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Impaired associative inference in the early stage of psychosis

Kristan Armstrong[*], **Suzanne Avery**, **Jenni U. Blackford**, **Neil Woodward**, **Stephan Heckers**

Vanderbilt University Medical Center, Department of Psychiatry and Behavioral Sciences, Nashville, TN, USA

Abstract

Relational memory is impaired in chronic schizophrenia. It is unclear if similar deficits are already present in the early stage of psychosis. We used the Associative Inference Paradigm to test relational memory ability in the early stage of a non-affective psychotic disorder. Eighty-two early stage psychosis patients and 67 healthy control subjects were trained on 3 sets of 30 paired associates: H-F1 (house paired with face), H-F2 (same house paired with new face), F3–F4 (two new faces). Subjects who reached 80% recall accuracy of the paired associates during training were then tested for their ability to recall the previously seen pairs and solve a novel, inferential pairing F1–F2 (faces linked through association to same house). Sixty early psychosis patients (73%) and 67 healthy control subjects (100%) successfully reached the accuracy threshold (80%) during training and were included in the analysis of relational memory. The early stage psychosis patients showed less of an associative inference effect than the healthy controls (pair type by group interaction: $F(1,125) = 5.04$, $p < 0.05$). However, the majority of early psychosis patients (52%) displayed intact inferential memory, compared to our prior study which revealed just 16% of chronic schizophrenia patients had intact inferential memory. Patients in the early stage of psychosis show a relational memory deficit, although less pronounced than in chronic schizophrenia. Longitudinal studies are needed to examine the progression of relational memory deficits in schizophrenia and its associations with clinical, functional, and biological measures.

Keywords

Relational memory; Early stage psychosis; Associative inference; Schizophrenia; Episodic memory

[*]Corresponding author at: Department of Psychiatry, 1601 23rd Avenue South, Room 3060, Nashville, TN 37212, USA. kristan.armstrong@vanderbilt.edu (K. Armstrong).

Contributors

Ms. Armstrong conducted clinical interviews, collected data, analyzed data, and wrote the manuscript. Dr. Avery wrote and edited the manuscript and contributed to literature review. Dr. Blackford edited the manuscript and gave feedback on the analysis plan. Dr. Woodward edited the manuscript and gave feedback on the analysis plan. Dr. Heckers designed the study, interpreted the findings, and contributed significantly to the editing of the manuscript. All authors have contributed to and approved the final manuscript.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.06.049.

1. Introduction

Cognitive deficits are prominent in chronic schizophrenia patients (Schaefer et al., 2013). Impairments are present during the prodrome and further deteriorate in the early stages of psychosis and generally remain stable through the chronic phase of illness (Bozikas and Andreou, 2011; Lewandowski et al., 2011; Saykin et al., 1994; Townsend and Norman, 2004). Learning and memory are particularly affected (Aleman et al., 1999; Saykin et al., 1991) and deficits in these areas are associated with poor social and occupational functioning (Green, 1996, 2006).

Relational memory, broadly defined as the ability to bind items together in memory, is particularly affected in chronic schizophrenia as studies show greater impairments in relational than non-relational memory tasks (Achim and Lepage, 2003; Armstrong et al., 2012a,b; Danion et al., 2007; Leavitt and Goldberg, 2009; Lepage et al., 2006; Ongur et al., 2006; Titone et al., 2004; Williams et al., 2010). Since relational memory depends on the proper function of the hippocampus (Bird, 2017; Davachi, 2006; Hannula et al., 2006), the specific impairment of relational memory in chronic schizophrenia has been interpreted as support for hippocampal models of psychosis (Heckers and Konradi, 2010; Lisman et al., 2008; Tamminga et al., 2010). However, the few studies of relational memory in the early stage of psychosis have produced mixed results: two studies report intact relational memory (Bartholomeusz et al., 2011; Williams et al., 2012) and two studies report impaired relational memory (Achim et al., 2007; Greenland-White et al., 2017). It is therefore unclear when during the disease process relational memory impairments become apparent in schizophrenia. Answering this question will provide further information on the timeline of hippocampal dysfunction in psychotic disorders.

The Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative recommended the Associative Inference Paradigm (AIP) (Preston et al., 2004) as the preferred task for investigating relational memory in schizophrenia (Ragland et al., 2009). Two previous studies using the AIP have confirmed a relational memory impairment in chronic schizophrenia (Armstrong et al., 2012a,b). Here we investigated relational memory early in the course of psychotic illness using the AIP (Preston et al., 2004) to determine if a relational memory impairment is present at the onset of a non-affective psychotic disorder. We expected early stage psychosis patients to show impaired relational memory ability compared to healthy control subjects.

2. Methods

2.1. Subjects

We recruited 82 early stage psychosis patients and 67 demographically matched healthy control subjects (see Table 1). Early psychosis patients were recruited from the Vanderbilt Psychiatric Hospital inpatient unit and outpatient clinic. All patients were only approached following consultation with the treating physician to ensure clinical stability and ability to provide informed consent for research participation. Healthy control subjects were recruited from the community via recruitment email. The Vanderbilt Institutional Review Board approved the study. The informed consent document was reviewed in detail with all subjects

and signed prior to study participation. Following completion of the experiment, subjects were thanked for their participation and compensated for their time.

All subjects were free of major physical and neurological illness, active substance abuse or dependence, and significant head injury. Healthy control subjects had no history of Axis I psychiatric disorders and psychosis patients met criteria for a non-affective psychotic disorder (Schizophreniform disorder n = 59, 72%; Schizophrenia n = 19, 23%; Schizoaffective disorder n = 4, 5%) as assessed by a trained rater using the SCID (Structured Clinical Interview for DSM-IV-TR) (First et al., 1995). Psychiatric diagnoses were confirmed via consensus meetings with an expert psychiatrist (SH).

To be included in this study, patients had to be in the first two years of a non-affective psychotic disorder. The mean duration of psychosis at the time of task completion was 28.7 weeks and the majority of patients were diagnosed with schizophreniform disorder (Table 1). Current mood and psychotic symptoms were rated using the HAM-D (Hamilton Depression Rating Scale) (Hamilton, 1960), YMRS (Young's Mania Rating Scale) (Young et al., 1978), and PANSS (Positive and Negative Syndrome Scale) (Kay et al., 1987). Most early psychosis patients were medicated at the time of task administration (Table 1); twelve early psychosis patients were not treated with antipsychotic medication at time of task completion. Patients currently taking anti-psychotic medications did not differ from those not taking anti-psychotic medication on any demographic or clinical measure.

2.2. Experimental task

The AIP (Armstrong et al., 2012a; Preston et al., 2004) [see Fig. 1] was used to assess relational memory ability. Stimuli included 30 color photographs of houses and 120 color photographs of faces (60 males, 60 females). These stimuli were obtained from photograph databases on the internet. Briefly, subjects were trained on three sets of 30 pairs: 1) House paired with a Face (H-F1); the same House paired with a second Face of opposite gender (H-F2); and 3) two new faces, one of each gender, Face 3-Face 4 (F3–F4). During training for a set, subjects passively viewed each stimulus pair for 4 s. Following each viewing set, they completed a self-paced 2 alternative forced-choice matching test without feedback. For the matching of face and house stimuli, subjects completed four sessions. For the Face-Face pairs, subjects completed only one session. Following training, subjects completed a test presented in a self-paced, 2 alternative forced-choice format without feedback. This included 90 trials of previously trained data (H-F1, H-F2, F3–F4) and a new set of 30 Face-Face pairs (F1–F2). F1–F2 pairs were linked by their relationship to the same House stimulus, and we will refer to this as the inferential memory condition. No explicit instructions for solving the F1–F2 pairs were provided. Inferential memory was tested by the ability to infer the relationship between Face 1 and Face 2 (F1–F2) via link to the same House without seeing the three objects together simultaneously. Limited training on the trained, non-inferential F3–F4 pairs provided a control task of similar difficulty as the novel test of F1–F2 pairs. The F3–F4 pairs will be referred to as the non-inferential memory condition. The entire session was completed in roughly 1 h. The experiment was presented on a computer using E-Prime software, version 2.0 (Psychology Software Tools, 2007).

Success in learning during training was required to ensure proper encoding of the House-Face pairs, which was necessary before a subsequent inference in F1–F2 can be made. To be included in the relational memory analysis, subjects were required to demonstrate successful learning during the training phase, specified as 80% accuracy for the final training block for H-F1 and H-F2. All healthy subjects met the criterion, but 22 early psychosis patients (poor learners) were unable to meet this criterion (Supplemental Fig. 1). These 22 poor learners in the early psychosis group displayed higher current PANSS positive scores and were more likely to be African American, but did not differ on any other clinical or demographic measure (see Table 1). To determine whether psychosis symptoms were associated with learning or task performance, we conducted secondary analyses in patients who reached criterion.

2.3. Statistical analysis

We performed repeated measures ANOVAs to test for group differences in memory. For training data, the within-subjects factors were repetition (first, second, third, and fourth practice) and pair type (H-F1, H-F2). For the relational memory test, the within-subjects factor was pair type (the inferential F1–F2 pair, the non-inferential F3–F4 pair). Demographics were analyzed with independent samples t-test for continuous variables of age, parental education, and IQ and categorical variables of gender and race were analyzed with chi-square analyses. To examine individual differences in the early psychosis patients, clinical symptom measures (HAMD, YMRS, PANSS, duration of illness, CPZ equivalent) were analyzed with independent samples *t*-tests for good learners versus poor learners and univariate analysis of variance with post-hoc tests analyzed for any significant overall differences when examining performance groups (Group 1: intact inferential memory, Group 2: success in learning, impaired inferential memory, Group 3: poor learners). Correlation and regression were used to assess predictors of inferential memory performance. All analyses were completed using the Statistical Package for the Social Sciences (SPSS) software (version 24) (Corp, Released 2015).

3. Results

3.1. Training

The 67 healthy control subjects and 60 early stage psychosis patients who met the training criterion were included in a statistical analysis of training performance. All subjects improved with practice (main effect of repetition: $F(3, 125) = 271.91$, $p < 0.001$, $\eta^2 = 0.68$). See supplement for further details of between-group differences during training (Supplemental Fig. 1).

3.2. Relational memory test

Subjects were tested for their ability to correctly identify both inferential and non-inferential Face-Face pairs (Fig. 2). The ANOVA for the relational memory portion of the experiment revealed higher overall accuracy in healthy subjects (81.64%) compared to patients (71.14%) (main effect of group: $F(1, 125) = 19.44$, $p < 0.001$, $\eta^2 = 0.13$), higher accuracy for inferential (84.17%) compared to non-inferential pairs (69.28%) (main effect of pair type: $F(1, 125) = 115.53$, $p < 0.001$, $\eta^2 = 0.48$), and a pair type-by-group interaction (F (1,

125) = 5.04, $p < 0.05$, $\eta^2 = 0.04$). The interaction was due to a greater accuracy difference between healthy controls and early psychosis patients in inferential (90.6% versus 77.0%) and non-inferential (72.7% versus 65.28%) performance (Post-hoc independent samples *t*-tests: F1–F2 accuracy: $p < 0.001$, F3–F4 accuracy: $p < 0.01$).

3.3. Predictors of performance

We explored the relationship between psychotic symptoms and inferential memory performance (F1–F2 accuracy) in the patient group. Inferential memory performance was not correlated with PANSS scores ($p = 0.10$) or antipsychotic dose (CPZ equivalent) ($p = 0.32$). IQ was a significant predictor of inferential memory performance ($F (1, 57) = 22.27$, $p < 0.001$) explaining 28.1% of the variance. Duration of illness did not account for additional variance beyond IQ ($F (2, 56) = 0.275$, $p = 0.602$).

3.4. Subgrouping patients on the basis of relational memory performance

Consistent with our prior investigation of chronic patients, we divided patients based on task performance (Group 1: F1–F2 accuracy of 66.67% or greater; Group 2: successful training but F1–F2 test accuracy <66.67%; Group 3: failed training requirement) (Armstrong et al., 2012a,b). This analysis revealed that the majority of early stage psychosis patients displayed intact inferential memory (N = 43, 52%) (Fig. 3). An additional 21% of patients (N = 17) showed success in learning the House-Face pairs during training, but impaired inferential memory, while 27% of patients (N = 22) failed to learn the House-Face pairs during training (minimum of 80% accuracy of both H-F1, H-F2 pairs). For comparison, performance groups in the previous chronic schizophrenia sample are displayed in Fig. 3: Group 1: 16.4%, Group 2: 44.3%, Group 3: 39.3% (Armstrong et al., 2012a).

To further characterize the three patient groups, we explored demographic and clinical measures across the three groups (see: Supplement, Table S1). We found significant differences in IQ ($F (2, 80) = 4.97$, $p < 0.01$), parental education ($F (2, 81) = 3.80$, $p < 0.05$) and depression ($F (2, 80) = 3.53$, $p < 0.05$). Post-hoc tests revealed that Group 1 had significantly higher IQ than both Group 2 ($p < 0.05$) and Group 3 ($p < 0.05$). Group 1 also demonstrated higher parental education levels than Group 2 ($p < 0.05$).

To determine if training patterns had an effect on inferential memory performance, we examined differences in training data between Groups 1 and 2. The two patient groups displayed significantly different learning patterns (see: Supplement, Fig. S2). Both groups improved with repetition (main effect of repetition: $F (3, 56) = 81.13$, $p < 0.001$, $\eta^2 = 0.81$), but overall performance was higher (main effect of group: $F (1, 58) = 36.44$, $p < 0.001$, $\eta^2 = 0.39$) and learning was more rapid (significant repetition by group interaction: $F (3, 56) = 5.6$, $p < 0.01$, $\eta^2 = 0.23$) in Group 1. We confirmed this pattern in a supplemental analysis of all patients with above chance training performance on H-F1 & H-F2 (N = 70) (see Supplemental results for further detail).

4. Discussion

We investigated relational memory in the early stages of a non-affective psychotic disorder. When compared with a matched healthy control group, relational memory was impaired in

early psychosis patients. However, there was considerable heterogeneity within the patient group. 52% of patients demonstrated intact inferential memory. In contrast, in a previous study, only 16% of chronic schizophrenia patients were able to reach normal inferential memory performance on the same task (Armstrong et al., 2012a).

Our findings may clarify discrepancies in the extant literature on relational memory in psychosis in a large sample of early psychosis patients. While numerous studies have demonstrated that relational memory is impaired in patients with chronic schizophrenia (Achim and Lepage, 2003; Armstrong et al., 2012a,b; Leavitt and Goldberg, 2009; Ongur et al., 2006; Williams et al., 2010), studies of early psychosis have found equivocal results: two studies report no relational memory differences in early psychosis patients (Bartholomeusz et al., 2011; Williams et al., 2012), while two report relational memory deficits (Achim et al., 2007; Greenland-White et al., 2017). Here we used a well-established relational memory paradigm, recommended by the CNTRICS initiative (Ragland et al., 2009), to study a large sample of early psychosis patients. Our findings provide compelling evidence that relational memory is impaired in early stage psychosis patients. However, this finding is in the context of significant heterogeneity as half of the early stage psychosis patients display intact relational memory ability. Further studies are needed to better understand the trajectory of relational memory ability during the course of a psychotic disorder.

Relational memory may present a unique opportunity for cognitive intervention, in contrast to other cognitive domains which show precipitous decline prior to the onset of frank psychosis and initial treatment (Lewandowski et al., 2011). As our sample is early in the stage of illness, it is likely that relational memory decreases as the illness progresses. Longitudinal studies of relational memory are needed to study individual patterns of relational memory in schizophrenia patients and their relationship to clinical and biological measures.

Relational memory is critically dependent on hippocampal function (Bird, 2017; Davachi, 2006; Hannula et al., 2006). In chronic schizophrenia, impaired relational memory ability is associated with abnormal hippocampal function and structure (Ongur et al., 2006; Ragland et al., 2015). However, it is not clear whether relational memory is also associated with hippocampal pathology in the early stages of a psychotic disorder. For example, hippocampal volume change is less prominent in the early stage of schizophrenia (Achim et al., 2007; Adriano et al., 2012; Bartholomeusz et al., 2017; Steen et al., 2006; Velakoulis et al., 2006; Williams et al., 2012). Here we find that relational memory ability is impaired in only some early psychosis patients, suggesting that deterioration in relational memory ability may index progression of hippocampal pathology in schizophrenia.

Our study has several limitations. First, most patients were medicated at the time of the study. However, we did not find a significant relationship of inferential memory performance with chlorpromazine equivalent dose. Additionally, the 12 non-medicated patients did not differ from the 48 patients who were taking anti-psychotic drugs on any demographic or clinical measure. Second, 22 out of the 82 patients enrolled did not reach the learning criterion. This did not allow us to test the hypothesis of a specific relational memory impairment in these subjects. However, supplemental analyses, including all patients with

training scores above chance level, confirmed the initial results. This suggests that our training threshold did not bias our relational memory findings.

In summary, in this largest study to date we provide novel evidence of relational memory impairment in the early stage of a non-affective psychotic disorder. In contrast to chronic schizophrenia patients, early psychosis patients show remarkable heterogeneity in relational memory performance, with the majority demonstrating preserved performance. Longitudinal studies are needed to assess the progression of relational memory deficits in psychosis. This will allow us to better define the individual differences in relational memory performance (e.g., impaired early on; normal early on with subsequent decline; and normal throughout the illness). Such studies can also identify the clinical and biological correlates of relational memory deficits in patients with a non-affective psychotic disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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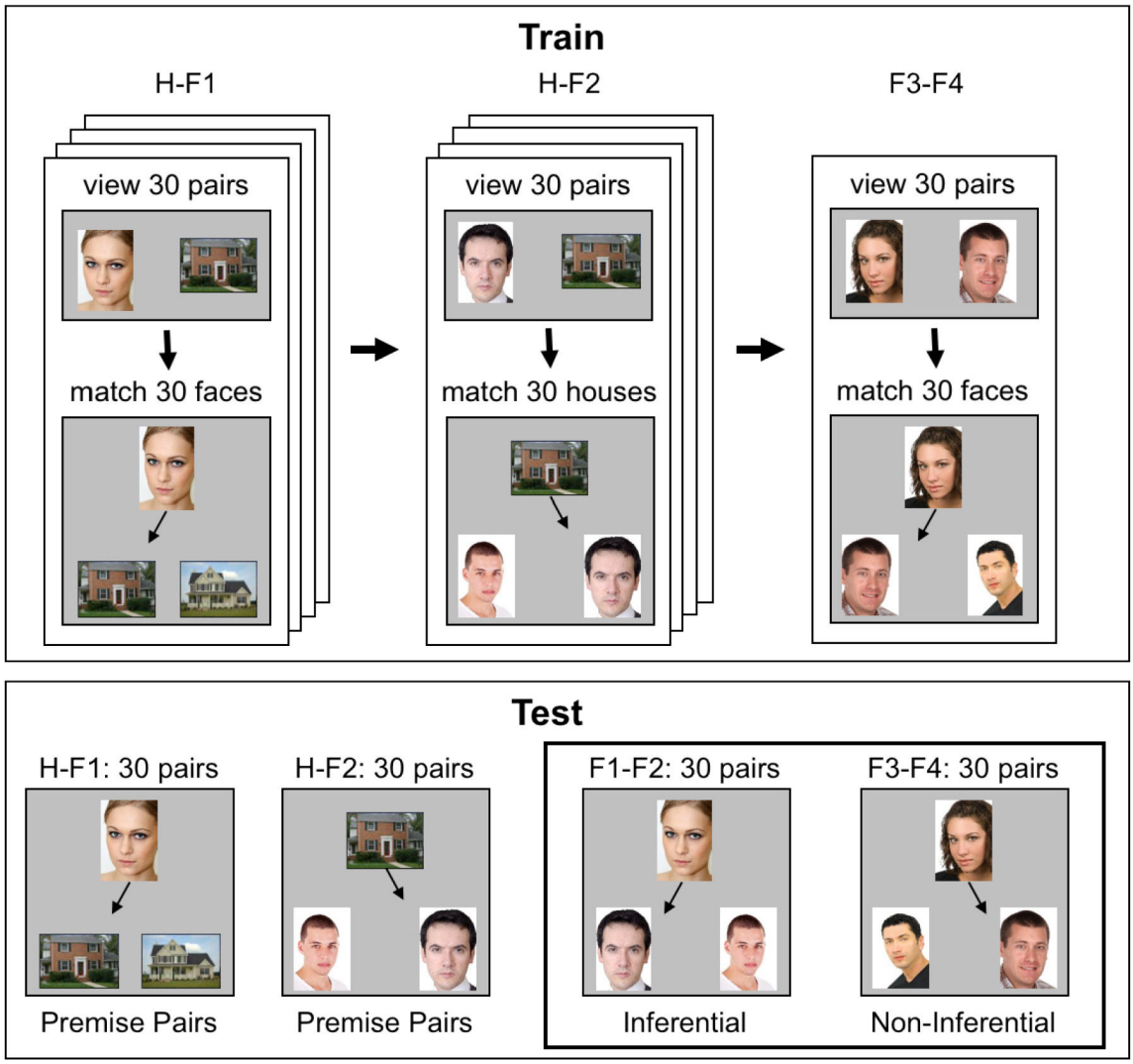

Fig. 1.

Experimental paradigm. Subjects learned three sets of paired associates: House paired with Face (H-F1), same House paired with new face (H-F2), and two new faces (F3–F4). Four view-test phases were provided for the premise pairs H-F1 and H-F2, while F3–F4 was given one study-test phase. Following training, subjects were tested on the three previous pair types and a new set of face-face pairs, F1–F2, which subjects were not directly trained on but could identify via association with the same house. The F1–F2 pairs are the **inferential** condition and F3–F4 pairs the **non-inferential** condition.

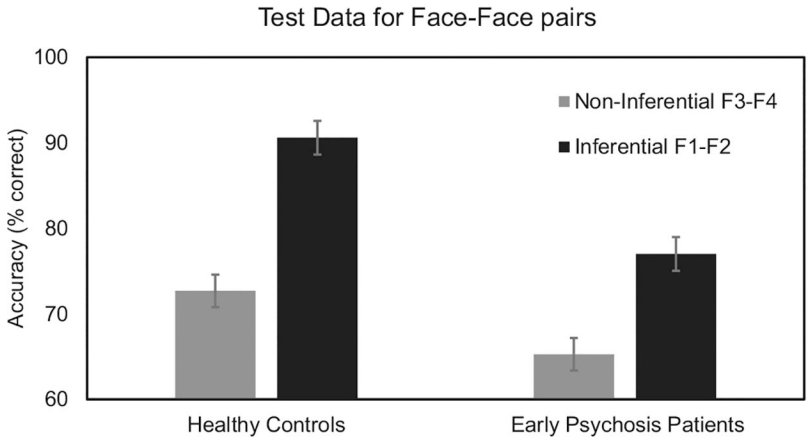

Fig. 2.

Test Accuracy (mean ± standard error) for Face-Face pairs: a) novel, inferential F1–F2 pairs and b) trained, non-inferential F3–F4 pairs for healthy control subjects and early stage of psychosis patients.

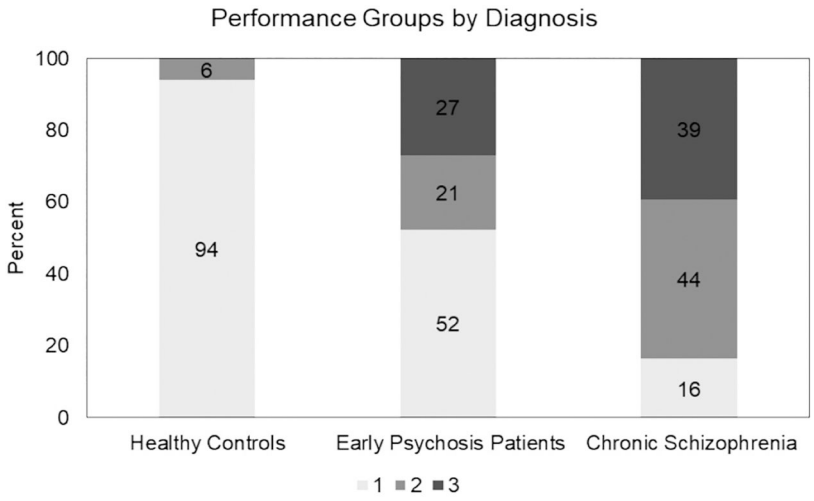

Fig. 3.

Three patterns of memory performance: Group 1 with intact inferential memory (F1–F2 accuracy ≥ 66.67%), Group 2 with successful learning, but impaired inferential memory (F1–F2 accuracy b 66.67%), and Group 3, who failed to learn House-Face pairs. Data from this study in healthy control subjects and early stage of psychosis patients are compared to previously published data in chronic schizophrenia patients (Armstrong et al., 2012a).

Table 1

Subject demographic and clinical information.

Characteristic	Healthy controls (n = 67)	Early psychosis: good learners (n = 60)	Early psychosis: poor learners (n = 22)
	Mean ± SD	Mean ± SD	Mean ± SD
Demographics			
Age	21.9 ± 2.2	21.0 ± 3.1	20.77 ± 2.0
NAART IQ *	112.7 ± 4.8	107.8 ± 6.9	103.1 ± 15.0
Subject education *	14.8 ± 1.8	13.3 ± 1.9	12.9 ± 1.6
Parental education	14.8 ± 2.1	15.3 ± 2.7	14.7 ± 2.7
Gender	52M, 15 F	50 M, 10 F	18 M, 4 F
Race **	55W, 11 B, 1 O	43 W, 17 B, 0 O	10 W, 11 B, 1 O
Clinical characteristics			
Diagnosis	-	47 SZF, 11 SZ, 2 SZA	12 SZF, 8 SZ, 2 SZA
Duration of illness (weeks)	-	27.6 ± 25.4	31.7 ± 24.5
HAM-D	-	8.1 ± 6.1	9.8 ± 7.0
YMRS	-	3.6 ± 6.4	6.1 ± 9.5
PANSS-positive **	-	17.2 ± 7.2	21.3 ± 7.3
PANSS-negative	-	17.7 ± 7.3	20.0 ± 8.9
PANSS-general	-	32.9 ± 8.7	35.4 ± 8.5
PANSS-total	-	67.8 ± 19.4	76.6 ± 18.5
Chlorpromazine equivalent	-	309.1 ± 202.2	242.7 ± 153.2

Note: NARRT, North America Adult Reading Test; HAM-D, Hamilton Rating Scale for Depression; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale; SZF; Schizophreniform; SZ, Schizophrenia; SZA, Schizoaffective disorder.

* $p < 0.05$ Healthy controls vs. early psychosis: good learners.

** $p < 0.05$ Early psychosis: good learners vs. early psychosis: poor learners.