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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,

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Conflict of Interest

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

Contributors

Elena Ivleva, M.D., Ph.D. was a co - Principal Investigator for the study, contributed to designing the study, supervised 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 Mihalakos, 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.

Thomas J. Carmody, Ph.D. Conducted the statistical analyses of the clinical, neuropsychological, and Acquired Equivalence data, and contributed to overall editing of the manuscript.

Carol A. Tamminga, 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.

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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.

Keywords

psychosis; schizophrenia; bipolar disorder; generalization memory; hippocampus

1.1 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 (Arts et al., 2008; Glahn et al., 2004; Hill et al., 2008; Schretlen et al., 2007; Stefanopoulou et al., 2009) and their biological relatives (Glahn et al., 2010; Sitskoorn et al., 2004; Toomey et al., 1998). Novel cognitive paradigms translated from animal and computational models have allowed the dissection of memory function (Myers et al., 2003; Preston et al., 2005; Shohamy and Wagner, 2008; Titone et al., 2004) 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; Preston et al., 2005; Shohamy and Wagner, 2008; Titone et al., 2004). Deficits in generalizing learned information to novel choices, thought to be mediated by hippocampus (Eichenbaum et al., 2011; Heckers et al., 1998; Heckers et al., 2004; Myers et al., 2003; Shohamy et al., 2010; Shohamy and Wagner, 2008), 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) (Glahn et al., 2010; Hill et al., 2008), 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; Shohamy et al., 2010; Titone et al., 2004), 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 phenotypes characterization.

1.2 EXPERIMENTAL MATERIALS and METHODS

1.2.1 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 **1.2.3 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 symptoms severity; BPRS psychosis and affective subscales 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 symptoms 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.

1.2.2 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 tests 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.

1.2.3 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 (Figure 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.

1.2.4 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 x 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 of the same family were accounted for in the error structure by inclusion of a random family effect. An unstructured covariance matrix was used. Estimated group means were compared within each stage of learning using the Tukey-Kramer adjustment for the 3 pair-wise comparisons; adjusted probability values below .5 were considered significant.

Since the performance on trials testing *memory for learned associations* was high in all groups (close to 100%), producing a ceiling effect, we were not able to analyze these data

using the mixed-effect model. Therefore, to evaluate the memory for learned associations outcome, the proportion of individuals in each group who showed 'trained' trials accuracy below 95% was estimated, and subsequent Fisher exact chi-square test was applied.

The *memory 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.

1.3 RESULTS

1.3.1 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 x stage interaction [$F(2,76)=.97$, $p=.39$] [Figure 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 x stage interaction [$F(2,77)=.97$, $p=.38$] [Figure 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 ($r=-.45$, $p=.009$), WTAR IQ ($r=-.37$, $p=.034$), and LM-II ($r=-.53$, $p=.022$). The number of errors during the 2nd stage of learning was inversely correlated with WTAR IQ ($r=-.44$, $p=.014$). 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.

1.3.2 Test

1.3.2.1 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), HC (98.46 ± 2.63) [Figure 3(A, B)]. Three out of 33 SZP, 4/20 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 was observed (all $p > .23$).

1.3.2.2 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, $t(76)=0.0$, $p=.99$, $d=.02$] [Figure 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 [SZR vs. SZP, $t(77)=2.1$, $p=.09$, $d=.53$; SZR vs. HC, $t(77)=.6$, $p=.85$, $d=.29$] [Figure 3(B)].

No correlations were found between memory generalization and learning across all stages; memory recall; any of the DM tests; WTAR 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.

1.4 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 (Keri et al., 2005; Myers et al., 2003; 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 with prior reports (Shohamy et al., 2010). All probands, however, showed lower memory generalization performance compared to HC (statistically significant in SZP vs. HC, and at a trend level ($p=.069$) in BDP vs. HC), with no differences found between SZP and BDP. This finding suggests a specific deficit in memory-guided generalization common to the psychosis probands that is independent of learning or memory for previously learned associations.

In the SZ proband vs. relative comparison, SZR did not separate statistically from either SZP or HC in the generalization memory outcome; however the effect sizes supported generalization performance of the SZR as similar to HC. Overall, the pattern of AE performance in SZR observed here resembles the commonly reported pattern of DM function measured by traditional neuropsychological tests with milder deficits in SZR as compared to SZP (Cirillo and Seidman, 2003; Gur et al., 2007).

Interestingly, generalization performance did not correlate with any of the other AE outcomes (learning or recall), DM or IQ scores, age, education, symptoms severity, level of general functioning, age at psychosis onset, age at the first psychiatric admission, or lifetime number of admissions in either SZP or BDP. This suggests that the ability to generalize based on memory may be a unique cognitive phenotype independent of other aspects of cognition tested here or disease severity.

Our finding of impaired memory generalization in SZP has confirmed previous reports (Farkas et al., 2008; Heckers et al., 2004; Keri et al., 2005; Shohamy et al., 2010). However, we have extended the literature with the observation that generalization memory deficits are similar in probands with SZ and psychotic BD. This suggests that it is the psychosis component of the two disorders that may be specifically associated with impaired memory generalization. It is likely that the inability to generalize past experience towards novel environmental cues – a process shown to be mediated by hippocampus (Eichenbaum et al., 2011; Heckers et al., 2004; Myers et al., 2003; Shohamy et al., 2010; Shohamy and Wagner, 2008) – is not specific to SZ, but rather may be common to diseases within the psychosis dimension.

Although the exact mechanisms underlying generalization deficits and its association with psychosis remain unknown, several intriguing observations have been made. Reports from animal studies suggest a differential role for hippocampal subfields in memory-based generalization and inference, where CA3 and its interactions with dentate gyrus (DG) and entorhinal cortex may play a crucial role (Nakazawa et al., 2002; Rajji et al., 2006). Postmortem studies in SZ offer evidence for reduction of adult neurogenesis markers in DG (Reif et al., 2006), localized reduction in glutamatergic transmission in DG and its efferent projections to CA3 (Eastwood et al., 1995; Gao et al., 2000; Law and Deakin, 2001), and decreased number of synapses of DG efferent fibers onto CA3 pyramidal neurons (Kolomeets et al., 2007). Translating animal and postmortem molecular findings to SZ pathophysiology, a recently proposed model of altered hippocampal plasticity (Tamminga et al., 2010) offers a hypothetical formulation for the relationship between impaired memory-based generalization and psychosis. This model suggests that a hypoglutamatergic lesion in DG possibly generates alterations in synaptic plasticity in CA3, specifically, a compensatory increase in sensitivity to incoming stimuli in CA3 excitatory synapses, and results in altered memory generalization, associational mistakes and, possibly, psychotic productions. This model, though hypothetical, offers a novel translational paradigm of molecular mechanisms of inferential memory and psychosis, and is currently being tested.

Recent studies have begun to examine the effect of antipsychotic medication on learning and memory generalization in SZP. Harris 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 (Jay et al., 2004; Kubota et al., 2001; Navakkode et al., 2007) and subsequent effect on hippocampal subfield metaplasticity may contribute. Taken together, these findings demonstrate a complex differential effect of antipsychotic treatment on various aspect 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 psychotropic 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 psychotropic 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 (Eichenbaum et al., 2011; Heckers et al., 2004; Myers et al., 2003; Shohamy et al., 2010; Shohamy and Wagner, 2008), 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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Figure 1. Acquired Equivalence Task

Over the three Learning stages, participants were trained simultaneously on two sets of stimuli (four faces of people and four color fish) in a feedback-guided procedure. After these were learned to a 95% accuracy, at the Test phase, participants were tested on the associations they learned (with no feedback), as well as on novel recombinations of stimuli that depend on the ability to generalize from the previously learned associations.

Figure 2. Acquired Equivalence Task: Learning Phase Performance

SZP – probands with schizophrenia, BDP – probands with psychotic bipolar disorder, SZR – relatives of SZP, HC – healthy controls

The bars show group means for the number of errors in each stage of learning, the error bars show standard deviations of the group means.

(A) Learning Phase performance for the Psychosis Probands and Healthy Controls: SZP made more errors in the first two stages of learning compared to HC: ** - Stage 1: SZP vs. HC, $p = .006$; * Stage 2, SZP vs. HC, $p = .01$. The three groups did not differ in associative learning performance at the final stage of learning.

(B) Learning Phase Performance for the Schizophrenia Probands, Relatives, and Healthy Controls: SZP made larger number of errors in the first two stages of learning compared to HC: ** - Stage 1: SZP vs. HC, $p = .008$; * Stage 2, SZP vs. HC, $p = .01$. SZR showed associative learning performance intermediate between SZP and HC, although not significantly different from either group. The three groups did not differ in associative learning performance at the final stage of learning.

Figure 3. Acquired Equivalence Task: Test Phase Performance

SZP – probands with schizophrenia, BDP – probands with psychotic bipolar disorder, SZR – relatives of SZP, HC – healthy controls

The bars show group means for percent of correct responses for trained and generalized associations, the error bars show standard deviations of the group means.

(A) Test Phase performance for the Psychosis Probands and Healthy Controls: All groups showed equally high performance on the test of trained (previously learned) associations. Both SZP and BDP showed selectively impaired ability to generalize previously learned associations: * SZP vs. HC, $p = .038$; BDP vs. HC, $p = .069$ (trend). No difference in generalization were obtained between the psychosis probands.

(B) Test Phase performance for the Schizophrenia Probands, Relatives, and Healthy Controls: All groups showed equally high performance on the test of trained (previously learned) associations, although SZR had higher performance variability. SZP showed lower generalization performance compared to HC (* $p = .013$). SZR showed generalization performance intermediate between SZP and HC and not significantly different from either group.

Table 1

Demographic, Clinical and Neuropsychological Characteristics of Study Sample

Demographic and clinical characteristics	SZP (n=33)	BDP (n=20)	SZR (n=21)	HC (n=26)	Test statistic	p value
Age, yrs; Mean (SD)	39.4 (9.2)	37.0 (9.1)	40.1 (12.6)	39.5 (12.2)	$F(3, 96) = .34$	.79
Gender/Male; n (%)	20 (60.6)	6 (30.0)	11 (52.4)	6 (23.1)	$\chi^2(3) = 10.52$	.02 ^a
Left-handed; n (%)	7 (21.2)	3 (15.0)	1 (4.8)	3 (11.5)	$\chi^2(3) = 3.06$	.38
Race; n (%)					$\chi^2(3) = 1.25$	.74
White	26 (78.8)	18 (90)	12 (57.1)	22 (84.6)		
Black	6 (18.2)	1 (5.0)	7 (33.3)	2 (7.7)		
Other	1 (3.0)	1 (5.0)	2 (9.5)	2 (7.7)		
Education, yrs; Mean (SD)	14.1 (2.7)	13.4 (1.9)	14.1 (2.4)	14.3 (1.9)	$F(3, 96) = .78$	.51
Age at psychosis onset, yrs; Mean (SD)	23.00 (8.53)	20.68 (8.32)	26.5 (9.54)	-	SZP vs. BDP: $F(51) = 0.84$	.41 ^b
Age at the 1st hospitalization, yrs; Mean (SD)	26.29 (7.96)	27.57 (8.65)	29.38 (8.78)	-	SZP vs. BDP: $F(43) = 0.67$	.15 ^c
Number of hospitalizations; Mean (SD)	8.78 (8.9)	2.65 (2.62)	0.19 (0.6)	-	$F(2, 71) = 14.02$	<0.001 ^d
BPRS total score; Mean (SD)	45.9 (11.4)	43.8 (10.3)	32.3 (9.7)	-	$F(2, 55) = 9.54$	<.001 ^e
BPRS psychosis subscale; Mean (SD)	12.89 (4.92)	9.35 (3.53)	5.35 (2.31)		$F(2, 55) = 17.97$	<.001
BPRS affective subscale; Mean (SD)	7.17 (2.38)	10.05 (2.74)	5.7 (2.05)		$F(2, 55) = 16.82$	<.001
GAF; Mean (SD)	61.0 (13.4)	58.3 (11.6)	77.1 (15.9)	-	$F(2, 58) = 11.27$	<0.001 ^f
DSM-IV Axis I/II lifetime diagnoses in SZR; n (%)						
No Axis I/II diagnosis			5 (23.8)			
MDD with psychotic features			4 (19.05)			
Psychotic disorder NOS			1 (4.76)			
Bipolar disorder, type II			1 (4.76)			
MDD without psychotic features			3 (14.29)			
Anxiety disorder			2 (9.52)			
Substance abuse/dependence			7 (33.33)			
Cluster A personality disorder (schizoid, paranoid, schizotypal)			6 (28.57)			
Avoidant personality disorder			1 (4.76)			
More than one Axis I/II disorder			11 (52.38)			

Demographic and clinical characteristics	SZP (n=33)	BDP (n=20)	SZR (n=21)	HC (n=26)	Test statistic	p value
Neuropsychological Measures						
WTAR IQ; Mean (SD)	101.1 (11.8)	100.3 (11.3)	100.0 (12.7)	105.9 (8.7)	$F(3, 91) = 1.45$	.23
LM-II; Mean (SD)	51.48 (11.84)	50.18 (10.51)	57.17 (7.44)		$F(2, 54) = 2.69$	.09
WARR-W; Mean (SD)	42.96 (14.86)	45.26 (11.88)	54.17 (7.79)		$F(2, 54) = 4.91$	.01 ^g
WARR-F; Mean (SD)	36.48 (11.69)	36.67 (8.53)	42.67 (12.77)		$F(2, 54) = 1.93$	.15
DM Composite; Mean (SD)	43.64 (10.79)	44.04 (7.57)	51.33 (5.11)		$F(2, 54) = 5.62$	.006 ^h
Concomitant medications						
Off medications; n (%)	0 (0)	0 (0)	13 (61.9)	26 (100.0)		
Antipsychotics; n (%)	33 (100.0)	12 (60.0)	0 (0)	0 (0)		
Mood stabilizers; n (%)	3 (9.1)	16 (80.0)	3 (14.3)	0 (0)		
Other; n (%)	15 (45.5)	13 (65.0)	8 (38.1)	0 (0)		
Combined medications; n (%)	16 (48.5)	16 (80.0)	3 (14.3)	0 (0)		

SD - standard deviation, SZP - probands with schizophrenia, BDP - probands with psychotic bipolar disorder, SZR - relatives of probands with schizophrenia, HC - healthy controls, BPRS - Brief Psychiatric Rating Scale, GAF - Global Assessment of Functioning scale, DSM-IV - the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, WTAR IQ - Wechsler Test of Adult Reading general intelligence estimate, LM-II - Logical Memory II/delayed story recall, the Wechsler Memory Scale, WARR-W - Warrington Word Recognition test, WARR-F - Warrington Face Recognition test, DM - declarative memory

^aSZP had a higher proportion of males compared to HC: $\chi^2(1) = 6.86, p = .009$

^{b, c} Since only 5/21 SZR met a lifetime diagnosis of psychotic disorder, and only 3/21 SZR reported history of psychiatric hospitalizations, SZR were not included in these statistical analyses

^dSZP reported a higher number of lifetime hospitalization compared to BDP ($p = .002$) and SZR ($p < .001$)

^eThe BPRS is used to rate active symptoms severity in the past week. The BPRS total score includes a sum of 20 BPRS variables, with a maximum score of 140. The BPRS psychosis subscale score includes BPRS items 4, 11, 12 and 15 (Conceptual Disorganization, Suspiciousness, Hallucinatory Behavior, and Unusual Thought Content), with a maximum score of 28. The BPRS affective subscale score includes BPRS items 8, 9, 10, and 17 (Grandiosity, Depressive Mood, Hostility, Excitement), with a maximum score of 28. Probands had higher BPRS total, psychosis and affective scores compared to relatives: a) total score: SZP vs. SZR, $p < .001$; BDP vs. SZR, $p = .003$; b) psychosis score: SZP vs. SZR, $p < .001$; BDP vs. SZR, $p = .007$; c) affective score: BDP vs. SZR, $p < .001$. Within the proband groups comparison, SZP and BDP did not differ in total BPRS scores; SZP had higher psychosis scores ($p = .012$) and lower affective scores ($p = .002$) compared to BDP.

^f Probands had higher GAF scores than relatives: SZP vs. SZR, $p = .001$; BDP vs. SZR, $p < .001$

^g Probands scored lower than relatives on Warrington Word Recognition test: SZP vs. SZR, $p = .013$, BDP vs. SZR, $p = .055$ (trend)

^h Probands had lower declarative memory composite scores compared to relatives: SZP vs. SZR, $p = .013$, BDP vs. SZR, $p = .018$