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Impaired relational memory in the early stage of psychosis

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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

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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