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Memory Based Prediction Deficits and Dorsolateral Prefrontal Dysfunction in Schizophrenia

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Abstract

Background: Theories suggest that people with schizophrenia (SZ) have problems generating predictions based on past experiences. The dorsolateral prefrontal cortex (DLPFC) and hippocampus participate in memory-based prediction. We used functional magnetic resonance imaging to investigate DLPFC and hippocampal function in healthy controls (HC) and people with SZ during memory-based prediction.

Methods: Prior to scanning, HC (N=54) and SZ (N=31) learned 5-object sequences presented in fixed or random orders on each repetition. During scanning, participants made semantic decisions (e.g., “Can this object fit in a shoebox?”) on a continuous stream of objects from fixed and random sequences. Sequence prediction was demonstrated by faster semantic decisions for objects in fixed vs random sequences because memory could be used to anticipate and more efficiently process semantic information about upcoming objects in fixed sequences. Representational similarity analyses (RSA) were used to determine how each sequence type was represented in posterior hippocampus and DLPFC.

Results: Sequence predictions were reduced in SZ relative to HC. RSA revealed stronger memory-based predictions in the DLPFC of HC than SZ, and DLPFC representations correlated with more successful predictions in HC only. For the posterior hippocampus, voxel pattern similarity was increased for fixed versus random sequences in HC only, but no significant between-group differences or correlations with prediction success were observed.

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Disclosures

All authors have nothing to disclose.

Conclusions: Individuals with SZ are capable of learning temporal sequences; however, they are impaired using memory to predict upcoming events as efficiently as HC. This deficit appears related to disrupted neural representation of sequence information in the DLPFC.

Keywords

Schizophrenia; Episodic Memory; Hippocampus; Prefrontal Cortex; Relational Memory; Prediction

INTRODUCTION

As we recollect past events ("episodic memory"), we can unfold an entire sequence of experiences happening at a particular place and time. Neuroscience highlighted the fact that this ability to encode and recall sequences of events serves several purposes beyond retrieval of past events. Past information is often useful for generating predictions helping us navigate an uncertain world. For instance, imagine watching a basketball game the first time. When a player shoots gets a basket, the score for that player's team goes up. Therefore, the next time a player shoots the ball into the basket, prior knowledge allows us to predict that the score will increase. Humans can be remarkably effective learning about arbitrary sequences of stimuli (1), and information about learned sequences can help us anticipate and efficiently process information even when explicit episodic memory retrieval is not required (2,3).

Episodic memory is impaired in people with schizophrenia (SZ). Although SZ affects a range of cognitive abilities, episodic memory is disproportionately impaired, and severity of memory deficits predicts patients' ability to work and live independently (4). A key finding is that people with SZ can sometimes perform well at recognizing familiar objects or events but are especially impaired at remembering relationships between objects and the context in which they were encountered (5,6,7,8,9). Results from functional magnetic resonance imaging (fMRI) studies suggest two possible explanations for these deficits. In one view, dysfunction might reflect impaired functioning of the hippocampus, which normally supports the ability to bind item and context information in a manner that can support episodic memory (2,10). Another explanation, that is not mutually exclusive (11), is that prefrontal dysfunction affects control processes that enable one to use learned information to make complex attributions about the context in which events take place (12,13).

Whereas studies of memory emphasize memory for past events, other work has focused on the idea that people with SZ might be impaired generating precise predictions about the future (14,15). Bayesian models propose that, in the healthy brain, higher-order brain areas generate predictions about upcoming sensory information and experience prediction errors encouraging belief updating and better future predictions (14,16,17,18). In this framework, people with SZ generate aberrant prediction errors impairing their learning about the statistical structure of the world. Prediction error research in SZ has informed a broad range of paradigms, including mismatch negativity (19), examination of hallucinations (20), and studies of reinforcement learning - demonstrating impaired learning (21) and dysfunction in dorsal and ventromedial prefrontal cortex and striatum (22,23).

At present, it is not clear whether people with SZ show more global deficits in the ability to predict future events based on learned memory representations. Although studies have shown deficits in explicit memory for temporal or sequential relationships, these deficits might reflect an inability to make complex memory attributions, rather than a prediction deficit per se. Accordingly, in the present study, we investigated the extent to which people with schizophrenia are able to utilize memory of learned sequences to successfully predict future events.

We adapted a paradigm from a recent study of healthy undergraduates which scanned participants while making semantic decisions about sequences of objects (24). In some sequences, object order was *fixed*, such that seeing the first object could enable generation of precise predictions about the remaining objects in the sequence. In other sequences, object order was changed on every repetition *(i.e., random*), allowing participants to become highly familiar with the objects, but unable to make accurate predictions. With this paradigm, healthy individuals had faster reaction times (RTs) when making semantic decisions about objects in fixed versus random sequences. Thus, after a sequence was learned, people used that sequence memory to facilitate response preparation by predicting upcoming objects during fixed sequences, resulting in faster semantic decisions.

Previously (3), we used electroencephalography (EEG) to examine sequence learning and found that both HC and SZ reached criterion for sequence learning and utilized sequence memory to predict future objects and make faster semantic decisions for objects in fixed versus random sequences. This RT facilitation is referred to as the “sequence prediction effect”. Although people with SZ also reached criterion during sequence learning, their learning was less efficient and accompanied by decreased alpha and beta1 power prior to stimulus onset for fixed versus random sequences (3). Interestingly, these frequency bands have also been found to mediate prediction feedback (14).

Here, we report the second part of this study, in which fMRI was used to identify brain regions that might underlie hypothesized deficits in sequence-based prediction in SZ (see Fig. 1). Based on previous work, we focused on two regions of interest (ROI): dorsolateral prefrontal cortex (DLPFC) - identified as dysfunctional during relational memory in fMRI studies of SZ (25), and right posterior hippocampus - identified as a key region mediating sequence representation in our previous sequence memory study (24). Using representational similarity analysis (RSA), we examined the extent to which activity patterns in these regions carry position information for objects in learned sequences, and whether the fidelity of these representations could identify individual differences in sequence-based item prediction for fixed versus random sequences. We hypothesized that neural sequence representations in DLPFC and posterior hippocampus are disrupted in people with SZ, resulting in attenuated sequence prediction effects.

METHODS AND MATERIALS

Participants

As previously (3), forty-four individuals (7 unmedicated) with SZ were recruited from the UC Davis Early Psychosis Programs (EDAPT and SacEDAPT). Sixty-six HC responded

to paid advertisements through the UC Davis Imaging Research Center (IRC). Clinical assessments were conducted to confirm SZ diagnosis and symptom severity. Clinicians with master's or doctoral level training confirmed diagnosis using the Structured Clinical Interview for DSM-V (SCID-V). Symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms (SANS), and Scale for the Assessment of Positive Symptoms (SAPS). Exclusion criteria included: substance abuse in past year, implants that may interfere with MRI scanning (e.g. ferromagnetic implants), neurological defects, loss of consciousness after head trauma, low IQ (i.e., <70), or less than 20/30 vision when corrected. Four participants were excluded for miscellaneous reasons including; a change in diagnosis (1 HC, 1 SZ), an incidental finding (1 SZ), and refusal to enter the scanner due to anxiety (1 SZ). Eleven participants (7 HC, 4 SZ) were excluded due to operator error which caused a mis-alignment of task onset and scanner onset. An additional 6 participants (2 HC, 4 SZ) were excluded due to poor quality behavioral data (greater than 30% non-responses), and 4 were excluded (2 HC, 2 SZ) for low quality structural/functional scans (signal dropout or excess motion greater than 1 voxel). Following exclusions, data are presented on a final sample of 85 participants (54 HC and 31 SZ). As seen in Table 1, groups were matched on age, gender and parental education, but the SZ sample had lower participant education as illness often interrupts educational attainment. Included in the table are CPZ equivalents for medicated SZ participants. The current study was approved through the University of California, Davis, Institutional Review board and participants provided informed consent prior to study.

Procedure and Design

Encoding Phase—Participants learned five sequences (see 24), during EEG (3) prior to entering the MRI scanner. Encoding conditions are illustrated in Figure 1, and details are provided in Zheng et al. (3).

Sequence Retrieval Task—Immediately following encoding, participants were positioned in the MRI scanner. During sequence retrieval, participants viewed previously encoded sequences (two fixed, two random, and one novel) for three repetitions per run across four runs. Sequence order was randomized and objects appeared in a continuous stream, with no delays between sequences. Each object in each sequence was presented for 1000ms. Before each run, a semantic question was provided, which participants answered for each object. Questions were: 1) Can this object fit in a shoebox? 2) Can you easily lift this object with one hand? 3) Is the presented object living? or 4) Does this object contain visible metal? Semantic questions were asked to maintain attention and gauge RT differences both within and between sequences to index sequence prediction success.

MRI Acquisition

Imaging was conducted at the University of California, Davis, Imaging Research Center (IRC) on a 3T Siemens Trio Total imaging matrix (Tim) MRI system with a 32-channel head-coil. Structural images were acquired using T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) pulse sequence (208 slices, sagittal; voxel size = $1.0mm^3$; TR = 2000ms; TE = 2.98ms; flip angle = 8°; FoV = 256mm). Functional images

were acquired with an echo planar imaging (EPI) sequence (235 time points; voxel size = $3.4mm^3$; TR = 2000ms; TE = 25ms; FoV = 218mm; 34 slices, interleaved).

Data Processing and Analysis

Behavioral Data—Sequence prediction effects were calculated by averaging RT across objects 2–5 for fixed and random sequences and calculating differences in RT between sequence types (fixed – random). Repeated-measures analysis of variance (ANOVA) identified main effects of group (HC vs. SZ), sequence type (fixed vs. random) or higher order interactions for averaged RT values. Pearson Product moment correlations examined associations between symptom severity (total scores on the BRPS, SANS, and SAPS) and sequence prediction effects. Significance levels were set at $p<0.05$ for all analyses.

fMRI Data Preprocessing—Preprocessing of fMRI data was modeled after Hsieh et al (2). Preprocessing was accomplished using fMRI Expert Analysis Tool (FSL version 5.0.9). To strip the skull and remove any non-brain tissue, the Brain Extraction Tool (BET) extracted brain volumes. All functional images were slice-time corrected and high-pass filtered with a 0.01 Hz cut-off. MCFLIRT was used for motion correction and functional images were co-registered with each individual's MPRAGE using FLIRT. Resulting transformation matrices were used to transform ROIs into native-space for each participant.

Regions of Interest—*A priori* regions of interest (ROIs) were bilateral DLPFC and bilateral hippocampus. Hippocampal ROIs utilized probabilistic maps based upon an average of 55 hand-traced T1 images using methods validated by Ritchey and colleagues (10). Hippocampal ROIs included the full body, and sub-regions for head, body and tail based on anatomical landmarks (10). The DLPFC ROI (36 voxels) utilized a probabilistic mask including Brodmann areas 9 and 46 based upon Talairach coordinates functionally defined by MacDonald and colleagues (26). After placing ROIs in standard space, they were transformed into native space prior to statistical analysis as described above.

We also performed an exploratory searchlight whole brain RSA analysis using 400 parcellations acquired from Schaefer and colleagues (27). As previously, parcellations were transformed into native space prior to statistical analyses (FWE corrected at $p<0.05$).

Representational Similarity Analysis—RSA is a multivariate approach correlating patterns of voxel activation across objects that share a similar feature of interest to determine if brain regions are sensitive to that feature (28,29). For example, imagine an area of the brain encoding representations of dogs. Patterns of activation in that area for one dog will be similar to patterns of activation for another dog. In contrast, patterns of activation for a cat in that area might show shared activation across some voxels because of some shared features (e.g. four legs, domestic animal, etc.), but the overall pattern of activation for the cat will be more dissimilar than either of the dog representations, confirming that the area is most sensitive to processing dog-related representations. For the current study, we utilized RSA to understand how DLPFC and posterior hippocampus represented fixed versus random sequences.

To do this, we first assessed patterns of activity across voxels within DLPFC and posterior hippocampus during single trials using parameter estimates (i.e. beta weights) for each object, estimated through the Least-Square2 (LS2) method (30). A general linear model (GLM) computed beta weight estimates for each object. For each functional run, there were 75 GLMs (5 objects/sequence x 5 sequences x 3 repetitions) for a total of 300 beta maps (4 runs x 75 beta maps/run). Outlier beta maps, determined by a signal intensity lying in the 1% of all beta maps, were excluded from analyses.

Next, we examined voxel pattern similarity for fixed and random sequences by calculating Pearson's correlation coefficient between beta weight vectors for pairs of trials, which were Fisher transformed and averaged in three ways (fig. 1). To examine fixed sequence representations, an average was taken for all fixed sequences across repetitions and runs, where each object was in the same position. For random sequences, an average was taken across all random sequences, where the position of objects varied. To include representations where object information was shared between objects in different sequences regardless of position, voxel patterns were rearranged within random sequences and averaged. These two averages were combined to create a full picture of random sequence representation. For bilateral DLPFC, we performed a three-way ANOVA to identify effects of group (HC vs. SZ), hemisphere (left vs. right), and sequence representation (fixed vs. random). Based on prior research using a similar paradigm (24), we limited analyses of the posterior hippocampus to the right hemisphere. We performed a two-way ANOVA in right posterior hippocampus examining effects of group (HC vs. SZ) and sequence representation (fixed vs. random). Correlation analyses were performed to determine associations between RT sequence prediction effects and similarity values (fixed – random) gleaned from RSA results.

Results

Behavioral Results—Based upon previous results (3), we hypothesized that people with SZ would show reduced sequence prediction effects. This was supported by the ANOVA, which revealed main effects of group ($F(1,83)=8.27$, $p=0.005$) and sequence type ($F(1,83)=21.90$, $p<0.001$), as well as a significant group by sequence interaction ($F(1,83)=8.93$, $p=0.004$). As shown in Figure 2, t-tests investigating sequence prediction effects (fixed minus random RT for objects 2–5) revealed that this interaction was due to HC showing a greater speeding of RT for fixed versus random sequences than people with SZ ($t=-2.99$, $p=0.004$). Thus, although people with SZ were able to learn and retrieve well-learned sequences and speed their RTs, these memory prediction effects were reduced relative to HC. (Supplemental figure 1 illustrates the difference between objects within each sequence.)

fMRI Results—Based on previous work (24), we hypothesized that DLPFC and posterior hippocampus are involved in supporting memory-based prediction for objects within a temporal context and that these representations would be reduced in people with SZ. We examined this separately for DLPFC and hippocampus using RSA to compare voxel pattern similarities for fixed and random sequences.

Supporting our hypothesis for the DLPFC, ANOVA revealed a main effect of sequence with fixed sequences showed higher similarity than random sequences ($F(1,83)=14.84$, $p<0.001$; fig 3). There was no main effect of hemisphere ($F(1,83)=3.37$, $p=0.07$). Although there was no main effect of group, there was an interaction between sequence and group ($F(1,83)=5.67$, $p=0.02$). Post-hoc tests revealed that in HC only, DLPFC voxel pattern similarity was higher for fixed sequences than for random sequences ($t=5.16$, $p<.001$). Conversely, in the SZ sample there were no differences in how the DLPFC represented objects in fixed versus random sequences ($t=0.92$, $p=0.36$). These data suggest that DLPFC dysfunction may be associated with memory-based prediction deficits in individuals with SZ.

In posterior hippocampus, ANOVA revealed no main effects of group or sequence. There was, however, a trend toward an interaction between group and sequence ($F(1,87)=3.20$, $p=0.08$; fig 3). Exploratory post-hoc analyses revealed that this trend-level interaction was due to increased pattern similarity for fixed versus random sequences in the right posterior hippocampus of HC ($t=2.26$, $p=0.03$) but not in people with SZ ($t=-0.55$, $p=0.58$). Results did not support our hypothesis that hippocampal dysfunction contributes to temporal sequence memory deficits in SZ.

Searchlight analyses did not reveal other areas showing increased pattern similarity for fixed versus random sequences. Thus, there were no effects in other parts of the brain.

Association with Performance: To determine the relationship between sequence prediction effects and representational similarity, we performed correlation analyses (Fig 4). In the left DLPFC, fixed sequence representations were significantly correlated with sequence prediction effects in HC ($r=-0.330$, $p=0.011$) but not in SZ ($r=-0.115$, $p=0.392$). In the right DLPFC, there was no correlation between sequence prediction and representational similarity. These data suggest that, in HC only, as sequence prediction increases (indicated by an increasingly negative value), representational similarity increases in the left DLPFC.

Similar analyses were performed in the bilateral posterior hippocampus, however none of the results from these analyses were significant, indicating that pattern similarity in the posterior hippocampus was not associated with sequence prediction effects.

Association with Clinical Symptoms: Correlational analyses did not reveal any significant relationships between DLPFC pattern similarity effects and severity of clinical symptoms (total SANS, SAPS and BPRS) in the SZ sample (all r-values > 0.08).

Discussion—We rely on memory to make accurate predictions about our changing environment. In the present study, we investigated whether people with SZ show deficits in memory-based prediction using a temporal sequence paradigm (2,3,31). Although both groups predicted and responded more quickly to objects within a previously learned sequence (i.e. faster RTs for fixed versus random sequences), this effect was reduced in people with SZ relative to HC. Multivariate analyses of fMRI data revealed that participants with SZ showed disrupted neural representations of learned sequences in the DLPFC. These

findings support the conclusion that people with SZ can learn temporal sequences but their ability to utilize this sequence memory to predict future events is dysfunctional.

Sequence prediction effects were measured indirectly as individuals responded to objects contained in sequences that could be learned (i.e., fixed) or could not be learned (i.e., random), with speeding of semantic decisions for learned versus unlearned sequences providing evidence of successful prediction. Behavioral results indicate that individuals with SZ were capable of forming and using memories to predict the next object in the sequence and, thereby, guide their behavior. As previously (3) both groups showed evidence of sequence learning, but memory prediction effects were reduced in people with SZ relative to HC. Therefore, memory impairments do not appear due to a lack of attention or a generalized memory deficit. However, individuals with SZ did not improve predictions to the same degree as healthy individuals, suggesting that people with SZ were less successful in using memory representations to guide predictions (14).

Although semantic priming deficits have been reported in SZ (32,33), it is notable that, in the present study, objects in learned and random sequences were equally familiar. Thus, differential effects of sequence learning on semantic decisions between patients and controls cannot be explained by differences in semantic priming. Instead, our results are more consistent with the idea that people with SZ have a reduced ability to use sequential regularities to predict upcoming events.

To better understand these memory-related prediction impairments, we used RSA to characterize representations of information from temporal sequences in DLPFC and posterior hippocampus. Multivariate analyses revealed that, in HC, representational similarity was higher across repetitions of objects in learned sequences relative to repetitions of objects in random sequences in the DLPFC. These effects were not significant for people with SZ, and DLPFC voxel pattern similarity differences between objects in learned and random sequences were significantly higher in HC than in SZ. Moreover, the fidelity of DLPFC representations of objects in learned sequences was predictive of sequence prediction success in HC only, although there were no significant group differences in the size of the association. Results are consistent with a large body of behavioral, eye-tracking, EEG and fMRI research linking both memory (25,34) and prediction (23) impairments to DLPFC dysfunction in people with SZ. Impaired DLPFC control of memory encoding and retrieval has been repeatedly demonstrated in people with SZ on both an individual study (31,34) and meta-analytic level (25).

In addition to the DLPFC, numerous studies supported the idea that hippocampal abnormalities might contribute to relational memory deficits in SZ (35). Several studies documented reductions in hippocampal volume in SZ (36) and others (37,38,39), including results from our group (31,40), demonstrated reduced hippocampal activation during relational memory retrieval in people with SZ relative to HC. In the present study, however, we did not observe any evidence for hippocampal dysfunction in people with SZ. Exploratory analyses of data restricted to the HC group revealed that, consistent with our previous study (24), pattern similarity in right posterior hippocampus was higher for objects in learned relative to random sequences. Although these effects were not significant

in people with SZ, we did not observe any significant between group differences in hippocampal sequence representations, nor did we find significant relationships between hippocampal results and sequence prediction effects in either group. Thus, results did not support the hypothesis that sequence-based prediction deficits in people with SZ were related to impaired hippocampal function.

As described in Zheng et al. (3), people with SZ learned sequences more slowly than HC, consistent with a deficit in relational memory. As previously (2,41), participants were highly trained on fixed and random sequences prior to scanning, thus enabling people with SZ to compensate for any learning deficits. During scanning, participants were not asked to explicitly recall sequences, so we would only expect them to show faster decisions for objects in fixed sequences if they proactively used memory for the learned sequences to accurately predict upcoming objects. Thus, results are consistent with concluding that, even when learning is sufficient to overcome relational memory deficits, people with SZ are impaired using what was learned to predict upcoming events, with this deficit strongly associated with DLPFC dysfunction.

A challenge of studying people with SZ is the heterogeneity of the disorder which can increase variability and in addition to potential medication effects and differences in clinical presentations. One might expect that we would have found correlations with positive symptoms given literature linking predictive coding deficits with severity of positive symptoms (18). One notable difference between our study and previous work is that participants in this study were early psychosis patients who were clinically stable with mild to moderate symptoms. Therefore, a restricted range may have contributed to lack of clinical correlations. Most participants in the SZ group were receiving second generation antipsychotics and when analyses were repeated after excluding un-medicated participants there was no difference in the pattern of behavioral or fMRI results. We also did not find any significant correlations with standardized medication dose (i.e., CPZ equivalents). Thus, results do not appear to be influenced by medication or symptom severity effects. We did experience significant data loss due to excess motion and operator error. This was likely related to both operator and participant fatigue as fMRI recordings were obtained immediately following an EEG study (3). Finally, our primary fMRI analysis examined *a priori* regions in the hippocampus and prefrontal cortex based upon previous fMRI studies (2,31), raising the possibility that there were task effects or group differences within other regions of the brain. To address this, we conducted an exploratory whole-brain searchlight analysis which did not reveal any task effects or group differences in other brain regions.

In conclusion, results indicate a key finding: individuals with SZ are able to learn sequences, but there is dysfunction in using prior knowledge about sequences to aid in prediction of upcoming objects. HC were more successful than people with SZ engaging their DLPFC to form object/sequence representations to facilitate prediction of upcoming objects in learned sequences. These findings support prior theories proposing that there are aberrant prediction processes in people with SZ (14,17). Ongoing efforts to remediate memory-based prediction deficits in SZ using neurostimulation, pharmacology or behavioral interventions may be most successful if they target DLPFC-related control processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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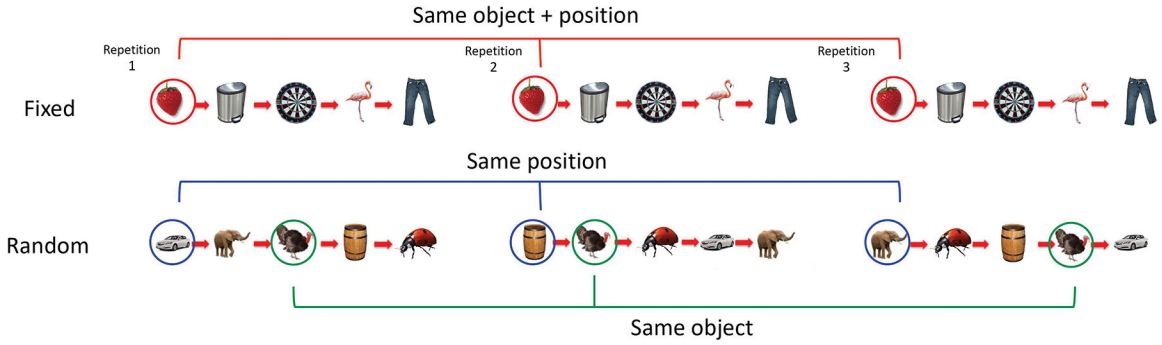

Figure 1.
Schematic of the paradigm. Fixed sequences show the same objects in the same position for each repetition. Random sequences show the same objects but in a different position each repetition.

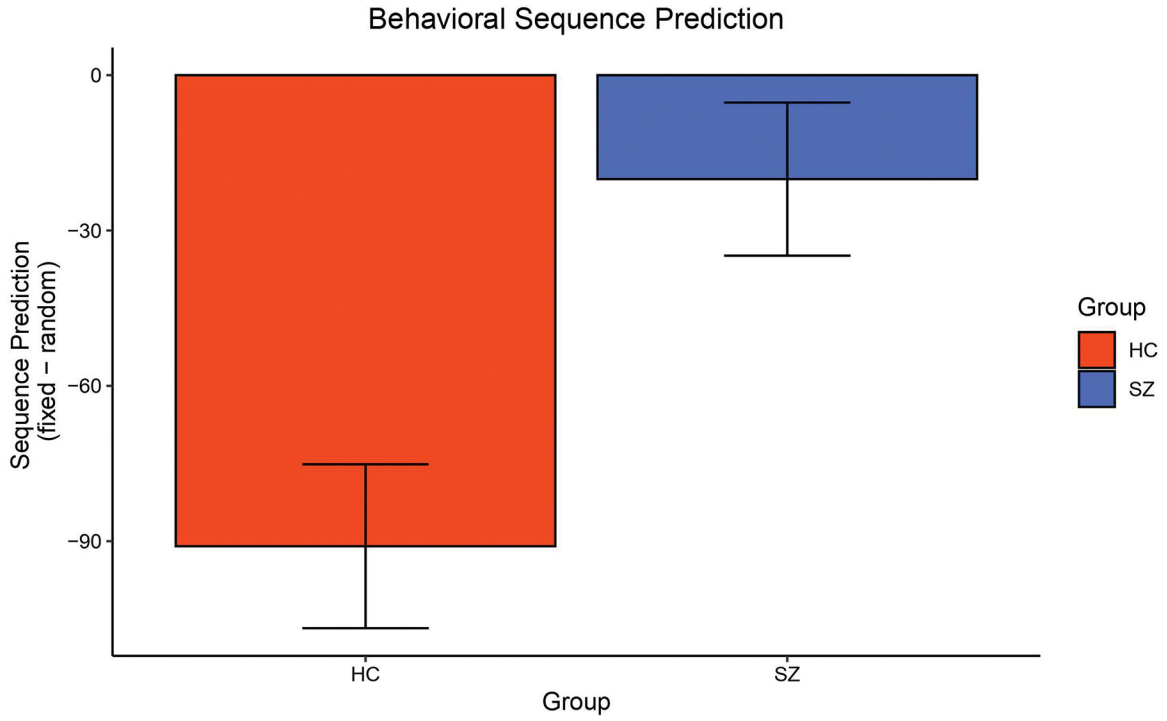

Figure 2.

Sequence prediction indicated by the difference in RT for objects 2–5 between fixed and random sequences. RT for fixed sequences was faster than random sequences for both groups with HC showing a significantly greater difference.

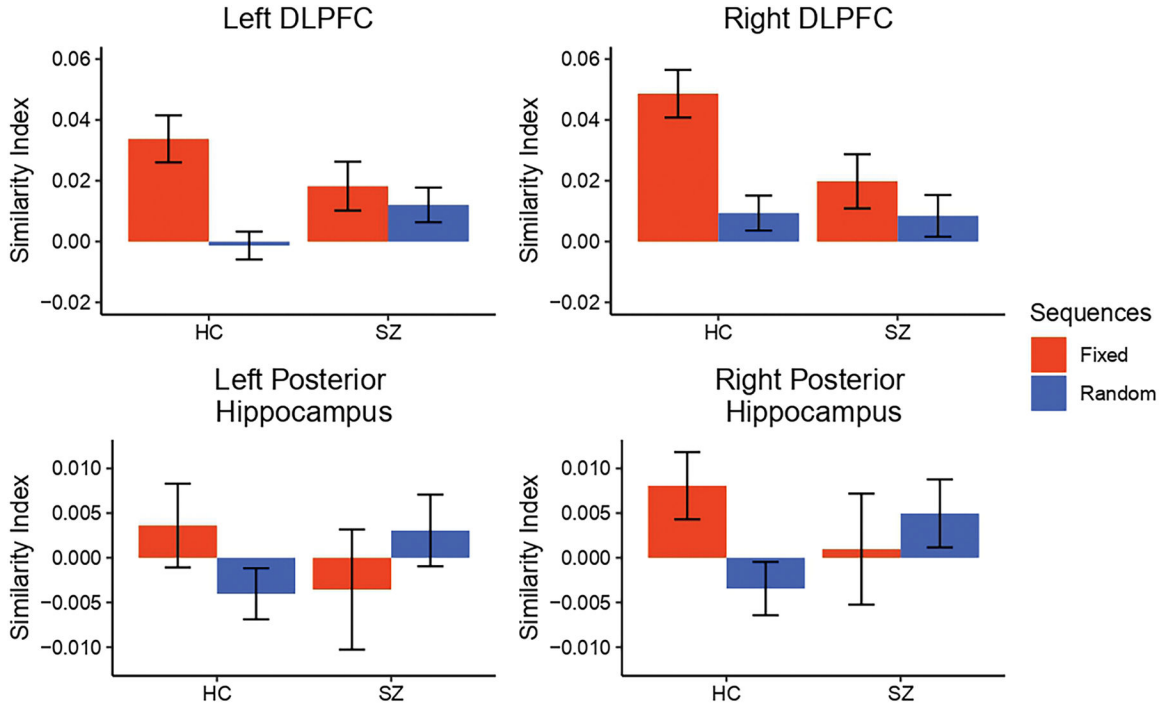

Figure 3.

In the bilateral DLPFC (Fig. 3A and 3B), HC showed significantly greater similarity for fixed sequences compared to random while SZ did not. The left posterior hippocampus showed no group or sequence differences (Fig. 3C and 3D). In the right posterior hippocampus, in HC only, fixed sequences showed significantly greater similarity for fixed versus random sequences.

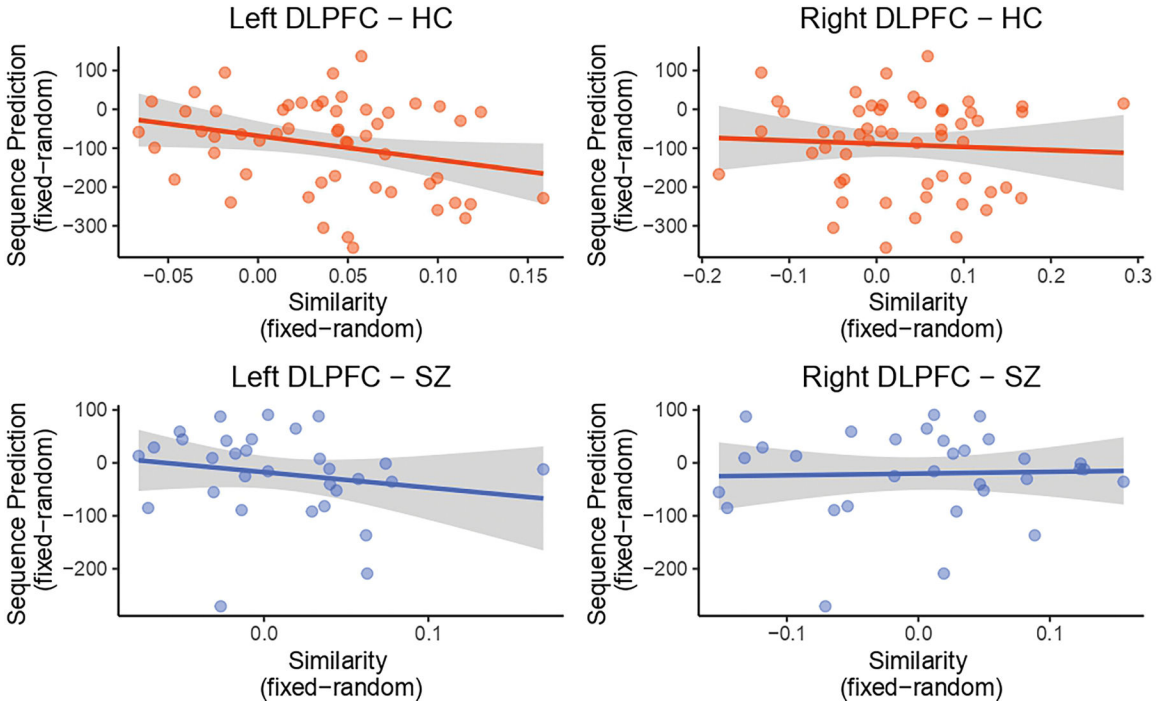

Figure 4.

Scatter plot of correlations between pattern similarity in the left DLPFC and sequence prediction success. For HC (Fig. 4A and 4B), greater pattern similarity for fixed versus random sequences in the left DLPFC was correlated with better sequence prediction. These correlations were not significant in people with SZ (Fig. 4C and 4D).

Table 1.

Sample Demographics

	Healthy Controls (n=54)	Schizophrenia (n=31)	*p-values*
	Mean ± SD	***Mean ± SD***	
Age (years)	24.10 ± 4.38	23.05 ± 4.23	0.28
Sex (% male/female)	72%/28%	81%/19%	0.39
Education (years)	15.07 ± 1.98	13.50 ± 1.80	0.00047***
Parental Education (years)	13.70 ± 3.03	14.69 ± 2.57	0.13
BPRS (total)		37.77 ± 10.09	
SANS (total)		18.10 ± 10.71	
SAPS (total)		7.45 ± 12.00	
CPZ Equivalents		244.22 ± 161.22	

SZ, schizophrenia; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; CPZ, chlorpromazine