stage of learning stage, and group×learning stage interaction. Stage of learning (ETC 1–3) was the repeated effect. Group was a fixed between-subjects effect while intercepts and stage of learning were random effects. For the analysis involving SZR, correlations between members effect while intercepts and stage of learning were random effects. Stage of learning stage, and group×learning stage interaction. Stage of learning (ETC 1–3) was the repeated effect. Group was a fixed between-subjects effect while intercepts and stage of learning were random effects. For the analysis involving SZR, correlations between members effect while intercepts and stage of learning were random effects. Stage of learning stage, and group×learning stage interaction. Stage of learning (ETC 1–3) was the repeated effect. Group was a fixed between-subjects effect while intercepts and stage of learning were random effects. For the analysis involving SZR, correlations between members effect while intercepts and stage of learning were random effects. Stage of learning stage, and group×learning stage interaction. Stage of learning (ETC 1–3) was the repeated effect. Group was a fixed between-subjects effect while intercepts and stage of learning were random effects. For the analysis involving SZR, correlations between members effect while intercepts and stage of learning were random effects.

The model generalization outcome was analyzed using a mixed-effects analysis. The mixed-effects model contained only a fixed between-subjects term for group. As in the learning outcome mixed model, intercepts were random effects, a random family effect was included in models with SZR subjects, and an unstructured correlation matrix was used. Also, the Tukey–Kramer adjustment was used to adjust pair-wise comparisons of estimated means.

The magnitude of pair-wise between group differences in the AE outcomes was also assessed using Cohen’s d.
Correlation coefficients (Pearson’s) were used to examine associations between the AE outcomes that showed significant between group differences and clinical/neuropsychological measures. The Bonferroni correction for multiple comparisons was used for the correlation analyses.

3. Results

3.1. Learning

The psychosis probands and controls contrast (SZP vs. BDP vs. HC) for learning performance revealed a significant between group effect \(F(2,76)=3.37, p=.04\) but no learning stage effect \(F(1,76)=.02, p=.89\) or group\×stage interaction \(F(2,76)=.97, p=.39\) [Fig. 2(A)]. Subsequent pair-wise comparisons showed that the differences in learning were accounted for by lower performance in SZP compared to HC in the initial stages of learning [stage 1: \(t(76)=3.2, p=.006, d=.77\); stage 2: \(t(76)=2.9, p=.01, d=.77\], but not in stage 3 [\(t(76)=.9, p=.63, d=.3\]. No differences were obtained between the psychosis probands in any stage of learning (SZP vs. BDP, all \(p>.58, d=.18–.39\)). No significant differences were found between BDP and HC (all \(p>.15\), although the effect sizes supported lower performance in BDP in stages 1 and 2 (stage 1: \(d=.62\); stage 2: \(d=.87\), but not in the last stage of learning (\(d=.16\)).

The SZ probands, relatives and controls comparison (SZP vs. SZR vs. HC) revealed a significant between group effect \(F(2,77)=3.17, p=.048\) but no learning stage effect \(F(1,77)=.05, p=.82\) or group\×stage interaction \(F(2,77)=.97, p=.38\) [Fig. 2(B)]. Similar to the probands and HC contrast, SZP showed lower performance compared to HC in the initial stages of learning [stage 1: \(t(77)=3.1, p=.008, d=.77\]; stage 2: \(t(77)=3.0, p=.01, d=.77\], but not in stage 3 [\(t(77)=.9, p=.63, d=.3\]. No differences were obtained between either SZR vs. SZP (all \(p>.31, d=.23–.39\), or SZR and HC (all \(p>.35, d=.13–.65\) in any stage of learning.

In SZP, the number of errors during the 1st stage of learning was inversely correlated with education (\(r = -0.45, p = .009\), WTAR IQ (\(r = -0.37, p = .034\), and LM-II (\(r = -0.53, p = .022\). The number of errors during the 2nd stage of learning was inversely correlated with WTAR IQ (\(r = -0.44, p = .014\). All results were non-significant after Bonferroni correction. No correlations emerged between learning performance and other DM measures; age; total, psychosis or affective BPRS scores; GAF scores; or the disease severity markers, including age of psychosis onset, age at the first psychiatric hospitalization, or lifetime number of hospitalizations.
Subsequent pair-wise comparisons showed lower generalization in the psychosis probands, relatives, and controls: all groups showed equally high performance on the test of trained (previously learned) associations, although not significantly different from either group. The three groups did not differ in associative learning performance at the final stage of learning.

3.2. Test

3.2.1. Memory for trained associations

The average scores for performance on the trained associations in all groups fell within normal ranges (≥95% accuracy): SZP (99.09±2.25), BDP (97.4±3.5), SZR (94.86±17.47), and HC (98.46±2.63) [Fig. 3(A,B)]. Three out of 33 SZP, 2/20 BDP, 2/21 SZR and 3/26 HC showed accuracy for trained associations below 95%. No between group differences in memory for trained associations performance were observed (all p > .23).

3.2.2. Memory generalization

For memory generalization performance, the psychosis probands and controls comparison (SZP vs. BDP vs. HC) revealed a significant between group effect [F(2,76) = 3.8, p = .026] accounted for by lower performance in SZP compared to HC [t(76) = 2.5, p = .038, d = .8]. Furthermore, there was a trend for lower generalization performance in BDP than in HC [t(76) = 2.3, p = .069, d = .95]. No difference in generalization was obtained between the psychosis probands [SZP vs. BDP, t(76) = 0.0, p = .99, d = .02] [Fig. 3(A)].

The SZ probands, relatives and controls contrast (SZP vs. SZR vs. HC) revealed a significant between group effect [F(2,77) = 4.8, p = .011]. Subsequent pair-wise comparisons showed lower generalization in SZP compared to HC [t(77) = 2.9, p = .013, d = .8]. SZR showed generalization performance intermediate between SZP and HC and more similar to controls, but not significantly different from either group [SZR vs. SZP, t(77) = 2.1, p = .09, d = .53; SZR vs. HC, t(77) = .6, p = .85, d = .29] [Fig. 3(B)].

No correlations were found between memory generalization and learning across all stages; memory recall; any of the DM tests; WTR IQ; age; education; total, psychosis and affective BPRS scores; GAF scores; age of psychosis onset, age at the first psychiatric hospitalization, or lifetime number of hospitalizations in either SZP or BDP.

4. Discussion

This study sought to characterize differential phenotypes of DM, with the focus on hippocampus-mediated memory generalization in SZP vs. BDP, as well as in SZP vs. SZR. We chose the AE task that has been validated to dissociate associative learning, memory for learned associations, and memory generalization in both HC and SZP (Myers et al., 2003; Keri et al., 2005; Shohamy et al., 2010). Here, we extended the testing of the generalization memory phenotype to bipolar psychosis and SZR. The outcomes showed no differences in overall learning and memory retrieval in either psychosis probands or SZR, as compared to HC, although SZP demonstrated slower initial learning, consistent
tered hippocampal plasticity (Tamminga et al., 2010) offers a

Generalization and inference, where CA3 and its interactions with

DG and its efferent projections to CA3 (Eastwood et al., 1995;

Shohamy et al., 2010; Eastwood et al., 2009) demonstrated an adverse effect of risperidone on procedural learning in predictive saccade paradigm in medication-naïve SZP, and linked this impairment to altered dopamine regulation in the frontostriatal system. Beninger et al. (2003) found a differential effect of typical and atypical antipsychotics on learning processes in SZP: typical antipsychotics were associated with impaired probabilistic classification learning thought to be mediated by striatum, while atypical antipsychotics were associated with impaired learning of a gambling task thought to be mediated by ventromedial prefrontal cortex. Keri et al. (2005) reported a direct correlation between the number of errors in the AE learning phase and the daily chlorpromazine-equivalent doses of antipsychotics in SZP. However, a more recent study that contrasted SZP on- and off-antipsychotic medication (Shohamy et al., 2010) showed no differences in AE learning with antipsychotic treatment. Furthermore, this study suggested that memory generalization may be selectively improved by antipsychotic treatment. Although specific mechanisms underlying this effect of antipsychotic drugs on memory generalization remain unknown, their ability to diminish a long-term potentiation in hippocampal subfields through D1 dopamine receptors action (Kubota et al., 2001; Jay et al., 2004; Navakkode et al., 2007) and subsequent effect on hippocampal subfield metabolism may contribute. Taken together, these findings demonstrate a complex differential effect of antipsychotic treatment on various aspects of learning and memory, and call for future studies to gain a deeper understanding of molecular mechanisms underlying these medication effects. Since our sample included moderately symptomatic, actively medicated probands, our findings demonstrate that deficient generalization persists in SZP and BDP despite treatment, but may be underestimated. Since the majority of probands in this sample were medicated with a combination of psychotrophic agents, we were not able to distinguish between ‘primary’ generalization abnormalities and medication effect, or to test effects of specific medications.

There were several limitations to this study, despite its unique dimensional psychosis emphasis. First, the modest sample size limited statistical power of the analyses of cognitive function, despite our ability to show meaningful differences. Second, the group of SZR was heterogeneous and included both affected and unaffected relatives, though all affected relatives were asymptomatic at the time of testing, thus it is unlikely that the cognitive outcomes were influenced by active clinical state. It would be interesting to pursue a comparison of memory phenotypes in relatives with and without lifetime psychotic phenomena which could not be done here due to lack of sufficient power. Finally, since most probands and a proportion of relatives had a long history of medication use and were treated with a combination of various psychotrophic agents during this study, the effect of medication on cognitive performance cannot be ruled out. Future studies in larger samples of unmedicated probands and unaffected relatives could help to further characterize memory phenotypes free of medication and disease burden effect.

In summary, the three critical components of learning and memory tested here – associative learning, memory for learned associations, and memory-based generalization – did not distinguish probands with SZ and psychotic BD. Both psychoses were associated with diminished memory generalization, independent of overall learning and memory retrieval. SZR showed memory generalization that appeared to be intermediate between SZP and HC. Together with prior reports (Myers et al., 2003; Heckers et al., 2004; Shohamy and Wagner, 2008; Shohamy et al., 2010; Eichenbaum et al., 2011), these findings suggest that altered hippocampal function may contribute to both memory generalization and psychosis. Future research employing cognitive, high resolution imaging and genetic paradigms in larger family psychosis samples may provide further understanding of the molecular bases for memory and psychosis.

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data; in the writing of the report; and in the decision to submit the manuscript for publication.

Contributors
Elena Ileva, M.D., Ph.D. was a Co-Principal Investigator for the study, contributed to designing the study, performed clinical and neurocognitive data collection, contributed to the clinical, neuropsychological and Acquired Equivalence test data analysis and interpretation, and took the lead role in the preparation and writing of the manuscript.

Daphna Shohamy, Ph.D. was a study collaborator, provided guidance on the Acquired Equivalence test data analysis and interpretation, and contributed to writing and editing of the manuscript.

Perry Mihalakis, B.S. collected the Acquired Equivalence test primary data, and contributed to the analysis, interpretation and editing the Introduction and Discussion sections pertinent to the Acquired Equivalence data.

David W. Morris, Ph.D. helped with the statistical analysis and interpretation of the clinical and neuropsychological data, and contributed to overall editing of the manuscript.

Carol A. Tammenga, M.D. was a Principal Investigator for the study and provided senior expertise for the interpretation of the clinical, neuropsychological, and Acquired Equivalence data, and contributed to overall editing of the manuscript.

All authors contributed to and have approved the final manuscript.

Conflict of interest
All authors report no biomedical financial interests or potential conflicts of interest.

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