Schizophrenia Research 212 (2019) 113–120

Contents lists available at ScienceDirect

Schizophrenia Research

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

Impaired relational memory in the early stage of psychosis

Suzanne N. Avery [a,*], Kristan Armstrong [a], Jennifer U. Blackford [a,c], Neil D. Woodward [a], Neal Cohen [b], Stephan Heckers [a]

[a] Department of Psychiatry and Behavioral Sciences, Vanderbilt University, Medical Center, Nashville, TN 37212, USA
[b] Beckman Institute for Advanced Science and Technology, and Interdisciplinary Health Sciences Institute, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA
[c] Research Health Scientist, Research and Development, Department of Veterans Affairs Medical Center, Nashville, TN, USA

ARTICLE INFO

Article history:
Received 21 March 2019
Received in revised form
28 May 2019
Accepted 30 July 2019
Available online 8 August 2019

Keywords:
First episode
Schizophrenia
Associative memory
Eye movements
Hippocampus

ABSTRACT

Background: Humans constantly take in vast amounts of information, which must be filtered, flexibly manipulated, and integrated into cohesive relational memories in order to choose relevant behaviors. Relational memory is impaired in chronic schizophrenia, which has been linked to hippocampal dysfunction. It is unclear whether relational memory is impaired in the early stage of psychosis.
Methods: We studied eye movements during a face-scene pairs task as an indirect measure of relational memory in 89 patients in the early stage of psychosis and 84 healthy control participants. During testing, scenes were overlaid with three equally-familiar faces and participants were asked to recall the matching (i.e. previously-paired) face. During *Match* trials, one face had been previously paired with the scene. During *Non-Match* trials, no faces matched the scene. Forced-choice explicit recognition was recorded as a direct measure of relational memory.
Results: Healthy control subjects rapidly (within 250–500 ms) showed preferential viewing of the matching face during *Match* trials. In contrast, preferential viewing was delayed in patients in the early stage of psychosis. Explicit recognition of the matching face was also impaired in the patient group.
Conclusions: This study provides novel evidence for a relational memory deficit in the early stage of psychosis. Patients showed deficits in both explicit recognition as well as abnormal eye-movement patterns during memory recall. Eye movements provide a promising avenue for the study of relational memory in psychosis, as they allow for the assessment of rapid, nonverbal memory processes.

1. Introduction

Throughout our day, virtually every encounter is interpreted and shaped through the lens of our memories. In patients with schizophrenia, memory for daily life events, or episodic memory, is significantly impaired (Aleman et al., 1999; Heinrichs and Zakzanis, 1998; McKenna et al., 1990; Saykin et al., 1991), and impairments are strongly associated with functional impairments and poorer outcomes in schizophrenia (Green, 1996; Green et al., 2000). Relational memory, or the ability to form flexible, contextual relationships between individual items encountered in daily life, is particularly impaired in schizophrenia in contrast to other forms of memory, such as memory for individual items (Achim and Lepage, 2003; Armstrong et al., 2012a, 2012b; Hannula et al., 2010b; Lepage et al., 2005, 2006; Luck et al., 2009; Ongür et al., 2006; Ragland et al., 2015; Titone et al., 2004; Williams et al., 2010), suggesting relational memory ability may be a core cognitive deficit in schizophrenia.

Relational memory ability may serve as a valuable proxy for neuropathology in schizophrenia (Lepage et al., 2015). Relational memory is dependent on the integrity of the hippocampus (Cohen and Eichenbaum, 1993; Konkel, 2008; Ryan et al., 2000), a region consistently associated with robust deficits in schizophrenia (Harrison, 2004; Heckers and Konradi, 2010). Additionally, hippocampal models of schizophrenia propose that structural and functional deficits progress with illness (Heckers and Konradi, 2010; Lisman et al., 2008; Tamminga et al., 2010), suggesting relational memory may track illness progression. However, preliminary evidence for relational memory deficits in the early course of psychosis is mixed: three studies reported intact relational memory (Bartholomeusz et al., 2011; Williams et al., 2012; Wood et al., 2002) while four studies found impaired relational memory (Achim et al., 2007; Armstrong et al., 2018; Greenland-White et al., 2017; Wannan et al., 2018). Recent findings suggest relational memory deficits in early stage psychosis are subtle (Armstrong et al., 2018), which may account for the mixed findings. Additionally, previous studies have

* Corresponding author at: Vanderbilt Department of Psychiatry, 1601 23rd Avenue South, Suite 3057, Nashville, TN 37212, USA.
E-mail address: suzanne.avery@vumc.org (S.N. Avery).

https://doi.org/10.1016/j.schres.2019.07.060
0920-9964/

used explicit measures such as accuracy and reaction times to index memory ability, which places heavy demand on prefrontal cortex-mediated cognitive abilities such as decision-making, explicit recognition, motivation, task comprehension, and response mapping (Eisenberg and Berman, 2010; Luck and Gold, 2008). Indirect, as opposed to explicit, measures of relational memory may be a better measure of hippocampal function. Hannula et al. showed that hippocampal activity predicted eye movement behavior, an indirect measure of relational memory ability, in healthy adults even when explicit recall failed (Hannula and Ranganath, 2009). In contrast, explicit recall was associated with prefrontal-hippocampal functional connectivity, indicating the recruitment of additional regions to support explicit recognition decisions.

To determine whether relational memory deficits exist in the earliest stage of psychotic illness, we incorporated two improvements in the current study: 1) we studied a large group of patients at the earliest stage of illness, with the majority of patients (80%) recruited during their first episode of psychosis; and 2) we tested for relational memory function using eye movements as an indirect measure of relational memory. Eye movements occur far in advance of explicit retrieval (Hannula and Ranganath, 2009), are uninfluenced by task demands (Ryan et al., 2007), and can occur without conscious awareness of memory retrieval (Ryan et al., 2000; Ryan and Cohen, 2004), indicating the obligatory nature of memory on eye movements (Ryan et al., 2007). Eye movement behavior is strongly linked to memory, yet does not require a consciously motivated response, making it advantageous in clinical populations. Previous studies have effectively used eye movements to measure relational memory ability in schizophrenia (Hannula et al., 2010b), and we have previously demonstrated relational memory impairment in a face-scene pairs task in chronic schizophrenia using eye movement measures (Williams et al., 2010). Here, we use eye movement measures to assess relational memory for face-scene pairs in patients in the early stage of psychosis. Explicit forced-choice recognition memory was also collected across participants. We hypothesized that patients would show subtle yet significant impairments in relational memory ability, even at the earliest stage of a psychotic disorder.

2. Methods

2.1. Participants

We studied 89 patients in the early stage of a non-affective psychotic disorder, including patients with: schizophreniform disorder ($n = 59$), schizophrenia ($n = 23$), schizoaffective disorder ($n = 4$), and brief psychotic disorder ($n = 3$). To specifically target early pathology (Newton et al., 2018), the majority of patients were recruited during the initial months of illness (i.e., the average duration of psychosis was 7 months, ranging from <1 month to no more than 24 months). Most patients (80%) were in the first episode of psychosis and half of the sample was studied after their first hospitalization for psychosis. On average, patients reported prodromal symptoms for 1.6 years. The majority of patients (88%) were treated with antipsychotic medication at the time of the study (Supplementary Methods). Patients were recruited from the inpatient units and outpatient clinics of the Vanderbilt Psychiatric Hospital.

Early psychosis patients were compared to a group of 84 healthy control participants recruited from the surrounding community. All participants were assessed by a trained rater using the Structured Clinical Interview for the DSM-IV (SCID I-P) (First et al., 2002), and diagnoses were confirmed by a senior clinician (S.H.) through patient interview, consensus conference, and available hospital records. Participants with a history of head injury, seizures, a serious medical condition (e.g., HIV, cancer), loss of consciousness for >30 min, drug dependence, or abnormal color vision were excluded. Healthy control subjects were excluded for history of major mood or psychotic disorders, a first-degree relative with a psychotic illness, current substance abuse or dependence, or current psychotropic medication use. A total of 100 early psychosis patients and 96 healthy control subjects were enrolled in the study. After task administration, 8 early psychosis patients and 12 healthy control participants were excluded due to quality concerns (early psychosis = 5; healthy control = 7; see Quality measures, below), technical problems during data collection (early psychosis = 1), diagnosis determined ineligible (early psychosis = 5), and demographic matching for age (healthy control = 5).

All participants were assessed for intellectual function using the Wechsler Test of Adult Reading (Holdnack, 2001), a measure sensitive to pre-morbid IQ in patients (Dykiert and Deary, 2013; Green et al., 2008). Early psychosis patients were assessed, but not excluded, for current depression and mania symptoms using the 17-item Hamilton Depression Rating Scale (Hamilton, 1960) and Young Mania Rating Scale (Young et al., 1978), respectively. Psychotic symptom severity was assessed using the Positive and Negative Syndrome Scale (Kay et al., 1988, 1987). Participants were predominantly white (73%), although groups differed by racial composition ($\chi^2_2 = 7.59$, $p = 0.02$). Secondary analyses were performed to test for potential effects of race on memory results. There were no significant between-group differences in age, sex, handedness, or years of parental education (Table 1).

Data were collected between October 2010 and August 2018. All subjects provided written informed consent. The study was approved by the Vanderbilt University Institutional Review Board, Nashville, TN.

2.2. Experimental paradigm

Relational memory was assessed using a face-scene pairs task, described in full previously (Hannula et al., 2007; Williams et al., 2010) (details of the face-scene pairs task are provided for reviewers). Eye movements were collected using an Applied Science Laboratories (ASL) model D6 remote eye-tracker. The face-scene pairs task included a training phase immediately followed by a testing phase. During training, participants viewed 36 background face-scene pairs and were instructed to remember which face was paired with each background scene. On each training trial, a unique, real-world background scene was presented alone for 3 s, followed by a face superimposed over the scene for 5 s. Participants viewed 3 blocks of 36 face-scene pairs presented in a randomized order. Test trials began with a 3 s display of a previously trained background, followed by 10 s during which three previously-seen faces were superimposed on the background in the upper left, upper right, and bottom middle portions of the screen. Testing consisted of 12 trials ($n = 6$ *Match*, $n = 6$ *Non-Match*). During *Match* trials, one of the three faces had been previously paired with the background scene. During *Non-Match* trials, none of the three faces had been previously paired with the background scene. All faces were equally familiar from the training phase, and on *Match* trials, the matching face was presented equally in each screen position (upper left, upper right, bottom middle). Participants were instructed to remember which face had been paired with the background during training, without giving an explicit response, and to look at that face as quickly as possible. Participants were instructed to keep their eyes on the screen even if no matching face was present. Lists of stimuli were rotated and counterbalanced across participants. Eye movements were recorded during the training and testing phase.

2.2.1. Quality measures

Test trials were excluded for poor quality if they were missing: 1) >50% of data during the first 2 s; 2) 3 consecutive time bins in the first 2 s; or 3) >50% of data over the full 10 s time series. Subjects

Table 1
Participant characteristics.

Demographics	Sample		Healthy control vs. early psychosis		
	Healthy control	Early psychosis	Statistic	df	p
Age, years	22 ± 2.6	21 ± 3.1	2.22	172	0.14
Sex (% male)	74%	80%	0.87	1	0.35
Race (white/black/other)	68/13/3	59/29/1	7.59	2	0.02*
Handedness (% right)	88%	85%	0.58	2	0.75
Participant education, years	15 ± 1.7	14 ± 2.2	18.34	172	<0.001*
Parental education, years	15 ± 2.1	15 ± 2.8	1.31	172	0.25
IQ, WTAR	112 ± 10.3	101 ± 15.4	32.56	172	<0.001*

Clinical	Mean	Range
Ham-D	9 ± 6.4	0–25
YMRS	4 ± 6.5	0–36
PANSS – total	69 ± 20.5	33–118
PANSS – positive	18 ± 7.8	7–37
PANSS – negative	18 ± 8.0	7–37
PANSS – general	33 ± 9.0	17–59
CPZ	283 ± 200.6	0–1000
Duration of illness, months	7 ± 5.9	0.7–24.0

Note: Mean values ± standard deviations are shown for each group. WTAR, Wechsler Test of Adult Reading; Ham-D, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; PANSS, Positive and Negative Syndrome Scale; CPZ, chlorpromazine equivalent.
* Denotes significant *p*-values ($p < 0.05$).

with ≥3 excluded *Match* or *Non-Match* trials were excluded from analysis. Five early psychosis patients and 7 healthy controls were excluded from analysis.

2.3. Eye movement behavior

Eye movements during the testing phase were analyzed to assess relational memory for face-scene pairs. Eye movements were categorized by display element: upper left face; upper right face; bottom face; and background. Viewing measures included: 1) the duration of fixations on each display element; and 2) time series measurements of the proportion of time spent looking at each display element across the 10 s trial. Proportion of viewing time was calculated as the viewing time for each display element corrected for total screen viewing time.

2.4. Explicit memory testing

Explicit recognition of the face-scene pairings was assessed using a four-alternative forced choice memory test consisting of three previously-viewed faces overlaid on a previously-viewed scene, with the option to indicate none of the faces had been paired with the scene during training. The explicit recognition test was administered immediately following the eye movement test block for the majority of participants ($n = 4$ healthy control participants did not receive an explicit recognition test).

2.5. Statistical analysis

Linear mixed effects models tested for group differences in viewing. Overall differences in the proportion of time spent viewing faces were tested with trial type (*Match*, *Non-Match*), face type (matching, non-matching), face position (upper left, upper right, bottom), and group as fixed factors and participant as a random factor, and differences in the proportion of time spent viewing scenes were tested with trial type (*Match*, *Non-Match*) and group as fixed factors and participant as a random factor. The time series of preferential viewing of the matching face during *Match* trials was compared between groups using a repeated-measures linear mixed effects model that examined viewing patterns with face type (matching, non-matching) and time (8 × 250 ms bins) and group (healthy control, early psychosis) as fixed factors and participant as a random factor. Explicit recall was compared between groups with 2-tailed, independent samples *t*-tests. Group performance greater than chance (33.33% preferential viewing, 25% explicit accuracy) was tested using one-sample *t*-tests.

3. Results

3.1. Eye movement behavior

Participants spent the majority of each 10 s test trial viewing the screen (*Match* trials: healthy control = 9.0 ± 0.7 s; early psychosis = 8.7 ± 0.8 s; *Non-Match* trials: healthy control = 8.6 ± 0.6 s; early psychosis = 8.4 s ± 0.8 s) with minimal time spent on blinks or transitions (Fig. 1).

To examine relational memory performance across participants, all trials were entered into a linear mixed effects analysis of total viewing time (Fig. 1). There were significant main effects of group ($F_{1,171} = 17.56$, $p < 0.001$) and face type ($F_{1,171} = 5469.40$, $p < 0.001$), as well as a face type by group interaction ($F_{1,171} = 339.12$, $p < 0.001$), due to the fact that preferential viewing of the matching face in early psychosis patients was 76% of healthy control viewing. Specifically, healthy control subjects preferentially viewed the matching face 6.5 times longer than non-matching faces, whereas early psychosis patients spent only 3 times as long on the matching compared to the non-matching faces, providing compelling evidence for a partial but not complete deficit of relational memory in early psychosis patients. There was no effect of face position ($p = 0.10$).

Post-hoc tests showed that, during *Match* trials, healthy control subjects spent nearly 2 s longer viewing the matching face than early psychosis patients (healthy control = 7.7 ± 1.5 s; early psychosis = 6.0 ± 2.2 s; face type by group interaction, $F_{1,171} = 282.43$, $p < 0.001$; Fig. 1). During *Non-Match* trials, there were no between-group differences in face viewing (face position by group interaction, $F_{2,342} = 0.28$, $p = 0.76$), suggesting overall eye-movement deficits did not account for preferential viewing during *Match* trials. During *Non-Match* trials, when there was no matching face on which to fixate, healthy control subjects spent more time viewing background scenes than early psychosis patients ($F_{1,171} = 246.68$, $p < 0.001$; Fig. 1).

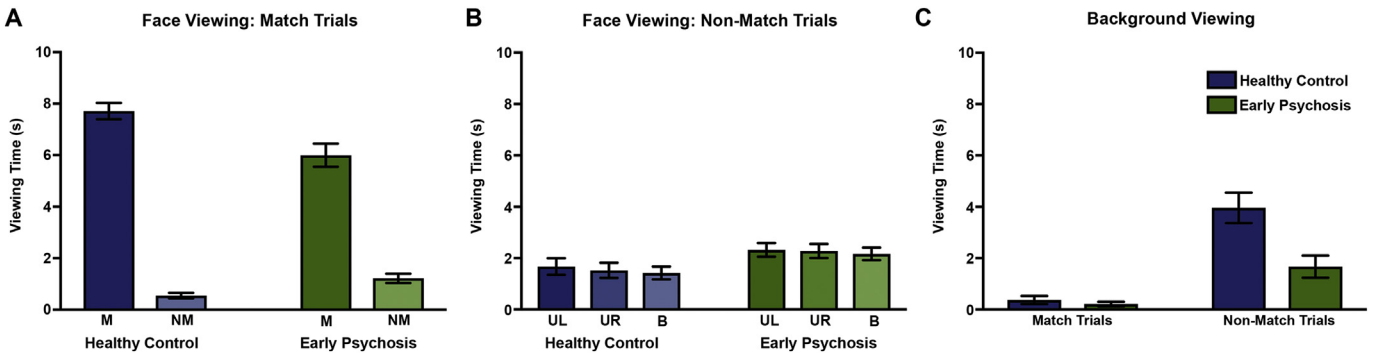

Fig. 1. Average viewing times by group of faces (A–B) and background scenes (C). During *Match* trials (A), healthy control subjects spent most of the 10 s trial viewing the matching face, relative to the non-matching faces. This preferential viewing was reduced in early psychosis patients. During *Non-Match* trials (B), a control condition where none of the three faces had been previously matched with the background scene, both groups viewed each of the three displayed faces similarly, suggesting preferential viewing during *Match* trials was indicative of memory processes. When there were no matching faces on which to fixate, healthy control subjects spent more time viewing the background scene than early psychosis patients (C; *Non-Match* trials). Error bars show the 95% confidence interval. Match face (M); Non-Match face (NM); Upper Left face (UL); Upper Right face (UR); Bottom face (B).

3.2. Time series analysis

To determine the onset of preferential viewing of the matching face, the proportion of match-face viewing in each group was tested within 250 ms time bins (Fig. 2). The onset of preferential match-face viewing was defined as greater than chance (33.33%) for two consecutive time bins. Healthy control subjects showed rapid preferential viewing of the matching face (250–500 ms time bin, $t_{83} = 1.99$, $p = 0.05$, Bonferroni-corrected) and maintained strongly preferential viewing throughout the 10 s time series (i.e., 70–85%). In contrast, early psychosis patients took longer to show preferential viewing of the match face (1000–1250 ms time bin, $t_{88} = 3.80$, $p < 0.001$, Bonferroni-corrected) and maintained lower preferential viewing throughout the time series (i.e. 50–70%).

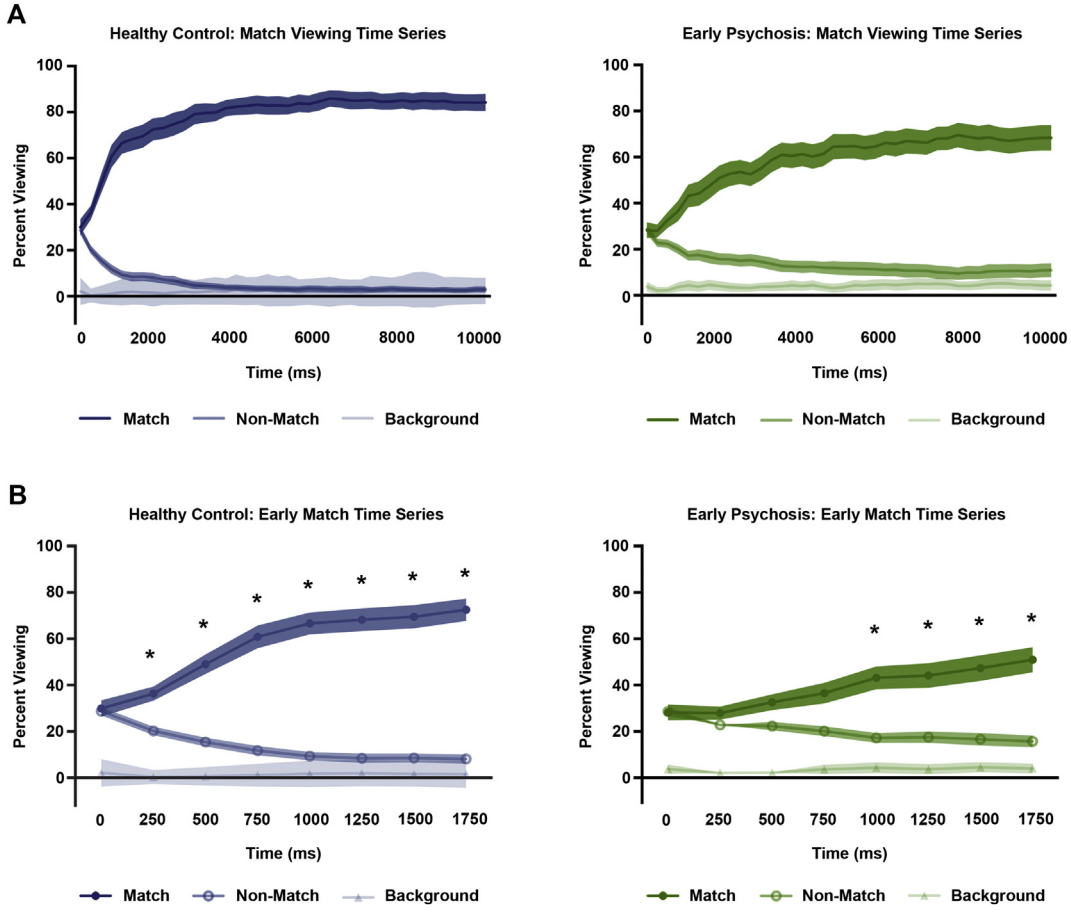

Fig. 2. Average proportion of viewing time for display elements by group over the 10 s trial (A) and during the initial 2 s of each trial (B). Shaded regions show the 95% confidence interval. Asterisks denote viewing greater than chance (33%) for each individual time bin during the first 2 s of display, $p < 0.05$, Bonferroni-corrected. Preferential viewing of the matching face was stronger in healthy control subjects compared to early psychosis patients (70–85% vs. 50–70%, respectively), with healthy control subjects showing a faster onset of preference compared to early psychosis patients (250 ms vs. 1000 ms, respectively).

Between-group differences in preferential viewing of the matching vs. non-matching face were confirmed using a repeated-measures linear mixed model over the first 2 s of viewing, which revealed group differences by face type ($F_{1,171} = 2333.02$, $p < 0.001$) and time ($F_{7,1197} = 2.01$, $p = 0.05$). There was also a group by face type by time interaction ($F_{14,1197} = 55.18$, $p < 0.001$), driven by a steeper change in match face viewing (relative to non-match faces) in the healthy controls relative to patients (250% increase in healthy controls compared to a 180% increase in early psychosis patients over 2 s).

3.3. Explicit recognition

Explicit relational memory was assessed in a separate test block immediately following the recording of eye movement. Healthy control subjects were more accurate than early psychosis patients in identifying previously-seen face-scene pairs (*Match* hits: healthy control = 90%; early psychosis = 72%; $F_{1,168} = 22.21$, $r^2 = 0.12$, $p < 0.001$) and rejecting untrained face-scene pairings (*Non-Match* correct rejections: healthy control = 82%; early psychosis = 48%; $F_{1,168} = 49.13$, $r^2 = 0.23$, $p < 0.001$; *d'*: healthy control = 0.89; early psychosis = −0.77; $F_{1,168} = 43.29$, $r^2 = 0.21$, $p < 0.001$). Although explicit accuracy was impaired, early psychosis patients performed greater than chance (chance performance = 25%, one-sample *t*-test, $t_{88} = 16.65$, $p < 0.001$), indicating impairment but not a complete inability to make relational memory judgments.

3.4. Correct trials analysis

We analyzed eye movements during *Match* trials for which the face-scene pairings were subsequently correctly identified (86% of trials in healthy control subjects and 60% in early psychosis patients). Both groups viewed the matching face preferentially, although the magnitude of the preference remained greater in healthy control subjects (8.0 ± 1.3 s) compared to early psychosis patients (6.7 ± 2.1 s), resulting in a significant face type by group interaction ($F_{1,164} = 21.14$, $p < 0.001$). Both groups showed more preferential viewing of the matching face during correct trials than during all trials during the first 2 s of *Match* trial viewing (healthy control, $F_{28,52} = 13.47$, $p < 0.001$; early psychosis, $F_{28,58} = 6.19$, $p < 0.001$; Fig. 3). However, preferential viewing in patients remained at 83% of healthy control viewing ($F_{28,137} = 1.91$, $p = 0.008$). These results indicate that early preferential viewing of the matching face was diminished in early psychosis patients, even when the patient was able to subsequently identify the face-scene pair correctly.

3.5. Correlates of relational memory performance

Effects of demographic and clinical variables were tested on both explicit and eye-movement measures of relational memory performance. In both groups, IQ was correlated with correct *Match*

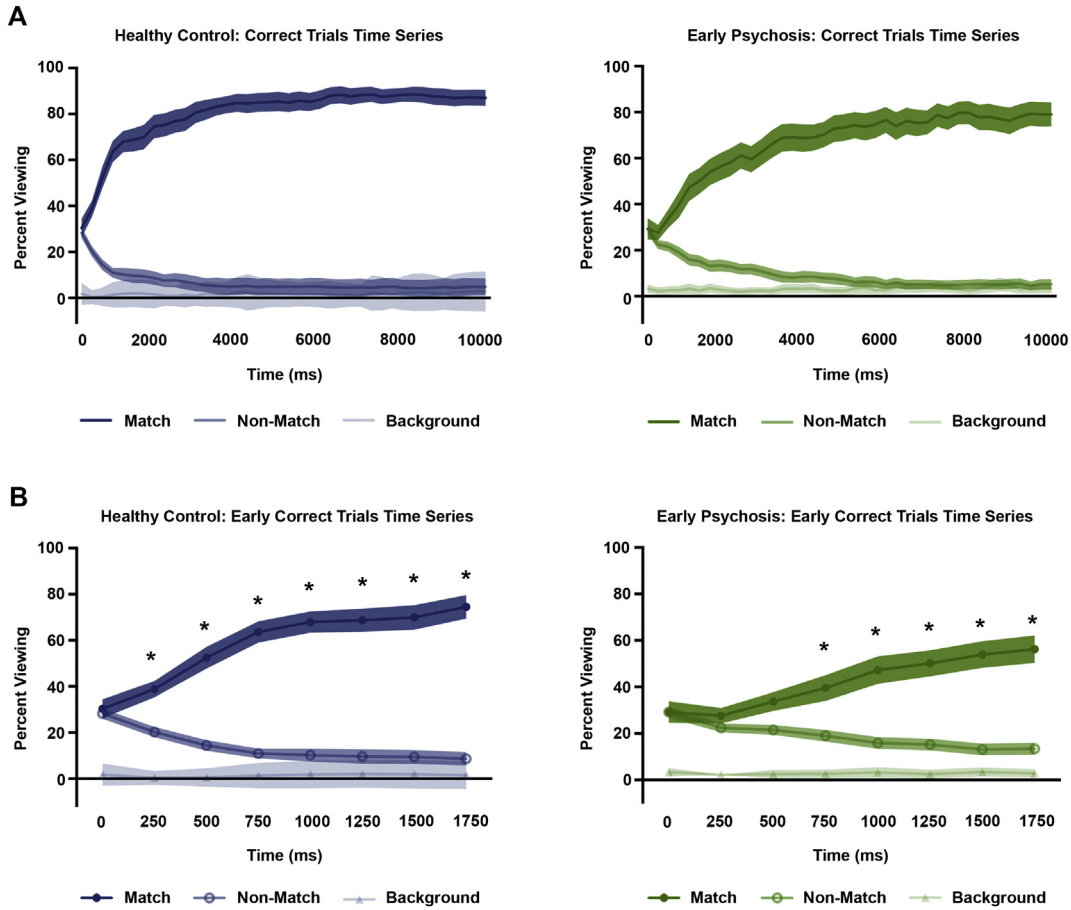

Fig. 3. Correct trials only analysis. Average proportion of viewing time for display elements for all correct trials by group over the entire 10 s trial (A) and the first 2 s of each trial (B). Error bars show the 95% confidence interval. Asterisks denote viewing greater than chance (33%) for each individual time bin during the first 2 s of display, $p < 0.05$, Bonferroni-corrected. Similar to the analysis of all trials, healthy control subjects showed rapid preferential viewing (250 ms) of the matching face (B), with consistent preference for the matching face at 75% to 85% throughout the 10 s trial (A). For early psychosis patients, preferential viewing occurred earlier than in all trials (750 ms; B), and although consistent at 60% to 80% throughout the 10 s trial, remained lower than the healthy control group (A). These data indicate that for the early psychosis group, eye movement measures of relational memory are abnormal relative to healthy control subjects, even for trials on which the face-scene pair is successfully identified during a subsequent recognition memory test.

trials performance (healthy control, $r = 0.25$, $r^2 = 0.06$, $p = 0.02$; early psychosis, $r = 0.22$, $r^2 = 0.05$, $p = 0.04$); however, entering IQ as an explanatory regressor did not alter the between-group findings (Supplementary Results). For patients, both negative and depressive symptoms were correlated with lower preferential *Match* viewing and lower explicit accuracy (Supplementary Results). To test the specificity of this shared clinical-behavioral relationship, we extracted a core item from each scale (Supplementary Results). We found that preferential *Match* viewing was correlated with a core negative symptom, passive social withdrawal (PANSS item N4, $r = -0.30$, $r^2 = 0.09$, $p = 0.005$), but was not correlated with endorsement of depressed mood (item 1 on the Ham-D, $p = 0.36$). Relational memory performance was not significantly correlated with any other demographic variables, current medication (chlorpromazine equivalent doses), or duration of illness (Supplementary Results).

4. Discussion

The results of this study provide novel and compelling evidence for impaired relational memory in the early stage of psychosis. We demonstrated this impairment by studying eye movements as an indirect measure of relational memory. Healthy control subjects were able to search and selectively view the one face—among three equally familiar faces—that matched (i.e., had been previously paired with) the scene within 250–500 ms of viewing. In contrast, preferential viewing of the matching face took longer in early psychosis patients, and never reached the same magnitude as in healthy control subjects. Patients showed a corresponding impairment in explicit recognition of studied face-scene pairs. Although both implicit and explicit recognition revealed impairment, both measures of relational memory performance were above chance in early psychosis patients, indicating impairment but not failure of relational memory ability.

Convergent evidence points towards a hippocampal basis for relational memory (Bird, 2017; Davachi, 2006; Hannula et al., 2006). For example, hippocampal amnesia patients show substantial deficits in eye movement-based relational memory tasks (Hannula et al., 2007; Ryan et al., 2000), while exhibiting normal eye movement-based memory behavior in tests of individual item memory (Hannula et al., 2010a, 2007; Ryan et al., 2000), an ability guided by the perirhinal cortex (Brown and Aggleton, 2001; Davachi, 2006; Davachi et al., 2003). Hippocampal dysfunction is a prominent feature of schizophrenia and has been linked to relational memory impairment in chronic patients (Avery et al., 2018; Ongür et al., 2006). However, it is not clear whether relational memory is also associated with hippocampal pathology in early stages of psychosis. For example, hippocampal volume and functional deficits are less prominent in the early stage of psychosis (Achim et al., 2007; Adriano et al., 2012; Bartholomeusz et al., 2017; Steen et al., 2006; Velakoulis et al., 2006; Williams et al., 2012) and findings of relational memory deficits early in psychotic illness have been mixed (Armstrong et al., 2018; Bartholomeusz et al., 2011). However, one longitudinal study of early schizophrenia patients found that visuospatial associative learning, a task that incorporates learning of relationships, may decline throughout the illness (Wannan et al., 2018). Here, we found that relational memory ability was impaired in early psychosis patients, although preferential viewing was significantly above chance. In contrast, chronic schizophrenia patients have near chance-level viewing on the same task, suggesting that relational memory is substantially impaired in later stages of illness (Williams et al., 2010). This suggests that relational memory may deteriorate between the early and chronic stages of schizophrenia and could provide a valuable index of progression of hippocampal pathology, although well-controlled longitudinal studies are necessary to test this.

We found strong correspondence between implicit and explicit measures of relational memory, although preferential viewing of the matching face remained impaired in psychosis patients even for trials that were later correctly identified. Specifically, even when the matching face was later explicitly recognized, preferential viewing of the matching face took longer in patients than control participants. This suggests that the timecourse of eye movements, i.e. the length of time it takes to detect a strong memory effect, may impart information about memory processes to which explicit measures are insensitive. For example, early psychosis patients may use slower, compensatory mechanisms to recognize trained face-scene pairs when rapid, hippocampal-based relational memory processes are deficient. Relationships between items can be encoded as a united representation or single entity (Cohen et al., 1997; Frank et al., 2003; O'Reilly and Rudy, 2001) mediated by the medial temporal lobe cortex (Haskins et al., 2008), a region responsible for slow learning of associations over multiple experiences (Haskins et al., 2008). Thus, the recruitment of slower cortical processes may account for patients delayed preferential viewing of the matching face, even when the face is explicitly recognized.

Lower preferential viewing across all trials may be partially accounted for by deficits in eye movements specific to the disorder rather than memory per se. Several studies have reported deficits in anti-saccade tasks (Fukushima et al., 1988; Hutton and Ettinger, 2006), raising concern of overall eye movement deficits in schizophrenia. However, studies have also consistently shown normal saccade latency, gain, and final eye position in reflexive saccade tasks (Hutton and Kennard, 1998). If patients in the current study suffered from overall eye movement deficits, we would expect to see eye movement differences during all trials; however, eye movements were similar between groups during the *Non-Match* condition, when memory could not guide eye movements, and only differed during the *Match* condition, indicating a primary effect of memory on eye movement behavioral differences.

The observed relational memory deficits in early psychosis patients may be due to failures in face-scene relationship encoding, retrieval, or both. Although relational memory function has been consistently linked to the hippocampus in both lesion and healthy population studies (Cohen et al., 1999; Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2004), this behavioral paradigm cannot directly test the neural basis of preferential viewing. Neuroimaging studies of relational memory function in schizophrenia have implicated both hippocampal (Avery et al., 2018; Ongür et al., 2006) and prefrontal regions (Lepage et al., 2006; Ragland et al., 2015), each of which may contribute to the observed group differences. Further assessment of encoding and retrieval using diverse tasks, combined with neuroimaging, may aide in disentangling these distinct memory processes in patients with schizophrenia.

There are several limitations that should be considered. The majority of patients (88%) were treated with antipsychotic medications, although relational memory performance was not significantly correlated with current medication dose. The number of trials was modest, including only 6 Match and 6 Non-Match trials, although this was consistent with other relational memory tasks used in schizophrenia patients (Ongür et al., 2006; Titone et al., 2004) and our results are similar to a recent study of early psychosis patients employing a task design with a greater number of relational memory trials (Armstrong et al., 2018).

In summary, our study provides novel evidence for a relational memory deficit in the early stage of psychosis. Importantly, we demonstrate relational memory deficits using eye movements as an implicit measure of relational memory that may be translated to studies in animals and non-verbal populations. Eye movements have been used to successfully study memory in nonhuman primates (Funahashi et al., 1989) and babies as young as nine months (Richmond and Nelson, 2009). As current medications are not

effective in ameliorating memory deficits (Harvey and Keefe, 2001; Keefe, 2007; Keefe et al., 2017), translational studies of relational memory function may reveal novel mechanisms for therapeutic intervention.

Funding

This work was supported by the Charlotte and Donald Test Fund, NIMH grant R01-MH70560 (Dr. Heckers), the Vanderbilt Psychiatric Genotype/Phenotype Project, and the Vanderbilt Institute for Clinical and Translational Research (through grant 1-UL-1-TR000445 from the National Center for Research Resources/NIH).

Contributors

NC and SH conceptualized and designed the study. KA managed data collection and performed initial statistical analyses. SA performed statistical analyses and drafted the manuscript. JUB consulted on the statistical analysis, and JUB and NW aided in interpretation of results. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgments

We thank the participants who chose to take part in this study. We would also like to thank Margo Menkes, Margaret Quinn, Katherine Seldin, and Rachel McKinney for their support in collecting the research data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.07.060.

References

Achim, A.M., Lepage, M., 2003. Is associative recognition more impaired than item recognition memory in schizophrenia? A meta-analysis. Brain Cogn. 53, 121–124.

Achim, A.M., Bertrand, M.C., Sutton, H., Montoya, A., Czechowska, Y., Malla, A.K., Joober, R., Pruessner, J.C., Lepage, M., 2007. Selective abnormal modulation of hippocampal activity during memory formation in first-episode psychosis. Arch. Gen. Psychiatry 64, 999–1014. https://doi.org/10.1001/archpsyc.64.9.999.

Adriano, F., Caltagirone, C., Spalletta, G., 2012. Hippocampal volume reduction in first-episode and chronic schizophrenia: a review and meta-analysis. Neuroscientist 18, 180–200. https://doi.org/10.1177/1073858410395147.

Aleman, A., Hijman, R., de Haan, E.H.F., Kahn, R.S., 1999. Memory impairment in schizophrenia: a meta-analysis. Am. J. Psychiatry 156, 1358–1366. https://doi.org/10.1176/ajp.156.9.1358.

Armstrong, K., Kose, S., Williams, L., Woolard, A., Heckers, S., 2012. Impaired associative inference in patients with schizophrenia. Schizophr. Bull. 38, 622–629. https://doi.org/10.1093/schbul/sbq145.

Armstrong, K., Williams, L.E., Heckers, S., 2012. Revised associative inference paradigm confirms relational memory impairment in schizophrenia. Neuropsychology 26, 451–458. https://doi.org/10.1037/a0028667.

Armstrong, K., Avery, S., Blackford, J.U., Woodward, N., Heckers, S., 2018. Impaired associative inference in the early stage of psychosis. Schizophr. Res. 202, 86–90. https://doi.org/10.1016/j.schres.2018.06.049.

Avery, S.N., Rogers, B.P., Heckers, S., 2018. Hippocampal network modularity is associated with relational memory dysfunction in schizophrenia. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3, 423–432. https://doi.org/10.1016/j.bpsc.2018.02.001.

Bartholomeusz, C.F., Proffitt, T.M., Savage, G., Simpson, L., Markulev, C., Kerr, M., McConchie, M., McGorry, P.D., Pantelis, C., Berger, G.E., Wood, S.J., 2011. Relational memory in first episode psychosis: implications for progressive hippocampal dysfunction after illness onset. Aust. N. Z. J. Psychiatry 45, 206–213. https://doi.org/10.3109/00048674.2010.547456.

Bartholomeusz, C.F., Cropley, V.L., Wannan, C., Di Biase, M., McGorry, P.D., Pantelis, C., 2017. Structural neuroimaging across early-stage psychosis: aberrations in neurobiological trajectories and implications for the staging model. Aust. N. Z. J. Psychiatry 51, 455–476. https://doi.org/10.1177/0004867416670522.

Bird, C.M., 2017. The role of the hippocampus in recognition memory. Cortex 93, 155–165. https://doi.org/10.1016/j.cortex.2017.05.016.

Brown, M.W., Aggleton, J.P., 2001. Recognition memory: what are the roles of the perirhinal cortex and hippocampus? Nat. Rev. Neurosci. 2, 51–61. https://doi.org/10.1038/35049064.

Cohen, N.J., Eichenbaum, H., 1993. Memory, Amnesia, and the Hippocampal System. MIT Press, Cambridge, MA.

Cohen, N.J., Poldrack, R.A., Eichenbaum, H., 1997. Memory for items and memory for relations in the procedural/declarative memory framework. Memory 5, 131–178. https://doi.org/10.1080/741941149.

Cohen, N.J., Ryan, J., Hunt, C., Romine, L., Wszalek, T., Nash, C., 1999. Hippocampal system and declarative (relational) memory: summarizing the data from functional neuroimaging studies. Hippocampus 9, 83–98. https://doi.org/10.1002/(SICI)1098-1063(1999)9:1<83::AID-HIPO9>3.0.CO;2-7.

Davachi, L., 2006. Item, context and relational episodic encoding in humans. Curr. Opin. Neurobiol. https://doi.org/10.1016/j.conb.2006.10.012.

Davachi, L., Mitchell, J.P., Wagner, A.D., 2003. Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. Proc. Natl. Acad. Sci. U. S. A. 100, 2157–2162. https://doi.org/10.1073/pnas.0337195100.

Dykiert, D., Deary, I.J., 2013. Retrospective validation of WTAR and NART scores as estimators of prior cognitive ability using the Lothian Birth Cohort 1936. Psychol. Assess. 25, 1361–1366. https://doi.org/10.1037/a0033623.

Eichenbaum, H., Cohen, N.J., 2004. From Conditioning to Conscious Recollection: Memory Systems of the Brain. Oxford University Press.

Eisenberg, D.P., Berman, K.F., 2010. Executive function, neural circuitry, and genetic mechanisms in schizophrenia. Neuropsychopharmacology 35, 258–277. https://doi.org/10.1038/npp.2009.111.

First, M., Spitzer, R.L., Gibbon, M., Williams, J., 2002. Structured Clinical Interview for the DSM-IV-TR Axis I Disorders, Research Version (Patient Edition (SCID-I/P)).

Frank, M.J., Rudy, J.W., O'Reilly, R.C., 2003. Transitivity, flexibility, conjunctive representations, and the hippocampus. II. A computational analysis. Hippocampus 13, 341–354. https://doi.org/10.1002/hipo.10084.

Fukushima, J., Fukushima, K., Chiba, T., Tanaka, S., Yamashita, I., Kato, M., 1988. Disturbances of voluntary control of saccadic eye movements in schizophrenic patients. Biol. Psychiatry 23, 670–677.

Funahashi, S., Bruce, C.J., Goldman-Rakic, P.S., 1989. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. J. Neurophysiol. 61, 331–349. https://doi.org/10.1152/jn.1989.61.2.331.

Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatry 153, 321–330. https://doi.org/10.1111/j.1530-0277.2006.00335.x.

Green, M.F., Kern, R.S., Braff, D.L., Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr. Bull. 26, 119–136.

Green, R.E.A., Melo, B., Christensen, B., Ngo, L.-A., Monette, G., Bradbury, C., 2008. Measuring premorbid IQ in traumatic brain injury: an examination of the validity of the Wechsler Test of Adult Reading (WTAR). J. Clin. Exp. Neuropsychol. 30, 163–172. https://doi.org/10.1080/13803390701300524.

Greenland-White, S.E., Ragland, J.D., Niendam, T.A., Ferrer, E., Carter, C.S., 2017. Episodic memory functions in first episode psychosis and clinical high risk individuals. Schizophr. Res. 188, 151–157. https://doi.org/10.1016/j.schres.2017.01.035.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.

Hannula, D.E., Ranganath, C., 2009. The eyes have it: hippocampal activity predicts expression of memory in eye movements. Neuron 63, 592–599. https://doi.org/10.1016/j.neuron.2009.08.025.

Hannula, D.E., Tranel, D., Cohen, N.J., 2006. The long and the short of it: relational memory impairments in amnesia, even at short lags. J. Neurosci. 26, 8352–8359. https://doi.org/10.1523/JNEUROSCI.5222-05.2006.

Hannula, D.E., Ryan, J.D., Tranel, D., Cohen, N.J., 2007. Rapid onset relational memory effects are evident in eye movement behavior, but not in hippocampal amnesia. J. Cogn. Neurosci. 19, 1690–1705. https://doi.org/10.1162/jocn.2007.19.10.1690.

Hannula, D.E., Althoff, R.R., Warren, D.E., Riggs, L., Cohen, N.J., Ryan, J.D., 2010. Worth a glance: using eye movements to investigate the cognitive neuroscience of memory. Front. Hum. Neurosci. 4, 166. https://doi.org/10.3389/fnhum.2010.00166.

Hannula, D.E., Ranganath, C., Ramsay, I.S., Solomon, M., Yoon, J., Niendam, T.A., Carter, C.S., Ragland, J.D., 2010. Use of eye movement monitoring to examine item and relational memory in schizophrenia. Biol. Psychiatry 68, 610–616. https://doi.org/10.1016/j.biopsych.2010.06.001.

Harrison, P.J., 2004. The hippocampus in schizophrenia: a review of the neuropathological evidence and its pathophysiological implications. Psychopharmacology 174, 151–162. https://doi.org/10.1007/s00213-003-1761-y.

Harvey, P.D., Keefe, R.S.E., 2001. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am. J. Psychiatry 158, 176–184. https://doi.org/10.1176/appi.ajp.158.2.176.

Haskins, A.L., Yonelinas, A.P., Quamme, J.R., Ranganath, C., 2008. Perirhinal cortex supports encoding and familiarity-based recognition of novel associations. Neuron 59, 554–560. https://doi.org/10.1016/j.neuron.2008.07.035.

Heckers, S., Konradi, C., 2010. Hippocampal pathology in schizophrenia. Curr. Top. Behav. Neurosci. 4, 529–553. https://doi.org/10.1007/7854_2010_43.

Heinrichs, R.W., Zakzanis, K.K., 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12, 426–445. https://doi.org/10.1037/0894-4105.12.3.426.
Holdnack, H., 2001. Wechsler Test of Adult Reading: WTAR. The Psychological Corporation, San Antonio, TX.
Hutton, S.B., Ettinger, U., 2006. The antisaccade task as a research tool in psychopathology: a critical review. Psychophysiology 43, 302–313. https://doi.org/10.1111/j.1469-8986.2006.00403.x.
Hutton, S., Kennard, C., 1998. Oculomotor abnormalities in schizophrenia: a critical review. Neurology 50, 604–609.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276. https://doi.org/10.1093/schbul/13.2.261.
Kay, S.R., Opler, L.A., Lindenmayer, J.P., 1988. Reliability and validity of the positive and negative syndrome scale for schizophrenics. Psychiatry Res. 23, 99–110.
Keefe, R.S.E., 2007. Cognitive deficits in patients with schizophrenia: effects and treatment. J. Clin. Psychiatry 68 (Suppl. 14), 8–13.
Keefe, R.S.E., Davis, V.G., Harvey, P.D., Atkins, A.S., Haig, G.M., Hagino, O., Marder, S., Hilt, D.C., Umbricht, D., 2017. Placebo response and practice effects in schizophrenia cognition trials. JAMA Psychiat. 74, 807. https://doi.org/10.1001/jamapsychiatry.2017.1574.
Konkel, A., 2008. Hippocampal amnesia impairs all manner of relational memory. Front. Hum. Neurosci. 2 https://doi.org/10.3389/neuro.09.015.2008.
Lepage, M., Menear, M., Montoya, A., Achim, A.M., 2005. Associative interference does not affect recognition memory in schizophrenia. Schizophr. Res. 80, 185–196. https://doi.org/10.1016/j.schres.2005.04.003.
Lepage, M., Montoya, A., Pelletier, M., Achim, A.M., Menear, M., Lal, S., 2006. Associative memory encoding and recognition in schizophrenia: an event-related fMRI study. Biol. Psychiatry 60, 1215–1223. https://doi.org/10.1016/j.biopsych.2006.03.043.
Lepage, M., Hawco, C., Bodnar, M., 2015. Relational memory as a possible neurocognitive marker of schizophrenia. JAMA Psychiat. 72, 1–3. https://doi.org/10.1001/jamapsychiatry.2015.0276.6.
Lisman, J.E., Coyle, J.T., Green, R.W., Javitt, D.C., Benes, F.M., Heckers, S., Grace, A.A., 2008. Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. Trends Neurosci. 31, 234–242. https://doi.org/10.1016/j.tins.2008.02.005.
Luck, S.J., Gold, J.M., 2008. The translation of cognitive paradigms for patient research. Schizophr. Bull. 34, 629–644. https://doi.org/10.1093/schbul/sbn036.
Luck, D., Montoya, A., Menear, M., Achim, A.M., Lal, S., Lepage, M., 2009. Selective pair recognition memory impairment with no response bias in schizophrenia. Psychiatry Res. 169, 39–42. https://doi.org/10.1016/j.psychres.2008.06.037.
McKenna, P.J., Tamlyn, D., Lund, C.E., Mortimer, A.M., Hammond, S., Baddeley, A.D., 1990. Amnesic syndrome in schizophrenia. Psychol. Med. 20, 967–972.
Newton, R., Rouleau, A., Nylander, A.-G., Loze, J.-Y., Resemann, H.K., Steeves, S., Crespo-Facorro, B., 2018. Diverse definitions of the early course of schizophrenia—a targeted literature review. NPJ Schizophr. 4, 21 https://doi.org/10.1038/s41537-018-0063-7.
Ongür, D., Cullen, T.J., Wolf, D.H., Rohan, M., Barreira, P., Zalesak, M., Heckers, S., 2006. The neural basis of relational memory deficits in schizophrenia. Arch. Gen. Psychiatry 63, 356–365. https://doi.org/10.1001/archpsyc.63.4.356.
O'Reilly, R.C., Rudy, J.W., 2001. Conjunctive representations in learning and memory: principles of cortical and hippocampal function. Psychol. Rev. 108, 311–345.
Ragland, J.D., Ranganath, C., Harms, M.P., Barch, D.M., Gold, J.M., Layher, E., Lesh, T.A., MacDonald, A.W., Niendam, T.A., Phillips, J., Silverstein, S.M., Yonelinas, A.P., Carter, C.S., 2015. Functional and neuroanatomic specificity of episodic memory dysfunction in schizophrenia: a functional magnetic resonance imaging study of the relational and item-specific encoding task. JAMA Psychiat. 72, 909–916. https://doi.org/10.1001/jamapsychiatry.2015.0276.
Richmond, J., Nelson, C.A., 2009. Relational memory during infancy: evidence from eye tracking. Dev. Sci. 12, 549–556. https://doi.org/10.1111/j.1467-7687.2009.00795.x.
Ryan, J.D., Cohen, N.J., 2004. The nature of change detection and online representations of scenes. J. Exp. Psychol. Hum. Percept. Perform. 30, 988–1015. https://doi.org/10.1037/0096-1523.30.5.988.
Ryan, J.D., Althoff, R.R., Whitlow, S., Cohen, N.J., 2000. Amnesia is a deficit in relational memory. Psychol. Sci. 11, 454–461. https://doi.org/10.1111/1467-9280.00288.
Ryan, J.D., Hannula, D.E., Cohen, N.J., 2007. The obligatory effects of memory on eye movements. Memory 15, 508–525. https://doi.org/10.1080/09658210701391022.
Saykin, A.J., Gur, R.C., Gur, R.E., Mozley, P.D., Mozley, L.H., Resnick, S.M., Kester, D.B., Stafiniak, P., 1991. Neuropsychological function in schizophrenia. Selective impairment in memory and learning. Arch. Gen. Psychiatry 48, 618–624.
Steen, R.G., Mull, C., McClure, R., Hamer, R.M., Lieberman, J.A., 2006. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br. J. Psychiatry 188, 510–518. https://doi.org/10.1192/bjp.188.6.510.
Tamminga, C.A., Stan, A.D., Wagner, A.D., 2010. The hippocampal formation in schizophrenia. Am. J. Psychiatry 167, 1178–1193. https://doi.org/10.1176/appi.ajp.2010.09081187.
Titone, D., Ditman, T., Holzman, P.S., Eichenbaum, H., Levy, D.L., 2004. Transitive inference in schizophrenia: impairments in relational memory organization. Schizophr. Res. 68, 235–247. https://doi.org/10.1016/S0920-9964(03)00152-X.
Velakoulis, D., Wood, S.J., Wong, M.T.H., McGorry, P.D., Yung, A., Phillips, L., Brewer, W., Proffitt, T., Desmond, P., Pantelis, C., 2006. Hippocampal and amygdala volumes according to psychosis stage and diagnosis. Arch. Gen. Psychiatry 63, 139–149. https://doi.org/10.1001/archpsyc.63.2.139.ABSTRACT.
Wannan, C.M.J., Bartholomeusz, C.F., Cropley, V.L., Van Rheenen, T.E., Panayiotou, A., Brewer, W.J., Proffitt, T.M., Henry, L., Harris, M.G., Velakoulis, D., McGorry, P., Pantelis, C., Wood, S.J., 2018. Deterioration of visuospatial associative memory following a first psychotic episode: a long-term follow-up study. Psychol. Med. 48, 132–141. https://doi.org/10.1017/S003329171700157X.
Williams, L.E., Must, A., Avery, S., Woolard, A., Woodward, N.D., Cohen, N.J., Heckers, S., 2010. Eye-movement behavior reveals relational memory impairment in schizophrenia. Biol. Psychiatry 68, 617–624. https://doi.org/10.1016/j.biopsych.2010.05.035.
Williams, L.E., Avery, S.N., Woolard, A.A., Heckers, S., 2012. Intact relational memory and normal hippocampal structure in the early stage of psychosis. Biol. Psychiatry 71, 105–113. https://doi.org/10.1016/j.biopsych.2011.09.016.
Wood, S.J., Proffitt, T., Mahony, K., Smith, D.J., Buchanan, J.A., Brewer, W., Stuart, G.W., Velakoulis, D., McGorry, P.D., Pantelis, C., 2002. Visuospatial memory and learning in first-episode schizophreniform psychosis and established schizophrenia: a functional correlate of hippocampal pathology? Psychol. Med. 32, 429–438. https://doi.org/10.1017/s0033291702005275.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435. https://doi.org/10.1192/bjp.133.5.429.