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Disrupted Modulation of Alpha and Low Beta Oscillations Mediates Temporal Sequence Memory Deficits in People with Schizophrenia

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Abstract

BACKGROUND: People with schizophrenia (SZ) exhibit impaired episodic memory when relating objects to each other in time and space. Empirical studies and computational models suggest that low-frequency neural oscillations may be a mechanism by which the brain keeps track of temporal relationships during encoding and retrieval, with modulation of oscillatory power as sequences are learned. It is unclear whether sequence memory deficits in SZ are associated with altered neural oscillations.

METHODS: Using electroencephalography, this study examined neural oscillations in 51 healthy controls and 37 people with SZ during a temporal sequence learning task. Multiple five-object picture sequences were presented across 4 study-test blocks in either fixed or random order. Participants answered semantic questions for each object (e.g., living/non-living), and sequence memory was operationalized as faster responses for fixed versus random sequences. Differences in oscillatory power between fixed versus random sequences provided a neural index of temporal sequence memory.

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Disclosures

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RESULTS: Although both groups showed reaction time (RT) differences in late blocks (blocks 3 and 4), this evidence of sequence memory was reduced in people with SZ relative to healthy controls. Decreases in globally-distributed pre-stimulus alpha (8–12 Hz) and beta1 (13–20 Hz) power for fixed versus random sequences in late blocks were also attenuated in people with SZ relative to healthy controls. Moreover, changes in oscillatory power predicted individual RT differences, and fully mediated the relationship between group and sequence memory.

CONCLUSIONS: Disrupted modulation of alpha and beta1 EEG oscillations is a candidate mechanism of temporal sequence memory deficits in people with SZ.

Keywords

Electrophysiology; Episodic Memory; Neural Oscillations; Alpha; Beta; Schizophrenia

INTRODUCTION

Learning how events unfold temporally is crucial for recall from the past (episodic memory) and planning for the future. Schizophrenia (SZ) is a neurodevelopmental disorder associated with impaired episodic memory, especially when individuals are required to form relational memories such as during the associative inference task (1). For example, they have difficulty recalling the temporal order of objects even when they are correctly recognized as previously studied (2,3). In a previous electroencephalography (EEG) study, we found that people with SZ had problems maintaining temporal order in working memory (WM) related to disrupted theta oscillations (4). However, the impact of SZ on EEG oscillations during episodic memory for temporal information has not been studied. This is an important topic as episodic memory requires WM maintenance and relational binding processes demonstrated to be disproportionately impaired in people with SZ (5). Because time is a central context for many episodic memories (e.g., “I parked my car there yesterday, not today”) it is particularly crucial for understanding memory problems and related functional impairment (6) in SZ.

Low-frequency neural oscillations facilitate neural synchronization and are linked to episodic memory encoding and retrieval (7), and learning of temporal sequences (8–10). For example, Crivelli-Decker et al. (8) asked participants to learn different sequences embedded in a stream of objects while answering semantic questions about each object. EEG responses to repetitions of the same sequence were contrasted against responses to equally familiar objects presented in a random order. As the sequences were learned, participants could anticipate objects and speed responses to semantic questions for objects in fixed versus random sequences - producing a behavioral index of temporal sequence memory. Post-response mid-frontal theta oscillations predicted sequence memory in future trials, while pre-response posterior alpha and beta oscillations were associated with current processing of temporal sequences.

Given that neural oscillations are related to learning temporal order information, we predicted that disrupted low-frequency oscillations may contribute to deficits in temporal sequence memory in people with SZ. Disrupted neural oscillations have been identified as a potential pathophysiologic mechanism of cognitive dysfunction in SZ (11). Although many

studies focused on higher frequency gamma oscillations (12), more recent work focused on disruption of lower-frequency alpha and theta oscillations linked to impaired proactive cognitive control processes (13). Low-frequency neural oscillations have also been linked to other cognitive deficits in SZ (14), including episodic memory (15) and working memory (16). In a recent study (4), we found that disrupted theta and alpha power were associated with patient difficulties maintaining the temporal order of visual objects in working memory. However, we are not aware of any previous studies examining EEG oscillations during temporal sequence memory in SZ.

EEG was recorded while participants performed a sequence learning task, answering semantic questions about objects presented in fixed or random order, as previously described (8). If participants learned temporal order relationships for fixed sequences, they would be able to predict upcoming objects, thereby making faster responses to subsequent questions compared with that of random sequences. We, therefore, examined reaction time (RT) differences (fixed - random) as a behavioral index, and EEG power differences (fixed – random) as a neural index of sequence memory. The experiment was divided into early (blocks 1 and 2) and late blocks (blocks 3 and 4) to identify changes as fixed sequences were learned. We hypothesized that HC would show greater power differences between fixed and random sequences in late blocks, explaining reduced temporal sequence memory in people with SZ.

METHODS AND MATERIALS

Participants

Data were acquired on 45 people with SZ (10 unmedicated) and 55 healthy controls, of which 8 people with SZ and 4 controls were excluded due to EEG artifacts or invalid behavioral data recording, leaving a final sample of 37 SZ and 51 controls. Results for the full sample with valid behavioral data are illustrated in Supplementary Materials (Figure S1). People with SZ were recruited through the UC Davis Early Diagnosis and Preventative Treatment Clinic, and controls were recruited through paid advertisements. All but one medicated patient was receiving atypical antipsychotics. To examine medication, we also ran analyses without unmedicated patients, which produced similar results. As shown in Table 1, individuals matched at the group level for age, sex, education and parental education. Clinical symptoms were measured using the Scale for the Assessment of Negative Symptoms, Scale for the Assessment of Positive Symptoms, and Brief Psychiatric Rating Scale. All people with SZ were clinically stable and within 5 years of illness onset. Diagnoses were assessed using the Structured Clinical Interview for DSM-IV-TR (17) by Masters or Doctoral level clinicians with demonstrated reliability, established using the intraclass correlation-coefficient for continuous variables and kappa for categorical measures (both maintained at 0.8 or greater (18)). Participants with substance abuse in the previous year, ferromagnetic implants, neurological illness, head trauma leading to unconsciousness, low IQ (i.e., < 70), or corrected vision not achieving 20/30 were excluded. Controls with any first-degree relatives with a psychosis history were also excluded. All participants received a urine drug screen. The study was approved by the institutional review board of the University of California at Davis, and informed consent was provided by all participants.

Procedure and Design

EEG was recorded while participants performed a sequence learning task consisting of four repeated study-test blocks. During the Study Phase, participants viewed a continuous stream of 125 visual objects presented for 1000 ms each, separated by 1500 ms fixation crosses. As depicted in Figure 1A, the stream consisted of repetitions of five different sequences (2 fixed, 2 random, 1 novel). Fixed sequences consisted of five distinct objects, presented in the same order on each repetition, allowing participants to learn their temporal order relationships. To control for any potential confounding factors other than sequence learning, we included a random condition in which 5 objects were presented in a different pseudorandom order during each repetition. Novel sequences were utilized for analysis of fMRI data and will be described in a future manuscript.

Within each block, sequences were presented five times, with no back-to-back repetitions of the same sequence, and no repetitions until all 5 sequences had been viewed once. Participants answered semantic questions for each object (e.g., “Is the object living?”), provided at the beginning of study-test blocks. Using temporal sequence memory to speed semantic question responses was encouraged. During the self-paced Test Phase of each block, five objects were presented simultaneously in a random order and participants were asked to re-order them in their correct temporal order. Participants were instructed to re-order objects randomly if they were presented as random sequences. At the end of each test trial, the correct order of the objects was displayed to provide corrective feedback (pseudorandom order for random sequences). Each sequence was tested two times in each test phase. Participants were not alerted to the test phase at the beginning of the experiment.

Behavioral Data Analysis

Test phase performance—Test phase performance was examined by calculating average number of fixed sequence items placed in the correct temporal order during trial 1. Trial 2 was not examined because of potential confounds from testing effects (19). These values were entered into a mixed-design analysis of variance (ANOVA) performed in MATLAB (MathWorks, Natwick, MA) to examine effects of group (healthy controls versus people with SZ), block (early versus late), and higher order interactions.

Sequence learning—Sequence learning was divided into early (blocks 1 and 2) and late (blocks 3 and 4) blocks. Previous studies (8,20) found that as participants remembered fixed sequence temporal order, they were able to respond more quickly to the semantic questions for objects 2–5 in fixed versus random sequences. Thus, **behavioral sequence memory effects** were operationalized as the difference (fixed – random) in RTs averaged for objects 2–5 across repetitions within each block and sequence type. Average RTs were entered into a mixed-design ANOVA to examine effects of block (early versus late blocks), condition (fixed versus random), group (healthy controls versus people with SZ), and higher-order interactions. To examine the relationship between sequence memory and clinical symptoms, we examined correlations with total BPRS, SANS and SAPS scores. Type I error was controlled by setting significance levels at $\alpha = .05$ for all analyses.

Time-frequency Analysis

EEG acquisition and pre-processing procedures are detailed in Supplementary Materials. Time-frequency analyses focused on the **neural sequence memory effects**, defined as averaged oscillatory power differences between fixed and random sequences across objects 2–5. Separate analyses were performed on time-frequency representations (TFRs) for theta (4–7 Hz), alpha (8–12 Hz), beta1 (13–20 Hz), and beta2 (21–30 Hz) based on cluster-based permutation tests in Fieldtrip (21), which identified significant spatio-temporal clusters without any *a priori* assumptions. These clusters were defined as electrode-time pairs with at least one other significant neighboring electrode exceeding a significance threshold of $\alpha = .05$. To find clusters revealing neural sequence memory effects, we contrasted TFRs of fixed and random sequences using two-tailed paired sample permutation tests. To identify group differences in neural sequence memory effects, i.e., interaction between Group and Condition, TFRs of condition differences in healthy controls and people with SZ were contrasted using two-tailed independent sample permutation tests. Permutation tests were based on t-statistics. To correct for multiple comparisons, test statistics were compared to reference distributions approximated by Monte-Carlo simulation, with 2000 random shuffle repetitions in each approximation.

Linear Regression

To identify any links between behavioral sequence memory effects and neural sequence memory effects including group differences, we performed linear regression analyses, with behavioral sequence memory effects as the dependent variable, and neural sequence memory effects, group, and the interaction term as independent variables. To determine whether oscillations before object onsets could predict behavioral performance, we averaged oscillatory power across the time window identified through the time-frequency analysis performed across all electrodes. This analysis was restricted to frequency bands that demonstrated significant Group and Condition interactions during the cluster analysis described previously. Regression models were performed at the individual participant level separately for each frequency band.

Mediation Analysis

To test the hypothesis that temporal sequence memory deficits are mediated by impaired modulation of EEG oscillations in frequency bands identified through time-frequency analysis, we tested seven alternative models (Figure S2), including parallel and chained mediation models with direct effects between Group and RTs using structural equation modeling[1].

[1]Model fit was assessed with a joint consideration of the $\chi 2$ statistic, the $\chi 2$/df ratio, the standardized root mean residual (SRMR), the Comparative Fit Index (CFI), Tucker–Lewis index (TLI) and the root mean square error of approximation (RMSEA). Acceptable model fit is defined by a non-significant $\chi 2$, a $\chi 2$/df ratio of 3 or less, an SRMR of .05 or less, a CFI of .95 or greater, a TLI of .95 or greater and an RMSEA of .08 or less (24).

RESULTS

Test Phase Performance

Healthy controls were more successful reproducing fixed sequence orders during trial 1 of the test phase than people with SZ ($F(1, 86) = 12.1$, $p < .001$). There was also a main effect of early versus late blocks ($F(1, 86) = 112.5$, $p < .001$), with no Group by Block interaction ($F(1, 86) = 3.1$, p = .084), indicating that both groups became more accurate as the study progressed. These results are illustrated in Supplementary Materials (Figure S3). Since test phase was self-paced and its results were impacted by strong ceiling effects, we focused our EEG analyses on the sequence learning phase.

Reduced Behavioral Sequence Memory Effects in People with SZ

We predicted that participants would speed responses to semantic questions for objects 2–5 for fixed versus random sequences, and that sequence memory would be reduced in people with SZ. ANOVA results supported these predictions. RTs were faster for fixed versus random sequences (Condition main effect; [$F(1, 86) = 47.5$, $p < .001$]), with larger time differences in late versus early blocks (Block main effect; [$F(1, 86) = 37.9$, $p < .001$]), and in healthy controls versus people with SZ (Group main effect; [$F(1, 86) = 6.5$, $p = .012$]). There were also significant interactions between Condition and Block [$F(1, 86) = 22.5$, $p < .001$] and Condition and Group [$F(1, 86) = 7.5$, $p = .007$]. As shown in Figure 1B/C/D, the Condition by Block interaction was due to larger RT differences for late [$F(1, 86) = 47.3$, $p < .001$] than early blocks [$F(1, 86) = 15.9$, $p < .001$]; the Condition by Group interaction was due to smaller RT differences between fixed versus random sequences for people with SZ [$F(1, 86) = 7.4$, $p = .008$] relative to healthy controls [$F(1, 86) = 55.2$, $p < .001$]. There was no three-way interaction [$F(1, 86) = 2.7$, $p = .104$] or Group by Block interaction [$F(1, 86) = 0.6$, $p = .436$]. Exploratory post-hoc analyses within each group are presented in Supplementary Materials. The behavioral sequence memory effect was positively correlated with total ($r = 0.44$, $p = .007$) BPRS scores in people with SZ, indicating that people with more severe symptoms showed less of an improvement in RTs. Correlations with total SANS and SAPS scores were not significant.

Reduced Neural Sequence Memory Effects in People with Schizophrenia

Behavioral results found that controls were more successful than people with SZ remembering fixed sequences to predict subsequent objects and speed semantic decisions once sequences were learned (i.e., late blocks). We next examined oscillatory power differences (averaged across objects 2–5) between fixed and random sequences in late blocks to investigate EEG correlates of sequence memory.

Neural sequence memory effects were examined in theta, alpha, beta1, and beta2 bands in late blocks for healthy controls and people with SZ. There was a significant interaction between Group and Condition in globally-distributed alpha (p = .002, −1500 to 30 ms) and beta1 (p < .001, −1270 to −170 ms) bands before stimulus onsets (Figure 2A, B). Further tests revealed that for healthy controls, there were significant power decreases in fixed relative to random sequences in late blocks across all four frequency bands (Figure 2C). These neural sequence memory effects of globally averaged power were significant in

theta ($p < .001$, −1500 to 1000 ms), alpha ($p < .001$, −1500 to 1000 ms), beta1 ($p < .001$, −1500 to 1000 ms) and beta2 frequencies ($p = .013$, −1380 to −1170 ms; $p < .001$, −1170 to −160 ms; $p = .002$, −90 to 410 ms). For people with SZ, there was no cluster showing significant neural sequence memory effects (Figure 2D). Moreover, there were no clusters showing significant interactions between Group and Condition in any frequency bands in early blocks (Figure S4).

Thus, as with behavioral results, group differences in pre-stimulus neural sequence memory effects were found in late blocks – once the sequences were learned, suggesting that altered neural oscillatory patterns might underlie temporal sequence memory deficits in people with SZ.

Neural Sequence Memory Effects Predict Behavioral Sequence Memory Effects

Linear regression revealed no significant interactions between Group and Power [alpha: $B = -5.51$, $SE = 10.15$, $\beta = -.06$, $t = -.54$, $p > .05$ (model $R^2 = .15$, $p = .003$); beta1: $B = -8.38$, $SE = 10.70$, $\beta = -.08$, $t = -.78$, $p > .05$ (model $R^2 = .16$, $p = .003$)]. The model without interaction terms showed significant main effects of Power [alpha: $B = 26.86$, $SE = 9.99$, $\beta = .30$, $t = 2.69$, $p = .009$ (model $R^2 = .15$, $p = .001$); beta1: $B = 27.61$, $SE = 10.12$, $\beta = .31$, $t = 2.73$, $p = .008$ (model $R^2 = .15$, $p = .001$)], but group differences in behavioral sequence learning effects were no longer significant (alpha: $B = 13.26$, $SE = 9.99$, $\beta = .15$, $t = 1.33$, $p > .05$; beta1: $B = 12.32$, $SE = 10.12$, $\beta = .14$, $t = 1.22$, $p > .05$). As reported, alpha and beta1 neural sequence memory effects predicted behavioral sequence memory effects[2], with no group differences in these relationships (for individual raw data, see Figure S5). Furthermore, group differences in behavioral sequence memory effects were no longer significant when neural sequence memory effects were controlled, suggesting that group differences in behavioral sequence memory may be mediated by neural sequence memory effects in alpha and beta1 bands.

Alpha and Beta1 Neural Sequence Memory Effects Fully Mediate Group Differences in Behavioral Sequence Memory Effects

To test whether group differences in behavioral sequence memory were mediated by alpha and beta1 neural sequence memory effects we examined seven alternative mediation models (Figure S2). Although all chained mediation models showed better fit than parallel mediation models (Table S1), only the chained mediation model (Group −>Alpha −> Beta1 −> RTs) with an independent path through beta1 power (Group −> Beta1 −> RTs, Model 2(c)) showed acceptable fit.

To identify any remaining direct effects between Group and RT, after accounting for alpha and beta1 power, we tested a full mediation model after removing direct effects in the acceptable model and computed the change in $\chi 2$. As shown in Figure 3, removing the direct effects did not worsen the model [$\Delta\chi 2 = 1.531$, $\Delta df = 1$, $p = .216$] and fit statistics for the full model still indicated good fit ($\chi 2\,(2) = 2.936$, $p = .230$, $\chi 2/df = 1.468$, SRMR

[2]alpha and beta1 neural sequence memory effects could also predict performance in the test phase (see supplementary results for details).

= .040, CFI = .989, TLI =.968, RMSEA = .074), supporting a full mediational role of alpha and beta1 oscillations accounting for group differences in behavioral sequence memory effects.

DISCUSSION

We investigated temporal sequence learning in people with SZ to identify potential neural mechanisms of differential learning deficits documented in previous relational memory studies (5,22,23). Behaviorally, both healthy controls and people with SZ successfully learned to predict stimuli in fixed sequences, resulting in faster RTs for fixed versus random sequences. However, people with SZ showed smaller sequence memory effects relative to healthy controls in late blocks, indicating less successful sequence memory. Neurally, unlike healthy controls, who showed globally-distributed power decreases across the scalp in fixed relative to random sequences in late blocks, people with SZ did not show these neural sequence memory effects. Group differences in neural sequence memory effects were significant in alpha and beta1 bands in late blocks. These alpha and beta1 neural sequence memory effects predicted sequence memory on an individual level in both groups, and mediation analysis demonstrated that patient deficits in temporal sequence memory were fully mediated by difficulties modulating alpha and beta1 oscillations during late blocks. These results suggest that alpha and beta1 neural oscillations are a candidate mechanism underlying difficulties that people with SZ have forming temporal sequence memories, and may contribute to other types of relational memory deficits.

Results revealed that pre-stimulus alpha and beta1 oscillations for fixed versus random sequences decreased after learning occurred (i.e., in late blocks) in healthy controls compared to people with SZ. Previously, more traditional episodic encoding and retrieval paradigms also reported alpha and beta desynchronization that was positively correlated with behavioral performance (24–27). Several theoretical accounts explain how oscillatory desynchronization may relate to learning success. According to the *information via desynchronization hypothesis* (28), decreased alpha and beta power may reflect increased information processing thereby making specific episodic memories more distinctive. From this perspective, alpha and beta1 power decreases in late blocks would allow healthy controls to process more information (i.e., the temporal relationship between objects) in fixed relative to random sequences. Second, the *gating by inhibition theory* (29) relates cortical alpha power increases to inhibition in a local brain region, such that decreasing oscillatory power releases inhibition in regions processing task-relevant information. In the current study, sequence learning success resulted in decreased alpha oscillations in healthy controls, thereby facilitating processing of temporal information in fixed sequences. Third, power decreases in beta oscillations have been argued to gate access of sensory information to working memory and control its maintenance (30), and are often associated with motor planning or imagery (31). Reduced pre-stimulus beta1 power may enable healthy controls to switch from the previous to the next object flexibly and thereby better prepare responses to upcoming semantic questions in fixed sequences, whereas people with SZ were more inflexible in this proactive process.

Although current results from healthy controls are consistent with these previous studies and theoretical frameworks, Crivelli-Decker et al. (8) found increases, rather than decreases in alpha and beta1 power as learning occurred. The apparent contradiction likely reflects different baseline correction approaches used to normalize time-frequency data in the two studies. In Crivelli-Decker et al. (8), investigators used time windows of −800 to −500 ms relative to onset of each object in the sequence, whereas the current study used time windows of −1250 to −250 ms relative to onset of the first object in each sequence. Exploratory plots using the Crivelli-Decker et al. (8) baseline correction procedure found oscillatory power increases, confirming this explanation. In our study it was more appropriate to use pre-stimulus baseline periods for the first object in each sequence because participants could not generate any expectations prior to the first object. However, after seeing the first object in a fixed sequence, they might anticipate the remaining objects in the sequence. Thus, by baseline correcting to the period prior to the first object, we identified memory-related changes in pre-stimulus oscillations for objects 2–5.

Another key finding was that reduced alpha and beta1 oscillatory power was related to the behavioral index of sequence memory. Alpha and Beta power decreases during fixed sequences predicted the degree of RT facilitation for fixed versus random sequences on an individual level. Mediation analyses revealed that disrupted learning in patients was explained by failures to modulate oscillatory power in task-appropriate manners. These models revealed a primary role for beta1 oscillations as they fully mediated group differences in sequence memory effects both directly and in combination with lower-frequency alpha oscillations.

Current results are consistent with the idea that task-specific modulation of low-frequency oscillations reflects engagement of cognitive control (33), which is reduced in people with SZ - accounting for patient deficits in temporal sequence memory. Use of goal-relevant information in a task-specific manner to optimize cognitive processing ahead of a demanding event is termed “proactive cognitive control”, and is consistently documented as deficient in people with SZ (13,34,35). Cognitive control deficits in people with SZ account for impairment across a variety of cognitive domains, including measures of learning and memory (5,36,37). Several studies demonstrated associations between attenuated alpha and beta desynchronization in people with SZ and worse proactive attention selectivity (38) and motor preparation (39), respectively.

It is noteworthy that the current sequence learning paradigm cannot definitively dissociate effects of implicit versus explicit sequence memory. However, correlations between performance in the study phase and test phase and between test phase performance and neural sequence memory effects (Supplementary Materials) suggest that the sequence learning task engaged explicit memory for temporal orders. Another alternative explanation is that neural sequence memory effects may reflect post-stimulus processing of previous objects, rather than response preparation for upcoming objects. Although we cannot rule this out, it is highly unlikely as the majority of semantic responses were completed before onset of the next pre-stimulus interval and speeding of RTs for fixed versus random sequences were unlikely to have occurred if processing was focused on previous objects.

In summary, convergent results support the conclusion that impaired modulation of alpha and beta1 EEG oscillations is a candidate mechanism for temporal sequence memory impairments in people with SZ. Desynchronization of alpha and beta1 power as memories were formed during fixed versus random sequences was only present in healthy controls and fully mediated patient memory deficits. These results encourage investigation of interventions that impact regulation of oscillations, such as transcranial direct current stimulation - which was found to increase gamma power (40) and improve proactive cognitive control. Temporal sequence memory paradigms may also provide insight into the rate remapping processes that occur in the hippocampus (32). Although the current task occurs on a much longer time-scale than the temporal coding changes occurring during rate remapping, this remapping does occur within the theta cycle, providing additional motivation for future EEG studies of temporal sequence memory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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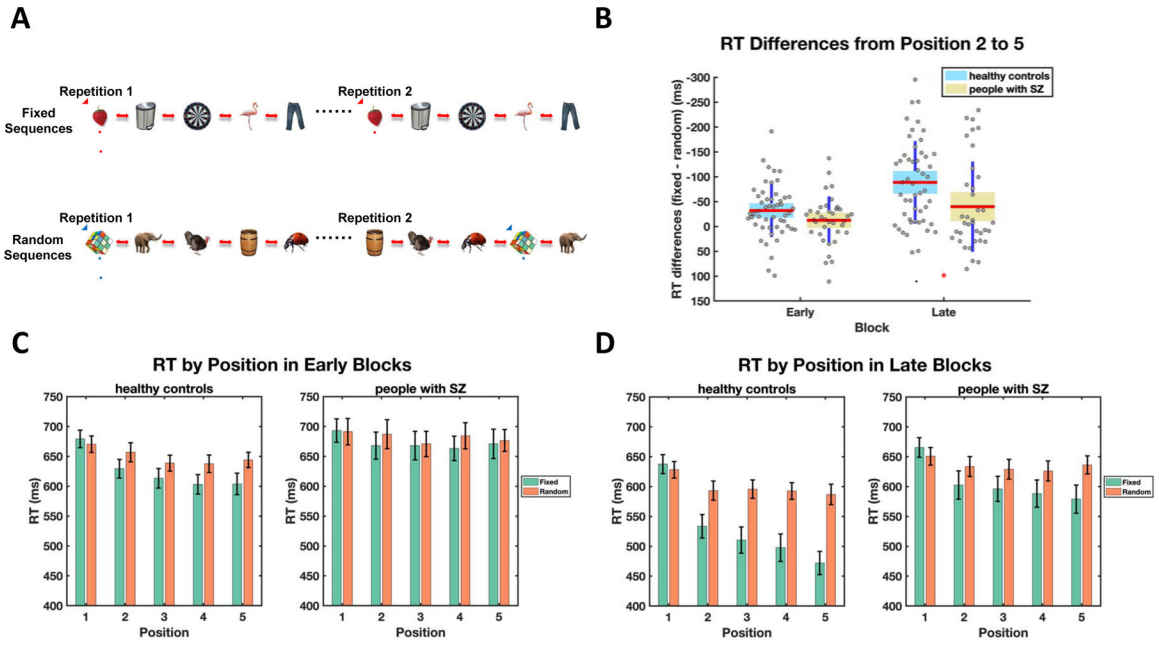

Figure 1.

Paradigm and behavioral results: (A) Example sequences in the experiment. (B) Average RT difference (fixed - random) values became more negative over time in both groups - reflecting faster RTs for fixed versus random sequences, with people with SZ (yellow box) showing smaller RT differences relative to healthy controls (blue box) in late blocks (block 3 and block 4), red asterisk indicates ($t(86) = -2.6$, $p = .011$). **Note**: dots indicate individual RT differences, boxes indicate 95% Confidence Interval, red lines indicate means, and blue lines indicate 1 standard deviation. (C) Average RTs for fixed (green bars) and random sequences (orange bars) for each object position in healthy controls and SZ group in early blocks (block 1 and block 2). (D) RT for healthy controls and people with SZ in late blocks (block 3 and block 4). **Note:** in (C) and (D) panels error bars denote ± standard error of the mean.

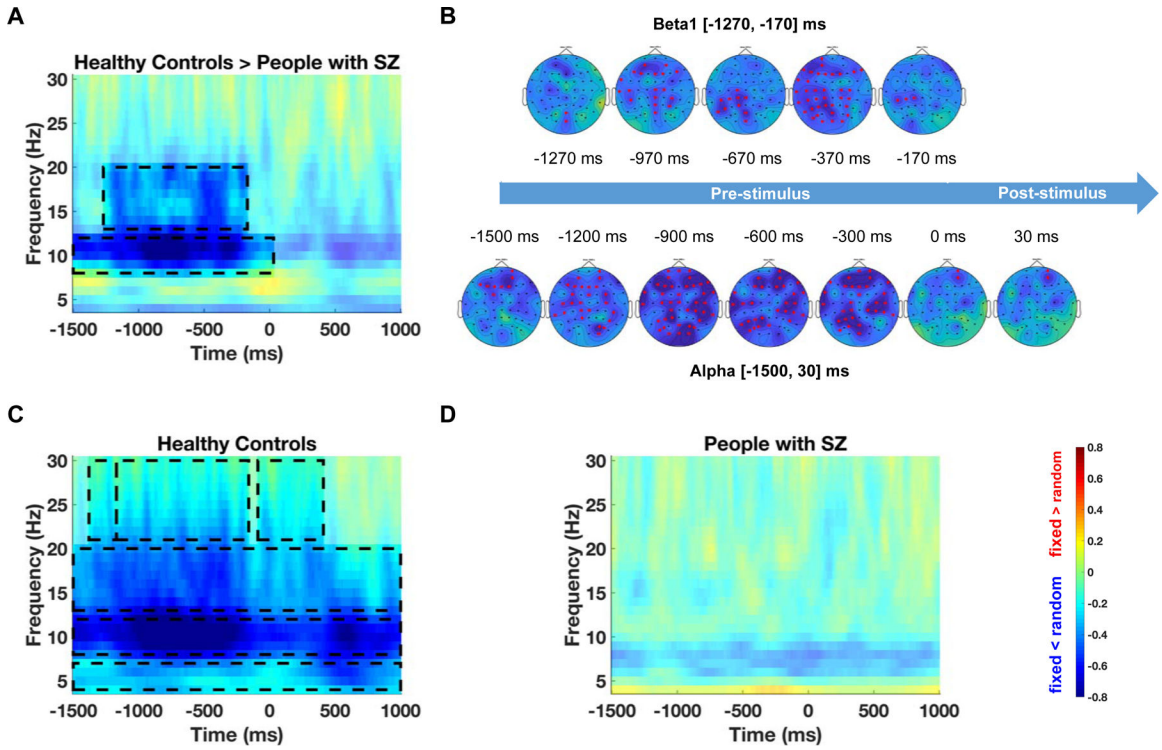

Figure 2.

(A) Group differences in neural sequence memory effect in late blocks across all electrodes. **(B)** Topographical maps of group differences in neural sequence memory effect in alpha and beta1 bands over time. As illustrated, pre-stimulus alpha and beta1 spatial-temporal clusters were revealed to be globally-distributed. This distribution is more visible in these topographic displays at specific time points. **Note**: Red dots in each topographical map indicate significant electrodes at that time. (C) Neural sequence memory effect in late blocks across all electrodes for healthy controls. (D) Neural sequence memory effect in late blocks across all electrodes for people with SZ. **Note**: Black dashed line boxes indicate significant time windows within specific frequency bands identified by spatial-temporal clusters. For every time point in these time windows at least two adjacent electrodes exceeded the significance threshold.

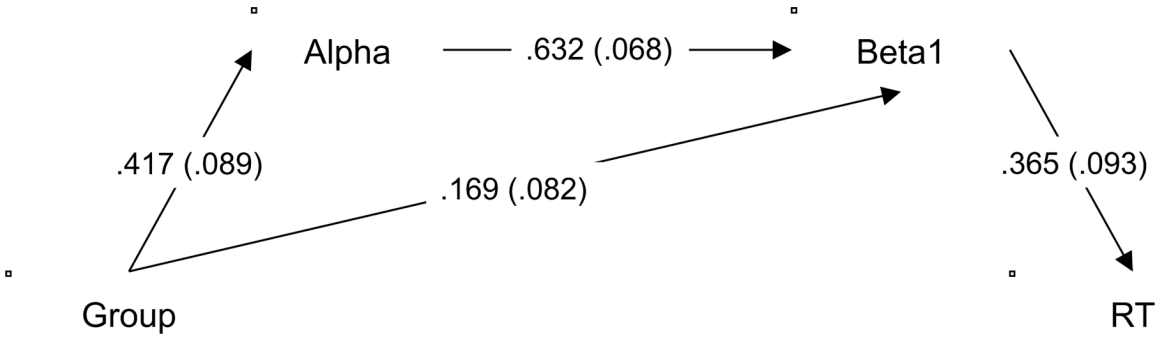

Figure 3.

Chained mediation model shows that oscillatory activity differences fully accounted for group differences in behavioral sequence memory effect. Standardized parameter estimates for the final model are illustrated with standard errors shown in parentheses.

Table 1.

Participant Demographics

	Healthy Controls (n=51)		People with SZ (n=37)		p-values
	Mean	**Range**	**Mean**	**Range**	
Age (years)	24.06	18–36	23.42	18–32	.65
Sex (% female)	31.37		21.62		.31
Education (years)	14.97	12–20	13.53	11–16	.83
Parental Education (years)	13.63	3–19.5	14.19	6.5–18.5	.95
SANS			21.32	0–50	
SAPS			6.54	0–29	
BPRS			20.81	12–37	
CPZ Equivalents			385.41	33.3–2000	

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