Task-specific Disruptions in Theta Oscillations during Working Memory for Temporal Order in People with Schizophrenia

Xiaonan L. Liu, Charan Ranganath, Liang-Tien Hsieh, Mitzi Hurtado, Tara A. Niendam, Tyler A. Lesh, Cameron S. Carter, and J. Daniel Ragland

Abstract

■ Prior studies demonstrated that neural oscillations are enhanced during working memory (WM) maintenance and that this activity can predict behavioral performance in healthy individuals. However, it is unclear whether the relationship holds for people with WM deficits. People with schizophrenia have marked WM deficits, and such deficits are most prominent when patients are required to process relationships between items, such as temporal order. Here, we used EEG to compare the relationship between oscillatory activity and WM performance in patients and controls. EEG was recorded as participants performed tasks requiring maintenance of complex objects ("Item") or the temporal order of objects ("Order"). In addition to testing for group differences, we examined individual differences in EEG power and WM performance across groups. Behavioral results demonstrated that patients showed impaired performance on both Item and Order trials. EEG analyses revealed that patients showed an overall reduction in alpha power, but the relationship between alpha activity and performance was preserved. In contrast, patients showed a reduction in theta power specific to Order trials, and theta power could predict performance on Order trials in controls, but not in patients. These findings demonstrate that WM impairments in patients may reflect two different processes: a general deficit in alpha oscillations and a specific deficit in theta oscillations when temporal order information must be maintained. At a broader level, the results highlight the value of characterizing brain–behavior relationships, by demonstrating that the relationship between neural oscillations and WM performance can be fundamentally disrupted in those with WM deficits. ■

INTRODUCTION

Working memory (WM) is a core cognitive function that enables active maintenance and manipulation of information, which contributes to performance on many other cognitive tasks. One possible neural mechanism underlying WM maintenance is oscillatory neuronal activity at different frequencies (Miller, Lundqvist, & Bastos, 2018; Roux & Uhlhaas, 2014). Oscillatory activity, particularly in low frequencies, may facilitate long-range communication between frontal and posterior cortical areas, thereby enabling active maintenance of goal-relevant information (Miller et al., 2018; Roux & Uhlhaas, 2014). Evidence of a relationship between neuronal oscillations and WM maintenance in humans has been provided by EEG (Fukuda, Mance, & Vogel, 2015; Manza, Hau, & Leung, 2014; Johnson, Sutterer, Acheson, Lewis-Peacock, & Postle, 2011; Gevins, Smith, McEvoy, & Yu, 1997) and electrocorticographic (Voytek et al., 2015; van Vugt, Schulze-Bonhage, Litt, Brandt, & Kahana, 2010; Howard et al., 2003; Raghavachari et al., 2001) recordings. These studies report enhanced oscillatory activity during WM maintenance at different frequencies, with inhibition of distractors and maintenance of sensory or item information linked to increased alpha-band (9–12 Hz) activity (Roux & Uhlhaas, 2014; Hsieh, Ekstrom, & Ranganath, 2011) as well as maintenance of sequential or temporal information associated with increased theta-band (5–7 Hz) oscillations (Roux & Uhlhaas, 2014; Roberts, Hsieh, & Ranganath, 2013; Hsieh et al., 2011). For example, Hsieh et al. (2011) asked healthy undergraduate participants to perform two WM tasks. On each trial, participants studied four sequential fractal images and kept either the item information or temporal order information in WM. After a short delay, they responded to a test screen by making either an item or temporal order decision. On Item trials, participants indicated which of two items (one old, one new) was previously studied. On Order trials, participants were presented with two previously studied items and indicated which item was presented earlier in the sequence. Contrasts of WM delay period activity revealed an increase in midline frontal theta oscillations during maintenance of temporal order

This article is part of a Special Focus deriving from a symposium at the 2019 annual meeting of Cognitive Neuroscience Society, entitled, "Mental Models of Time."
University of California, Davis

versus item information and increased posterior alpha during maintenance of item information compared with temporal order information.

It is well established that there are substantial individual differences in WM capacity and control processes (Cools & D'Esposito, 2011; Unsworth & Engle, 2007; Barrett, Tugade, & Engle, 2004; Vogel & Machizawa, 2004), and these individual differences are linked with functioning of the pFC (Gibbs & D'Esposito, 2005) and dopaminergic neuromodulation (Cools & D'Esposito, 2011). Recent work suggests that neural oscillations strongly correlate with individual differences in WM performance (Dong, Reder, Yao, Liu, & Chen, 2015; Fukuda et al., 2015; Hsieh et al., 2011). For instance, alpha activity was correlated with WM capacity in a visual WM task (Fukuda et al., 2015). Moreover, a prior study from our group (Hsieh et al., 2011) showed that, during WM maintenance of temporal order information, people with better performance also exhibited higher theta activity.

Although there is considerable support for the idea that neural oscillations contribute to WM maintenance in healthy individuals, it is unclear whether this relationship still holds for people with WM capacity limitations and/or control deficits. One possibility is that there is a functional continuum, such that people with WM deficits show reduced oscillatory activity and behavioral performance, but the relationship between oscillations and behavior is the same as in healthy participants. An alternative and underexplored possibility is that the relationship between neural oscillations and WM performance is fundamentally disrupted in those with WM deficits. In this study, we investigated this issue by comparing the relationship between oscillatory activity and WM performance in healthy individuals and people with schizophrenia in both a categorical manner by identifying group differences and in a dimensional manner by examining individual differences in EEG power and WM performance across groups.

People with schizophrenia exhibit debilitating cognitive deficits that can limit their psychosocial function and quality of life. WM capacity and control dysfunction are particularly impaired in people with schizophrenia (Barch & Sheffield, 2014), and individual differences in WM deficits are strongly predictive of functional outcomes. Existing studies suggest that patients are most impaired on WM tasks that require processing and maintenance of relationships between items and aspects of the encoding context, such as temporal order (Ragland et al., 2012; Burglen et al., 2004; Perlstein, Carter, Noll, & Cohen, 2001), rather than simple maintenance of stimulus representations per se.

Given the significant WM impairments in people with schizophrenia, it is reasonable to think that these deficits may be related to disruption in neural oscillations. There is some evidence for this idea (Basar-Eroglu, Schmiedt-Fehr, Mathes, Zimmermann, & Brand, 2009; Haenschel et al., 2009; Lisman & Buzsáki, 2008), but it is not yet fully clear how disruptions in oscillatory activity relate to patients' cognitive functioning. One possibility is that people with schizophrenia share similar brain–behavior relationships with healthy people and other patient populations in a continuous and dimensional manner rather than in a categorical manner as is being investigated to the recent Research Domain Criteria initiative (Cuthbert & Insel, 2010; Insel et al., 2010). If this is the case, we would expect that patients would show overall reductions in oscillatory activity and WM performance but that individual differences in oscillatory power would be predictive of performance in both patients and healthy individuals. Another possibility is that brain–behavior relationships may be fundamentally altered in schizophrenia. In this case, we would expect oscillatory activity to predict WM performance in healthy individuals, but not in patients with schizophrenia.

To test this hypothesis, we utilized the EEG paradigm in Hsieh et al. (2011). In that study, participants were asked to study sequences of fractal images and maintain either item information or temporal order information in WM. This paradigm allowed us to separately contrast the ability to maintain information about specific visual items, which has been linked to individual differences in alpha activity (Fukuda et al., 2015; Hsieh et al., 2011), and information about temporal order relationships between items, which has been linked to variability in theta activity (Hsieh & Ranganath, 2014; Hsieh et al., 2011). Although we would expect overall WM deficits and alterations of oscillatory activity in patients relative to healthy controls, this design allowed us to investigate the relationship between neural activity and cognitive performance across the two groups.

METHODS

Participants

Data were acquired on 50 individuals with schizophrenia and 61 healthy controls. All but 12 participants with schizophrenia were receiving medication with all but one medicated patient receiving second-generation atypical antipsychotics. Unfortunately, there were too few unmedicated patients to adequately test for group differences between medicated and unmedicated patients. However, previous research demonstrates that WM deficits are present in medication-naive individuals (Barch et al., 2001) in both acute and nonacute phases of the illness (Park, Püschel, Sauter, Rentsch, & Hell, 1999) and in unaffected relatives of people with schizophrenia (Park, Holzman, & Goldman-Rakic, 1995), suggesting that these deficits are a relatively stable trait-like measure that is not significantly influenced by medication status.

Data were excluded for one patient from both behavioral and EEG analyses because of below-chance performance in both tasks, and data were excluded for four controls and six patients from EEG analyses because of persistent artifacts. As shown in Table 1, individuals were matched at the group level for age, sex, and parental education. Participant education was lower in patients

Table 1. Participant Demographics

	Healthy Controls (n = 57)		*Patients (n = 43)*		
	Mean	*Range*	*Mean*	*Range*	*p Values*
Age (years)	24.26	18–36	23.51	18–38	.44
Sex (% female)	31.6		23.3		.36
Education (years)	15.22	12–22	13.45	11–17	<.001
Parental education (years)	13.85	3–19.5	14.26	6.5–18.5	.53
SANS			21.07	0–50	
SAPS			8.72	0–60	
BPRS			21.30	12–42	

BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms.

(Table 1), which has been attributed to illness disrupting educational attainment (Resnick, 1992). Clinical symptoms were measured using the Scale for the Assessment of Negative Symptoms (Andreasen, 1983), Scale for the Assessment of Positive Symptoms (Andreasen, 1984), and Brief Psychiatric Rating Scale (Ventura et al., 1993). Participants with schizophrenia were early in their illness (within 5 years of onset) and clinically stable, with mild to moderate symptoms. Diagnosis was assessed using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (First, Spitzer, Gibbon, & Williams, 2002) by master's or doctoral level clinicians with demonstrated reliability, established using the intraclass correlation coefficient (maintained at .8 or greater; Cicchetti, 1994). All participants were excluded for substance abuse or dependence in the previous year—and having received a urine drug screen before participation—and also for neurological illness, history of head trauma leading to unconsciousness, low IQ (i.e., <70), or corrected vision that does not achieve 20/30. Healthy participants were also excluded for any first-degree relatives with a history of psychosis. The study was approved by the institutional review board of the University of California at Davis, and informed consent was provided by all participants.

Materials

Stimuli were kaleidoscope images ("fractals") created by overlying three opaque hexagons of different colors (Hsieh et al., 2011). Stimuli used in each trial consisted of four fractal images with the same colors but different bisections and deflections in each hexagon. On the basis of pilot testing, fractal stimuli were made more discriminable than in the original study (Hsieh et al., 2011) to reduce difficulty and avoid floor effects in the patient group. The original paradigm was also modified by alternating task condition in a block rather than a fully randomized trial-by-trial design to reduce switching demands and facilitate comprehension in patients.

Procedure

Figure 1 illustrates task procedures. The experimental design consisted of two types of WM trials: Item trials and Order trials. On each WM trial, a fixation cross was presented for 3000 msec. After the fixation cross, each of four fractals were sequentially presented on the screen for 2000 msec, each with a 500-msec ISI. The four fractals were followed by a delay of 3000 msec, after which a test display appeared on the screen. On Order trials, the test display consisted of two fractals from the previous sequence, and participants were asked to choose the fractal image that appeared earlier in the sequence on each trial. On Item trials, the test display comprised one previously presented fractal along with another visually similar fractal that had not been presented. Participants were instructed to identify the previously studied "old" fractal image on each trial. For both tasks, test stimuli were randomly chosen from their respective stimulus pool on a trial-by-trial basis. None of the fractal images was repeated across trials. The test screen was self-paced but automatically advanced to the next trial after 10 sec.

Participants finished seven testing blocks in total, each composed of a continuous sequence of 10 Order trials and 10 Item trials. At the beginning of each sequence of trials, an instruction screen ("Order" or "Item") appeared to prepare the participant for the upcoming task. The order of the two trial types was randomized across blocks and participants. Thus, across the experiment, each participant completed 70 Order and 70 Item trials. Participants could take a self-paced short break between blocks.

EEG Recording

EEG data were recorded from 64 silver/silver chloride electrodes mounted in an elastic cap using a Neuroscan EEG

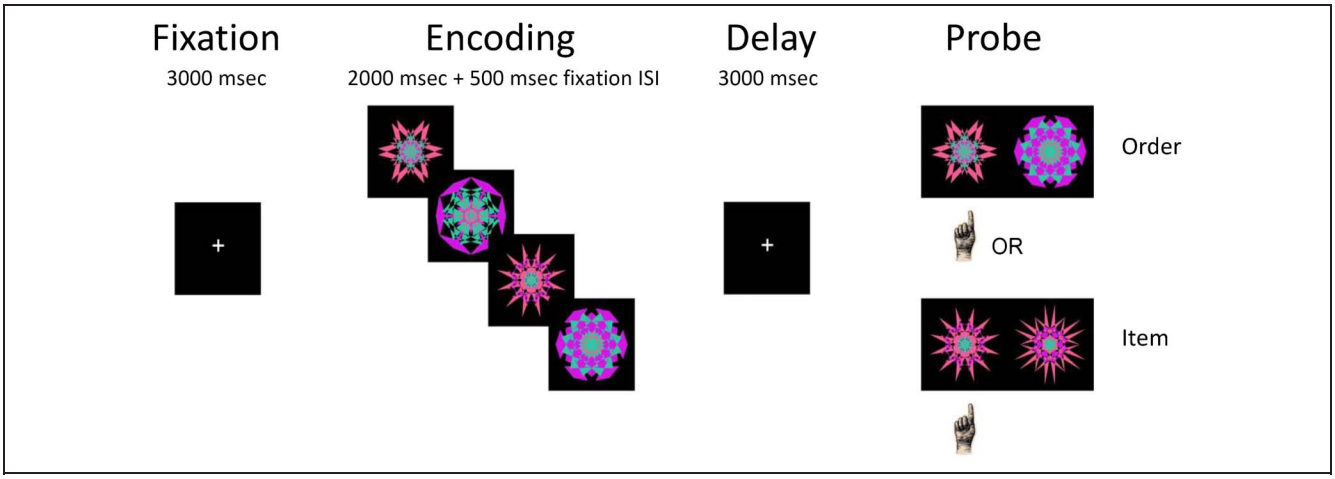

Figure 1. Illustration of the experimental paradigm, with an Order probe illustrated on the top right and an Item probe illustrated on the bottom right. On Order trials, the test display consisted of two fractals from the previous sequence, and participants were asked to choose the fractal image that appeared earlier in the sequence on each trial. On Item trials, the test display was composed of one previously presented fractal along with another visually similar fractal that had not been presented. The primary analyses focused on 600–2400 msec after the onset of the delay period, and the baseline was defined as −1000 to −500 msec before the onset of the first image.

recording system (Neuroscan Inc.). Electrode positioning was in accordance with an extended version of the International 10–20 system (Klem, Lüders, Jasper, & Elger, 1999). Reference electrode was placed on the left mastoid. The horizontal EOG was recorded from electrodes placed to the outer canthi. The vertical EOG was recorded from electrodes above and below the left eye. The EEG and EOG were recorded continuously at 1000 Hz and digitally high-pass filtered at 0.16 Hz and low-pass filtered at 100 Hz.

EEG Data Analysis

EEG analyses were performed for correct trials only, blind to group membership. All data analyses were performed off-line using EEGLAB toolbox (Delorme & Makeig, 2004). Continuous EEG data were down-sampled to 500 Hz, rereferenced to the average of the right and left mastoids, and high-pass filtered at 0.5 Hz. EEG epochs were extracted for each trial from 3 sec preceding to 12.5 sec after the onset of the first fractal. Each EEG epoch was then baseline-corrected by subtracting the mean voltage during the fixation before trial onset. To remove eye movement artifacts, the *fastICA* algorithm (Hyvärinen & Oja, 2000) implemented in EEGLAB toolbox was applied to all EEG epochs. Using independent component analysis, components associated with horizontal and vertical eye movements were visually identified and removed. Correlations between time series of horizontal EOG and vertical EOG channels and independent component analysis components were used to facilitate identifying components reflecting horizontal and vertical eye movements. Epochs containing voltages above +100 μV or below −100 μV were excluded. After artifact rejection, analysis was performed on an average of 50 Item trials and 47.6 Order trials in controls, and 42 Item trials and 38.6 Order trials in people with schizophrenia.

Single-trial EEG epochs were subsequently transformed to current density values using a surface Laplacian transformation (Kayser & Tenke, 2006a, 2006b) with the following parameters: m-constant = 4 and smoothing constant $\lambda = 10^{-6}$. The surface Laplacian transformation was performed to minimize negative impact of volume conduction, thereby providing a more sharply localized scalp topography of observed EEG effects derived from both superficial and deep generators (Tenke & Kayser, 2015). Moreover, surface Laplacian estimates are reference free, so any EEG recording reference choices will provide the same results. We then computed EEG spectral power by convolving single-trial EEG epochs from each scalp electrode using six-cycle complex Morlet wavelets (Roach & Mathalon, 2008). Oscillatory power, defined as the square of the modulus of the resulting complex number, was averaged across trials and log-transformed. To specifically look at neural oscillations during WM maintenance, oscillatory power during the delay was extracted and baseline-corrected with respect to oscillatory power during the time window (−1000 to −500 msec) before the onset of the first image. This baseline period was chosen to avoid contamination of oscillatory activity during the previous trial and the upcoming trial (i.e., because of the inherent temporal imprecision of wavelet analyses). Oscillatory power during the delay was binned into two frequency bands (theta: 5–7 Hz; alpha: 9–12 Hz).

The time window for these analyses was 600–2400 msec after the onset of the delay to avoid contamination from the encoding and probe. Therefore, only oscillatory effects during the middle part of the maintenance period were subjected to further statistical analyses. Statistical analyses used oscillatory power averaged over the delay

intervals. As in our previous study (Hsieh et al., 2011) regarding maximal topography of theta and alpha oscillations, theta band activity was examined over the middle-frontal cluster of electrodes (i.e., Fz, F1, F2), and alpha band activity was examined over the left-parietal cluster of electrodes (i.e., P5, P7, PO7).

For hypothesis testing, differences in oscillatory power during the delay period of correct Item trials versus correct Order trials were calculated for the middle-frontal cluster and left-parietal cluster recordings. To examine relationships between oscillatory power and performance, linear regression analyses were used to determine whether performance during temporal order WM and item WM could be predicted by the oscillatory activity at the theta band and alpha band, respectively. Accuracy in each task was used as the dependent variable, and predictor variables were oscillatory power (theta and alpha), group (controls vs. patients), and their interaction.

Several additional exploratory analyses were also performed. To rule out the possibility that the results of WM maintenance actually reflected differences during the encoding phase, we examined oscillatory activity of theta and alpha bands during encoding. Specifically, we averaged the presentation-period oscillatory activity across four stimuli and analyzed the oscillatory activity during encoding in the same way as the delay period. We also analyzed higher frequencies, namely, beta band (13–28 Hz) and gamma band (30–50 Hz), to examine possible WM deficits in other frequency bands. Finally, to examine whether the effects of theta and alpha oscillations were specific to the middle-frontal and left-parietal clusters or were also present in other regions, electrodes were grouped into nine clusters, namely, middle-frontal cluster (F1, Fz, F2), left-frontal cluster (AF3, F5, F7), right-frontal cluster (AF4, F6, F8), middle-central cluster (C1, Cz, C2), left-central cluster (C3, C5, T7), right-central cluster (C4, C6, T8), middle-posterior cluster (O1, Oz, O2), left-posterior cluster (PO7, P7, P5), and right-posterior cluster (PO8, P8, P6), and theta and alpha power was analyzed as a function of Group and Task in each of the other eight clusters.

RESULTS

Behavioral Results

Performance was examined using a Task (order vs. item) × Group (controls vs. patients) ANOVA. This revealed that performance was significantly higher on Item than Order trials (main effect of Task: $F(1, 108) = 36.47$, $p < .001$, $\eta_p^2 = .25$) and that performance was higher for healthy controls than for patients with schizophrenia, $F(1, 108) = 29.57$, $p < .001$, $\eta_p^2 = .22$ (see Table 2). There was no significant interaction between Task and Group, $F(1, 108) = 2.471$, $p = .12$, $\eta_p^2 = .02$. RTs (see Table 2) were generally faster on Item trials than on Order trials (main effect of Task: $F(1, 108) = 85.33$, $p < .001$, $\eta_p^2 = .44$), but neither the main effect of Group, $F(1, 108) = 0.623$, $p = .432$, $\eta_p^2 = .006$, nor the Group × Task interaction, $F(1, 108) = 1.80$, $p = .183$, $\eta_p^2 = .016$, was significant.

EEG Results

Because prior work has shown that frontal theta and parietal alpha oscillations are associated with WM performance, we focused our analyses on theta power (5–7 Hz) at the middle-frontal cluster and alpha power (9–12 Hz) at the left-posterior cluster. EEG analyses focused on the delay period (600–2400 msec), as this was the time window when we expected participants to actively maintain item and order information.

A Task (order vs. item) × Group (controls vs. patients) mixed ANOVA (Figure 2) on delay-period frontal theta power showed no main effect of Task, $F(1, 98) = 2.47$, $p = .12$, $\eta_p^2 = .025$, or Group, $F(1, 98) = 1.44$, $p = .23$, $\eta_p^2 = .015$. Critically, we observed a significant Group × Task interaction, $F(1, 98) = 5.28$, $p = .024$, $\eta_p^2 = .051$, such that delay-period theta power was higher in controls than in patients during order trials, $t(98) = 2.29$, $p = .024$, $d = .46$, but not during item trials, $t(98) = 0.75$, $p = .46$, $d = 0.15$.

Delay-period alpha activity for the left-posterior cluster was examined using Task × Group ANOVA. Consistent with prior studies (Hsieh et al., 2011), parietal alpha power was significantly higher during item than during order trials, $F(1, 98) = 4.67$, $p = .033$, $\eta_p^2 = .045$. Alpha power across both tasks was reduced in patients compared with controls, $F(1, 98) = 5.82$, $p = .018$, $\eta_p^2 = .056$. There was no significant interaction between Group and Task, $F(1, 98) = 0.074$, $p = .78$, $\eta_p^2 = .0008$.

To rule out the possibility that the theta and alpha effects were driven by differences during the baseline period, the same ANOVA was performed on oscillatory power during the baseline period. There was no significant main effect of Task (theta: $F(1, 98) = 0.51$, $p = .82$, $\eta_p^2 = .001$; alpha: $F(1, 98) = 0.002$, $p = .96$, $\eta_p^2 < .001$) or Group (theta: $F(1, 98) = 0.49$, $p = .49$, $\eta_p^2 = .005$; alpha: $F(1, 98) = 0.001$, $p = .97$, $\eta_p^2 < .001$) or an interaction between Task and Group for both theta and alpha power during the baseline period (theta: $F(1, 98) = 0.059$, $p = .81$, $\eta_p^2 = .001$; alpha: $F(1, 98) = 1.07$, $p = .30$, $\eta_p^2 = .011$).

Behavioral Performance and EEG Relationships

The analyses described above showed that, relative to controls, patients showed task-specific reductions in theta activity on Order trials and that alpha activity showed significant reductions during both Item and Order trials. Our next analyses turned to the relationship between individual differences in EEG power and behavioral performance. As noted earlier, one might expect that, although

Table 2. Behavioral Performance

	Healthy Controls		*Patients*	
	Order	*Item*	*Order*	*Item*
Accuracy	.81 (.12)	.85 (.08)	.69 (.14)	.75 (.11)
RTs (msec)	2837 (685)	2435 (561)	2880 (717)	2579 (636)

Standard deviations are shown in parentheses.

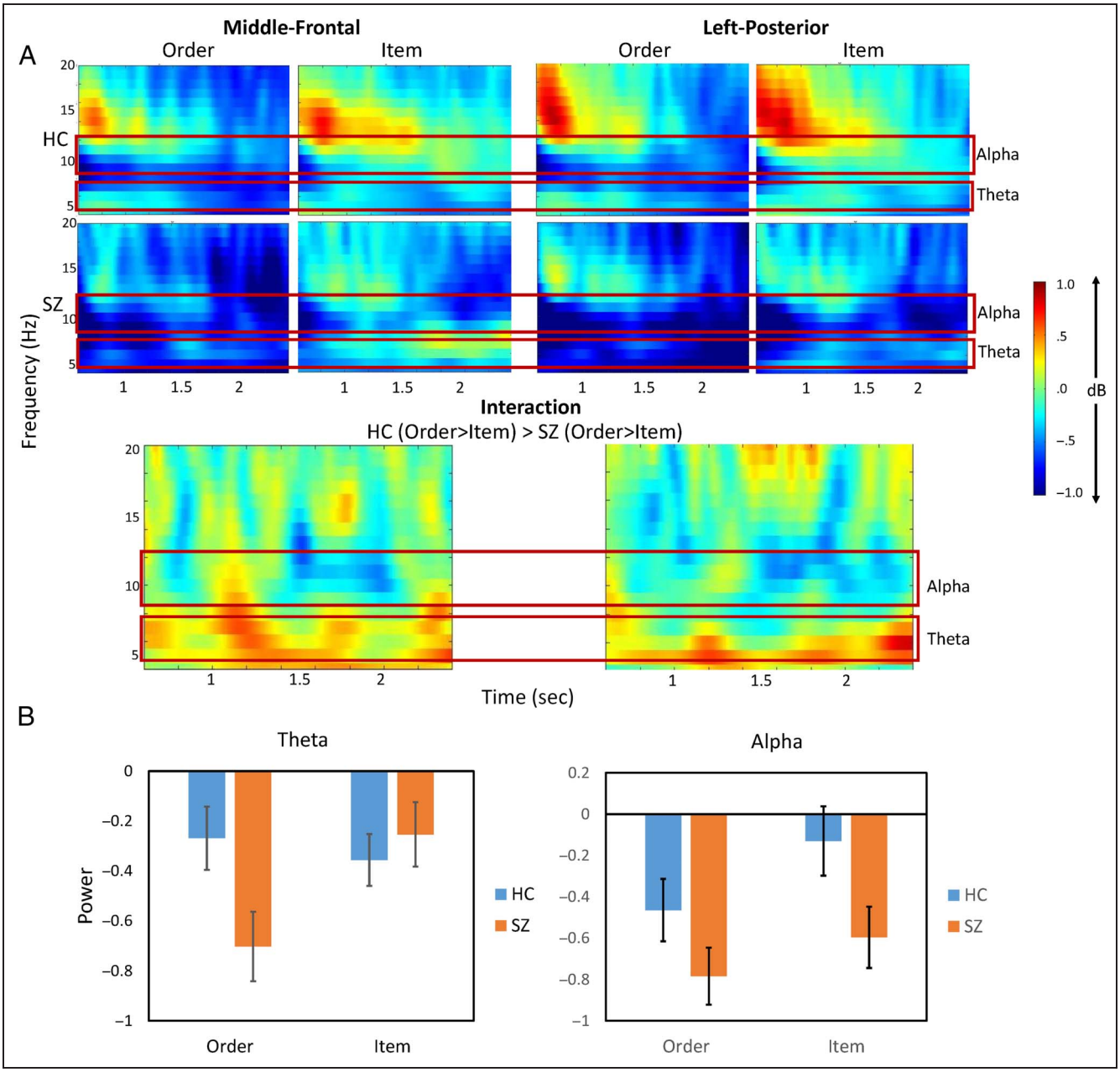

Figure 2. Theta oscillations in the middle-frontal cluster were reduced during maintenance of order information in patients compared with in healthy controls, but not during maintenance of item information. (A) Time–frequency spectrograms illustrate the oscillatory power of correct Order and correct Item trials in healthy controls and patients as well as the interaction between Task and Group in the middle-frontal (left) and left-posterior (right) clusters. The *x* axis represents time relative to the onset of the 3-sec delay period and, the *y* axis represents frequencies. (B) Mean theta (left) and alpha (right) band oscillatory power of correct Order and correct Item trials in controls and patients. Error bars indicate ±*SE*.

WM performance and oscillatory power were reduced in patients, the overall relationship between oscillatory activity and performance might remain the same. This would indicate that patients and healthy controls lie on a continuum of neurocognitive functioning. Alternatively, patients might show an altered relationship between WM performance and oscillatory power, which would indicate a qualitative disruption of normal mechanisms for the maintenance of item and order information.

To adjudicate between these possibilities, linear regression analyses determined whether individual differences in theta and alpha power during WM maintenance were predictive of accuracy on the Item and Order tasks (Figure 3). Accuracy in each task was used as the dependent variable, and predictor variables were oscillatory power, Group (controls vs. patients), and the interaction terms between oscillatory power and Group. For Order trials, the analysis revealed a significant interaction between Group and theta power when predicting accuracy on Order trials ($R^2 = .17, B = -.058, SE = .028, \beta = -.603, t = 2.04, p = .045$), indicating that the relationship between theta power and accuracy was significantly stronger in controls than patients. Simple slope tests showed that higher theta power predicted better temporal order WM performance in controls ($B = .042, SE = .016, \beta = .34, t = 2.63, p = .011$), but not in people with schizophrenia ($B = -.026, SE = .022, \beta = -.17, t = 1.17, p = .25$). There was also a main effect of alpha power when predicting performance on the temporal order WM task across both groups ($R^2 = .12, B = .041, SE = .014, \beta = .29, t = 2.93, p = .004$). There was no interaction between alpha power and Group for temporal order WM ($B = .037, SE = .028, \beta = .39, t = 1.31, p = .19$).

We next performed a similar linear regression analysis to test brain–behavior relationships on Item trials. This analysis revealed that higher alpha power predicted better item WM performance in both the control and patient groups ($R^2 = .17, B = .043, SE = .01, \beta = .40, t = 4.31, p < .001$), with no evidence of main effect of theta power ($B = .005, SE = .01, \beta = .046, t = .49, p = .63$) or Group × Oscillatory Power interactions (Group and theta: $B = -.006, SE = .02, \beta = -.086, t = .30, p = .77$; Group and alpha: $B = .026, SE = .022, \beta = .34, t = 1.16, p = .25$).

Exploratory Analyses

Theta and Alpha Power during Encoding

To rule out the possibility that the results of WM maintenance actually reflected differences during the encoding phase, encoding-period theta and alpha activity for the middle-frontal and left-posterior clusters, respectively, was examined using a Task (order vs. item) × Group (controls vs. patients) mixed ANOVA. As shown in Figure 4, in both bands, there were no significant main effects of Task or Group (theta/Task: $F(1, 98) = 2.50, p = .12, \eta_p^2 = .025$; theta/Group: $F(1, 98) = 0.061, p = .81,$

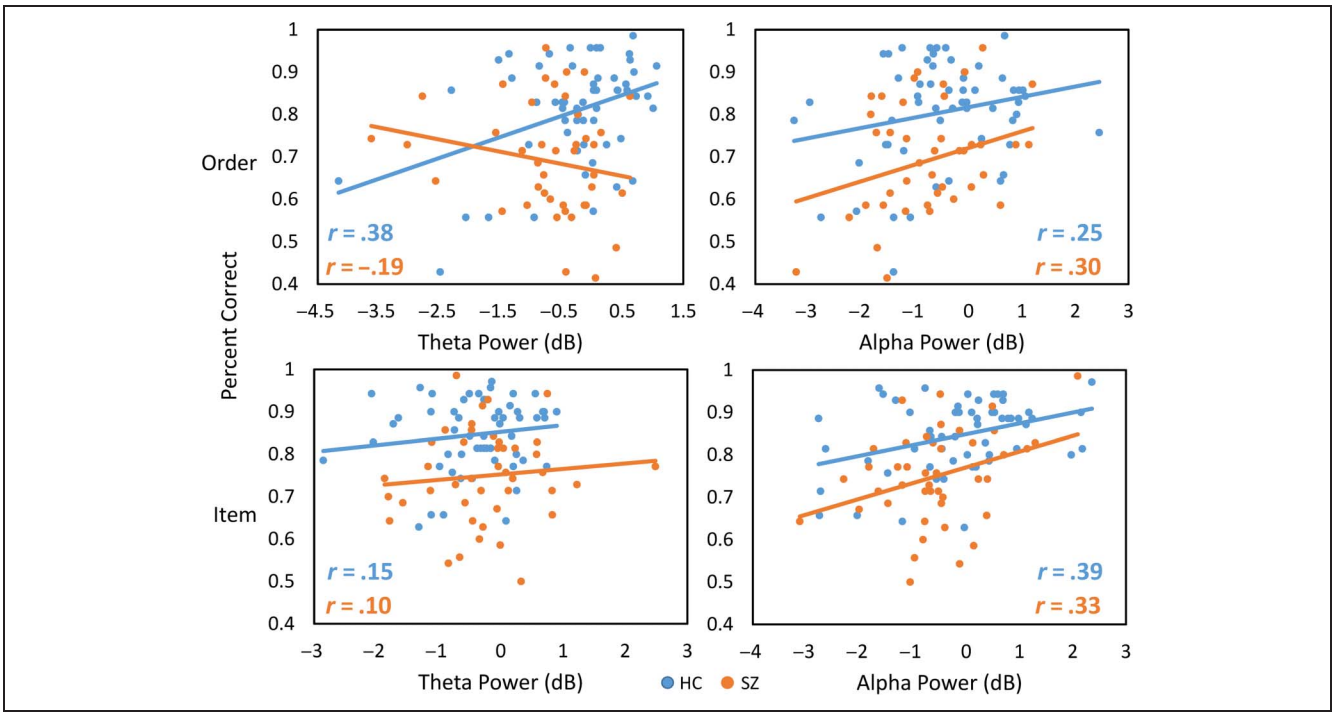

Figure 3. Correlations between accuracy during the Order task (top) and the Item task (bottom) as well as theta power and alpha power during the delay period. Whereas alpha power predicted both Item and Order performance in both groups, theta power only predicted Order performance in the control group.

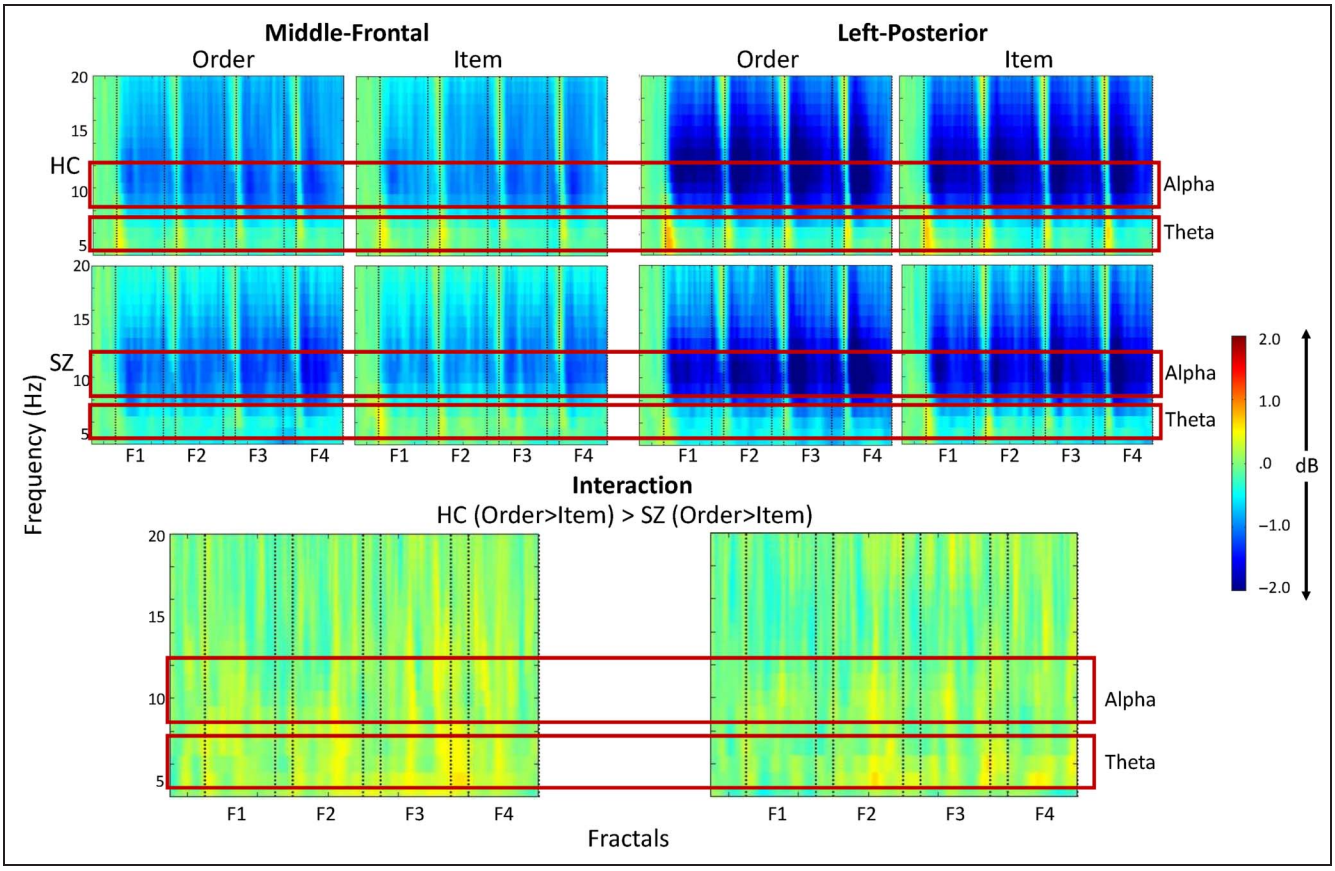

Figure 4. Time–frequency spectrogams illustrate the oscillatory power of correct Order and correct Item trials in healthy controls and patients as well as the interaction between Task and Group in the middle-frontal (left) and left-posterior (right) clusters during the baseline and encoding periods. The *x* axis represents the four fractals participants studied during the encoding period (F1–F4), and the *y* axis represents frequencies.

η_p^2 = .001; alpha/Task: $F(1, 98) = 1.22, p = .27, \eta_p^2 = .012$; alpha/Group: $F(1, 98) = 0.003, p = .95, \eta_p^2 < .001$). Moreover, there was no interaction between Task and Group (theta: $F(1, 98) = 0.17, p = .68, \eta_p^2 = .002$; alpha: $F(1, 98) = 0.10, p = .75, \eta_p^2 = .001$).

Gamma and Beta Power

We also examined oscillatory activity at higher frequencies, namely, beta (13–28 Hz) and gamma (30–50 Hz), in the middle-frontal and left-posterior clusters. There were no significant main effects of Task (middle-frontal: $F(1, 98) = 0.035, p = .85, \eta_p^2 < .001$; left-posterior: $F(1, 98) = 0.22, p = .64, \eta_p^2 = .002$) or Group (middle-frontal: $F(1, 98) = 0.88, p = .35, \eta_p^2 = .009$; left-posterior: $F(1, 98) = 1.69, p = .20, \eta_p^2 = .017$), or any interaction between Task and Group (middle-frontal: $F(1, 98) = 0.75, p = .39, \eta_p^2 = .008$; left-posterior: $F(1, 98) = 0.25, p = .61, \eta_p^2 = .003$) in gamma band power. For beta band power, a significant main effect of Task was found in the middle-frontal cluster with greater beta power for item WM versus temporal order WM across groups, $F(1, 98) = 9.84, p = .002, \eta_p^2 = .091$. There was no main effect of Group, $F(1, 98) = 1.31, p = .26, \eta_p^2 = .013$, or any significant interaction between Group and Task, $F(1, 98) = 0.13, p = .72, \eta_p^2 = .001$, in the middle-frontal cluster. There were no significant effects in the left-posterior cluster (Task: $F(1, 98) = 3.02, p = .085, \eta_p^2 = .030$; Group: $F(1, 98) = 2.38, p = .13, \eta_p^2 = .024$; interaction: $F(1, 98) = 0.042, p = .52, \eta_p^2 = .004$).

Theta and Alpha Power at Nine Electrode Clusters

Figure 5 illustrates the topography of frontal theta and posterior alpha effects. To examine whether the effects of theta and alpha oscillations were specific to middle-frontal and left-posterior clusters, respectively, we examined theta and alpha power as a function of Group and Task in each of the other eight electrode clusters. Results aligned with the targeted electrode cluster site analyses described above. There were no significant main effects or interactions in other clusters in addition to the middle-frontal cluster (ps > .1). For alpha power, a significant main effect of Task was observed in both frontal and posterior clusters (left-frontal: $F(1, 98) = 11.97, p = .001, \eta_p^2 = .109$; middle-frontal: $F(1, 98) = 5.60, p = .016, \eta_p^2 = .058$; right-frontal: $F(1, 98) = 8.27, p = .005, \eta_p^2 = .078$; left-central: $F(1, 98) = 12.06, p = .001, \eta_p^2 = .11$; right-central: $F(1, 98) = 4.43, p = .038, \eta_p^2 = .043$; middle-posterior: $F(1, 98) = 4.46, p = .037, \eta_p^2 = .044$; right-posterior:

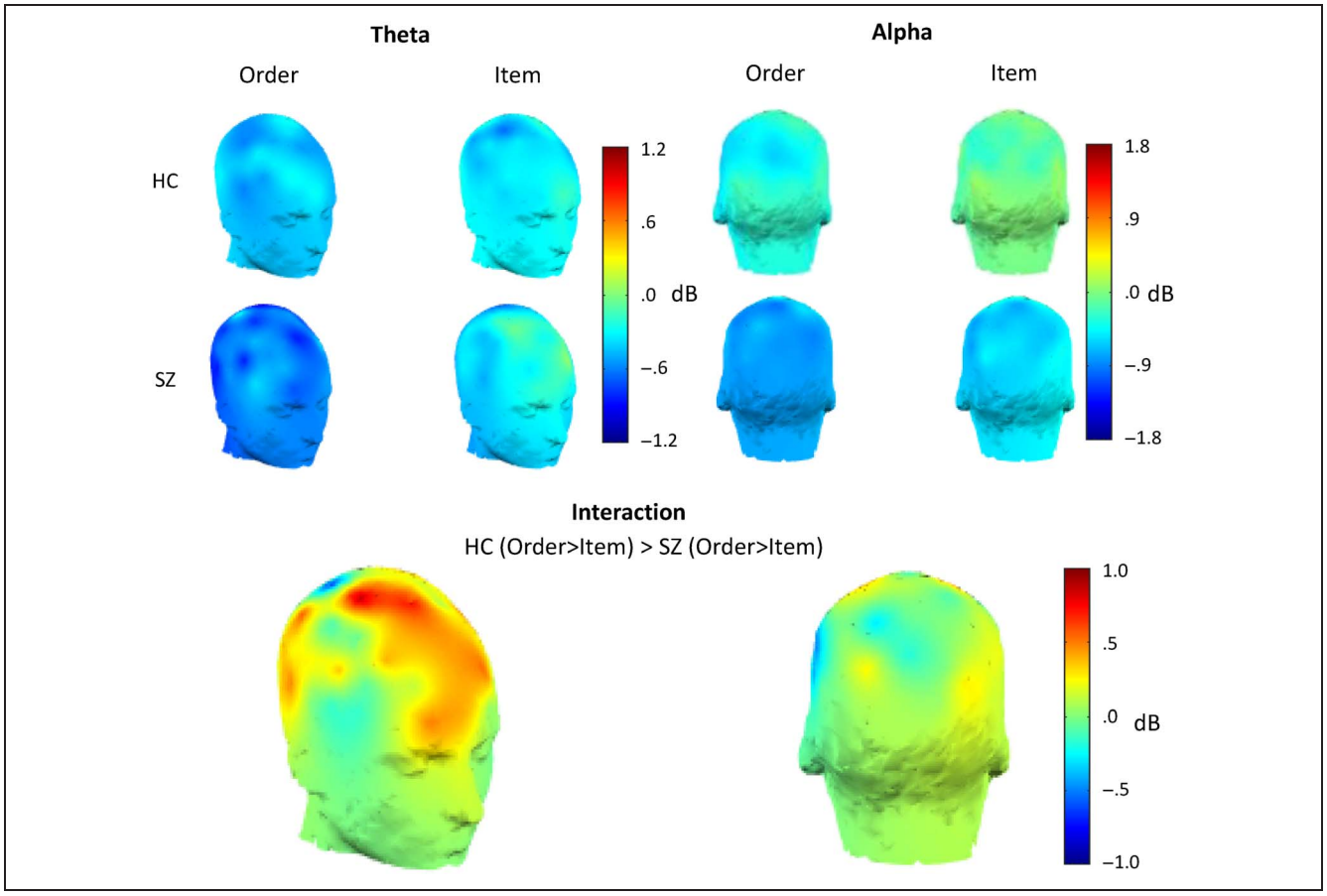

Figure 5. Topographic maps illustrate frontal theta and posterior alpha power of correct Order and correct Item trials in healthy controls and patients as well as the interaction between Task and Group. Theta power showed task-specific disruptions over the frontal midline regions in patients. Alpha power showed a general reduction in both tasks in patients, and the alpha effect was distributed across the scalp.

$F(1, 98) = 11.09$, $p = .001$, $\eta_p^2 = .10$) and a significant main effect of Group was only observed in posterior clusters (middle-posterior: $F(1, 98) = 6.85$, $p = .01$, $\eta_p^2 = .065$; right-posterior: $F(1, 98) = 5.57$, $p = .02$, $\eta_p^2 = .054$). These results indicate that overall delay-period alpha activity was higher on Item trials than on Order trials and alpha power in posterior clusters was lower in patients than in controls. There were no significant main effects in other clusters ($ps > .1$). There was no significant interaction between Group and Task in any of the nine clusters ($ps > .1$).

DISCUSSION

On the basis of evidence that neural oscillations are related to WM performance in healthy individuals, the current study tested whether disruption in different kinds of oscillations is related to WM deficits in people with schizophrenia. We found that patients showed a reduction in theta band power specific to Order trials and that theta power was predictive of performance on Order trials in healthy controls, but not in patients. In contrast, alpha power showed general reductions in patients relative to controls, and the relationship between alpha activity and behavioral performance was preserved across patients and healthy controls. These findings demonstrate that, although patients show overall deficits in WM performance and alterations in alpha activity, their deficits in maintenance of order information are specifically related to disruptions in theta activity. We consider the implications of these findings below.

At the behavioral level, WM performance was significantly poorer in patients with schizophrenia than in healthy controls. This result is consistent with a large body of evidence showing that WM maintenance is disrupted in patients with schizophrenia (Kraguljac, Srivastava, & Lahti, 2013; Ragland et al., 2012; Glahn et al., 2005; Burglen et al., 2004). On the basis of previous results showing that patients with schizophrenia show poorer performance on tasks that require processing of relational information (Ragland et al., 2012, 2015; Hannula et al., 2010; Williams et al., 2010), we expected patients to show a disproportionate deficit on Order trials. However, we did not see a significant interaction between Task and Group. Close examination revealed a large degree of variability in behavioral performance in patients with schizophrenia, especially in unmedicated patients. Consistent with this observation, when we

examined our data in medicated patients only, there was evidence of the hypothesized interaction, although performance did not correlate with medication dose.[1] The large degree of behavioral variability in the patient group enabled us to investigate the extent to which neural activity was related to behavioral performance.

The present results converge with results from previous studies showing that alpha activity is enhanced during visual WM tasks and that these EEG effects are related to behavioral performance (Hsieh et al., 2011; Jensen, Gelfand, Kounios, & Lisman, 2002). Specifically, we found that delay-period alpha oscillations were enhanced during Item trials relative to Order trials and that alpha power during the delay period was correlated with performance on the Item task. Our exploratory analyses additionally found that activity in the beta band (13–28 Hz) was enhanced during Item trials, relative to Order trials. One possible explanation for such an effect is that alpha oscillations reflect the inhibition of irrelevant visual representations in posterior cortical areas (Jensen et al., 2002). In a similar vein, Miller and colleagues proposed that alpha and beta oscillations have an inhibitory role in WM, gating activity related to modalities or spatial locations that are not currently relevant (Miller et al., 2018).

It is noteworthy that studies using a visual change detection WM paradigm have reported that better performance was associated with reduced alpha power (Fukuda et al., 2015) and that impaired higher alpha power during WM maintenance was associated with WM capacity deficits in patients with schizophrenia (Erickson, Albrecht, Robinson, Luck, & Gold, 2017). There are many important methodological differences between these change detection studies and this WM study (which reflects a very large and diverse sample of patients and controls) that could account for this apparent inconsistency. In change detection paradigms like those used by Fukuda et al. and Erickson et al., WM is studied by varying the number of items to be encoded ("set size") across trials. Erickson et al. varied the set size from one to six items, and they examined correlations between alpha power and individual differences in estimated WM capacity. Our study used a fixed set size of four items, and instead of estimating WM capacity, we varied the kind of information that was to be encoded. In addition, in our study, the memory set consisted of four complex shapes, sequentially presented for 2 sec each, and these stimuli were actively maintained across a 3-sec delay. In Erickson et al., the memory set consisted of simple colored squares simultaneously flashed for 200 msec, and these stimuli were actively maintained across a short 1800-msec delay. Finally, in Erickson et al., participants were simply instructed to detect a change in one of the colored squares, whereas on "Item" trials in our study, participants were required to discriminate between an item from the memory set and a visually similar lure item.

The methodological differences between our study and the study by Erickson et al. are directly related to two different ways that alpha oscillations have been linked to cognition. The large set sizes and short encoding times used in the change detection paradigm place heavy demands on vigilance and attention during stimulus encoding. Although these demands are not especially taxing for college student populations (Adam, Robison, & Vogel, 2018; Adam, Mance, Fukuda, & Vogel, 2015), we can expect that the paradigm would be more sensitive to attentional impairments in patient populations that are susceptible to attentional lapses, as even a brief period of distraction can lead to failures in encoding and subsequent WM maintenance. Indeed, Erickson et al. (2017) found that WM deficits in patients with schizophrenia were attributable to an increased probability of attentional lapses, leading the authors to conclude that "decreased attentional engagement is associated with poorer outcomes." Available evidence suggests that alpha power is increased during attentional lapses (O'Connell et al., 2009) and that attentional lapses in patients with schizophrenia are associated with increased alpha power (Boudewyn & Carter, 2018). In this study, participants had ample time to process each item. As noted above, on Item trials, a greater emphasis was placed on maintaining a high-resolution visual representation across the relatively long memory delay. It is therefore likely that our paradigm was more sensitive to detect deficits in cognitive control processes needed to suppress interference and actively maintain task-relevant visual information (see D'Esposito & Postle, 1999). In similar paradigms (e.g., Nenert, Viswanathan, Dubuc, & Visscher, 2012; Johnson et al., 2011), increased alpha power has been associated with better performance. In other words, whether better performance is associated with alpha suppression or enhancement may depend on the specific task demands.

Although the role of theta oscillations in WM is less well established than oscillations in the alpha band, prior studies have linked frontal midline theta to WM maintenance (Brzezicka et al., 2019; Hsieh & Ranganath, 2014; Roberts et al., 2013; Hsieh et al., 2011). The design of this study was specifically inspired by the paradigm introduced by Hsieh et al. (2011), which compared activity elicited during maintenance of visual item information against maintenance of temporal order relationships. Their study showed that, in a sample of university students, theta power was higher during the delay period of Order trials than Item trials, whereas the opposite result was seen for alpha activity. As noted above, we replicated the finding that alpha oscillations were increased during Item trials relative to Order trials in both controls and patients. However, results in the healthy controls in this study differed from the college student sample of Hsieh et al. in two ways. First, in Hsieh et al., the Item and Order tasks were matched for difficulty, whereas in this study, Order performance was significantly poorer than Item performance. Second, we did not find a disproportionate increase in frontal midline theta activity during Order trials relative to Item trials.

There are at least two key factors that explain the differences between the present results and those of Hsieh et al. First, to make the task more suitable for a patient population, we used a blocked trial design, such that Item and Order trials were performed in separate blocks. In contrast, Hsieh et al. used a randomized trial design such that the sequence of trial types was unpredictable. This might have encouraged healthy controls to use particular behavioral strategies for Item trials, such that overall performance was higher on Item trials than Order trials. In addition to the experimental design, the two experiments recruited different participant populations. In this study, healthy controls were drawn from the Sacramento community and matched for age and parental education with the patient group, whereas Hsieh and colleagues examined activity in college undergraduate and graduate students who generally differ from these participants in terms of age, parental education, and many other factors. In our experience, performance on memory tasks is generally higher in university students than when these tasks are translated to community samples. For this reason, it was critical to investigate the relationship between behavioral performance and EEG activity. Our EEG data suggest that, in healthy control participants, theta power was significantly correlated with behavioral performance on order trials. Close inspection of the results revealed that healthy controls whose performance on Order trials was comparable to participants in the Hsieh et al. study also showed increased theta power during Order trials in comparison to Item trials. Thus, our study and Hsieh et al.'s (2011) study provide converging evidence for the hypothesis that midline frontal theta supports the ability to actively maintain temporal order relationships.

In general, oscillatory power during the delay period was lower than that during the pretrial baseline period. One possible reason is that, during the baseline period, low-frequency activity was elevated as participants actively maintained the task set and expectation of stimuli. Thus, subtracting out baseline power from the delay period resulted in negative EEG values during the delay period. Consistent with this explanation, prior EEG studies also found that increased frontal theta and posterior alpha power reflects prestimulus top–down preparation for the subsequent tasks (Min & Park, 2010).

We performed several control analyses to rule out the possibility that baseline power differences could account for any of the current results. First, we repeated the analyses of activity during the delay period without baseline correction, and the pattern of results was essentially unchanged. Second, we performed a post hoc examination of oscillatory power during the baseline period, and this also revealed no effects of Task or Group. Third, our exploratory analyses of activity during the encoding period did not reveal any significant effects of Task or Group, although activity during this period was also referenced to the same pretrial baseline. Thus, there is no evidence to suggest that the delay period effects reported here reflected differences in baseline activity.

A key contribution of this study was to investigate the relationship between oscillatory activity and WM performance in healthy controls and patients with schizophrenia. Analyses of brain–behavior relationships in this study revealed an interesting dissociation between different neurocognitive processes that were not obvious from analyses of between-group differences. Although patients with schizophrenia tended to show reduced alpha power during WM maintenance, we found that, in patients, as in controls, alpha power was predictive of WM performance. In contrast, patients showed a specific reduction in theta activity during the Order task, and the relationship between theta band power and behavioral performance was altered. The fact that the relationship between theta power and Order performance was significantly stronger in controls than in patients suggests that the relationship between neural oscillations and WM performance is fundamentally disrupted in patients.

One possible explanation is that patients with schizophrenia may be able to generate large-scale theta oscillations, but these oscillations are inadequate to support computations in local neural circuits because of altered neuromodulation (Gonzalez-Burgos & Lewis, 2008; Lisman & Grace, 2005) or disrupted connectivity (Henseler, Falkai, & Gruber, 2010; Ragland, Yoon, Minzenberg, & Carter, 2007). At the behavioral level, we speculate that patients might have employed ineffective strategies while performing the Order task when theta oscillations are interrupted. For example, they might use an inefficient item-based strategy to facilitate performance in the Order task. That is, if a participant remembered the first item in a sequence and always chose this item when it was presented in the probe, the participant could make correct responses in 50% of trials. Whereas healthy controls might use item information only as a supplement to maintaining the temporal order, people with schizophrenia might rely on this strategy when theta oscillations were disrupted and temporal order could not be maintained. Consistent with this explanation, we found that both alpha and theta power predicted Order performance in healthy controls, but only alpha power predicted Order performance in patients. Previous EEG work on cognitive control deficits in patients (Boudewyn & Carter, 2018) also concluded that theta band dysfunction represents a key deficit and proposed that alpha band dysfunction may be a byproduct of attentional dysregulation.

Recent work has suggested that individual cognitive and affective abilities may continuously vary along a broad continuum (Cuthbert & Insel, 2010; Insel et al., 2010). In this framework, patients diagnosed with schizophrenia might vary along a continuum of cognitive functioning that is continuous with those who do not meet the diagnostic criteria. If this view is correct, then we might expect a continuous relationship between neural measures and behavioral performance across both patients and controls.

The current study demonstrates that the picture may be more complex. Although alpha power and WM performance tended to be lower in patients than controls, there was a consistent relationship between alpha power and behavioral performance across both groups, consistent with the dimensional perspective. In contrast, patients showed a disproportionate reduction in theta activity during maintenance of temporal order information, and theta activity was correlated with order performance in healthy individuals, but not in patients. Notably, a recent magnetic resonance spectroscopy study (Ragland et al., 2020) that included patients from the same cohort found that GABA levels in the dorsolateral pFC were positively correlated with WM performance in healthy individuals and negatively correlated with performance in patients. These combined results suggest that, in patients with schizophrenia, at least some cognitive deficits may reflect qualitative differences in neural function.

In summary, the current study showed an overall reduction in alpha power in patients with schizophrenia, but the relationship between alpha activity and performance was preserved. In contrast, patients showed a task-specific reduction in theta power specific on Order trials, and theta power could predict performance on Order trials in controls, but not in patients. These findings demonstrate that WM impairments in patients may reflect two different processes: a general deficit in alpha oscillations and a specific deficit in theta oscillations when temporal order information must be maintained. At a broader level, the results highlight the value of characterizing brain–behavior relationships, by demonstrating that the relationship between neural oscillations and WM performance can be fundamentally disrupted in those with WM deficits.

Acknowledgments

This study was supported by research funding from the National Institutes of Mental Health (R01MH105411) to J. D. R. and C. R. In addition, L.-T. H. was supported by a NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation.

Reprint requests should be sent to J. Daniel Ragland and Xiaonan L. Liu, Department of Psychiatry & Behavioral Sciences, University of California, Davis, 4701 X. Street, Sacramento, CA 95817, or via e-mail: jdragland@ucdavis.edu; xlliu@ucdavis.edu.

Note

1. Item task, $r = .245$, $p = .192$; Order task, $r = .275$, $p = .142$.

REFERENCES

Adam, K. C. S., Mance, I., Fukuda, K., & Vogel, E. K. (2015). The contribution of attentional lapses to individual differences in visual working memory capacity. *Journal of Cognitive Neuroscience*, *27*, 1601–1616. **DOI:** https://doi.org/10.1162/jocn_a_00811, **PMID:** 25811710, **PMCID:** PMC4494675

Adam, K. C. S., Robison, M. K., & Vogel, E. K. (2018). Contralateral delay activity tracks fluctuations in working memory performance. *Journal of Cognitive Neuroscience*, *30*, 1229–1240. **DOI:** https://doi.org/10.1162/jocn_a_01233, **PMID:** 29308988, **PMCID:** PMC6283409

Andreasen, N. C. (1983). *Scale for the assessment of negative symptoms (SANS)*. Iowa City, IA: University of Iowa.

Andreasen, N. C. (1984). *Scale for the assessment of positive symptoms (SAPS)*. Iowa City, IA: University of Iowa.

Barch, D. M., Carter, C. S., Braver, T. S., Sabb, F. W., MacDonald, A., III, Noll, D. C., et al. (2001). Selective deficits in prefrontal cortex function in medication-naive patients with schizophrenia. *Archives of General Psychiatry*, *58*, 280–288. **DOI:** https://doi.org/10.1001/archpsyc.58.3.280, **PMID:** 11231835

Barch, D. M., & Sheffield, J. M. (2014). Cognitive impairments in psychotic disorders: Common mechanisms and measurement. *World Psychiatry*, *13*, 224–232. **DOI:** https://doi.org/10.1002/wps.20145, **PMID:** 25273286, **PMCID:** PMC4219054

Barrett, L. F., Tugade, M. M., & Engle, R. W. (2004). Individual differences in working memory capacity and dual-process theories of the mind. *Psychological Bulletin*, *130*, 553–573. **DOI:** https://doi.org/10.1037/0033-2909.130.4.553, **PMID:** 15250813, **PMCID:** PMC1351135

Basar-Eroglu, C., Schmiedt-Fehr, C., Mathes, B., Zimmermann, J., & Brand, A. (2009). Are oscillatory brain responses generally reduced in schizophrenia during long sustained attentional processing? *International Journal of Psychophysiology*, *71*, 75–83. **DOI:** https://doi.org/10.1016/j.ijpsycho.2008.07.004, **PMID:** 18725254

Boudewyn, M. A., & Carter, C. S. (2018). Electrophysiological correlates of adaptive control and attentional engagement in patients with first episode schizophrenia and healthy young adults. *Psychophysiology*, *55*, e12820. **DOI:** https://doi.org/10.1111/psyp.12820, **PMID:** 28295391, **PMCID:** PMC5599306

Brzezicka, A., Kamiński, J., Reed, C. M., Chung, J. M., Mamelak, A. N., & Rutishauser, U. (2019). Working memory load-related theta power decreases in dorsolateral prefrontal cortex predict individual differences in performance. *Journal of Cognitive Neuroscience*, *31*, 1290–1307. **DOI:** https://doi.org/10.1162/jocn_a_01417, **PMID:** 31037988, **PMCID:** PMC6669115

Burglen, F., Marczewski, P., Mitchell, K. J., van der Linden, M., Johnson, M. K., Danion, J.-M., et al. (2004). Impaired performance in a working memory binding task in patients with schizophrenia. *Psychiatry Research*, *125*, 247–255. **DOI:** https://doi.org/10.1016/j.psychres.2003.12.014, **PMID:** 15051185

Cicchetti, D. V. (1994). Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. *Psychological Assessment*, *6*, 284–290. **DOI:** https://doi.org/10.1037/1040-3590.6.4.284

Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biological Psychiatry*, *69*, E113–E125. **DOI:** https://doi.org/10.1016/j.biopsych.2011.03.028, **PMID:** 21531388, **PMCID:** PMC3111448

Cuthbert, B. N., & Insel, T. R. (2010). Toward new approaches to psychotic disorders: The NIMH research domain criteria project. *Schizophrenia Bulletin*, *36*, 1061–1062. **DOI:** https://doi.org/10.1093/schbul/sbq108, **PMID:** 20929969, **PMCID:** PMC2963043

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*, 9–21. **DOI:** https://doi.org/10.1016/j.jneumeth.2003.10.009, **PMID:** 15102499

D'Esposito, M., & Postle, B. R. (1999). The dependence of span and delayed-response performance on prefrontal cortex. *Neuropsychologia*, *37*, 1303–1315. **DOI:** https://doi.org/10.1016/S0028-3932(99)00021-4

Dong, S., Reder, L. M., Yao, Y., Liu, Y., & Chen, F. (2015). Individual differences in working memory capacity are

reflected in different ERP and EEG patterns to task difficulty. *Brain Research*, *1616*, 146–156. **DOI:** https://doi.org/10.1016/j.brainres.2015.05.003, **PMID:** 25976774

Erickson, M. A., Albrecht, M. A., Robinson, B., Luck, S. J., & Gold, J. M. (2017). Impaired suppression of delay-period alpha and beta is associated with impaired working memory in schizophrenia. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *2*, 272–279. **DOI:** https://doi.org/10.1016/j.bpsc.2016.09.003, **PMID:** 28670630, **PMCID:** PMC5487003

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). *Structured clinical interview for DSM-IV-TR Axis I disorders, research version, non-patient edition (SCID-I/P)*. New York: Biometrics Research, New York State Psychiatric Institute.

Fukuda, K., Mance, I., & Vogel, E. K. (2015). α power modulation and event-related slow wave provide dissociable correlates of visual working memory. *Journal of Neuroscience*, *35*, 14009–14016. **DOI:** https://doi.org/10.1523/JNEUROSCI.5003-14.2015, **PMID:** 26468201, **PMCID:** PMC4604234

Gevins, A., Smith, M. E., McEvoy, L., & Yu, D. (1997). High-resolution EEG mapping of cortical activation related to working memory: Effects of task difficulty, type of processing, and practice. *Cerebral Cortex*, *7*, 374–385. **DOI:** https://doi.org/10.1093/cercor/7.4.374, **PMID:** 9177767

Gibbs, S. E. B., & D'Esposito, M. (2005). Individual capacity differences predict working memory performance and prefrontal activity following dopamine receptor stimulation. *Cognitive, Affective & Behavioral Neuroscience*, *5*, 212–221. **DOI:** https://doi.org/10.3758/CABN.5.2.212, **PMID:** 16180627

Glahn, D. C., Ragland, J. D., Abramoff, A., Barrett, J., Laird, A. R., Bearden, C. E., et al. (2005). Beyond hypofrontality: A quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Human Brain Mapping*, *25*, 60–69. **DOI:** https://doi.org/10.1002/hbm.20138, **PMID:** 15846819, **PMCID:** PMC6871703

Gonzalez-Burgos, G., & Lewis, D. A. (2008). GABA neurons and the mechanisms of network oscillations: Implications for understanding cortical dysfunction in schizophrenia. *Schizophrenia Bulletin*, *34*, 944–961. **DOI:** https://doi.org/10.1093/schbul/sbn070, **PMID:** 18586694, **PMCID:** PMC2518635

Haenschel, C., Bittner, R. A., Waltz, J., Haertling, F., Wibral, M., Singer, W., et al. (2009). Cortical oscillatory activity is critical for working memory as revealed by deficits in early-onset schizophrenia. *Journal of Neuroscience*, *29*, 9481–9489. **DOI:** https://doi.org/10.1523/JNEUROSCI.1428-09.2009, **PMID:** 19641111, **PMCID:** PMC6666530

Hannula, D. E., Ranganath, C., Ramsay, I. S., Solomon, M., Yoon, J., Niendam, T. A., et al. (2010). Use of eye movement monitoring to examine item and relational memory in schizophrenia. *Biological Psychiatry*, *68*, 610–616. **DOI:** https://doi.org/10.1016/j.biopsych.2010.06.001, **PMID:** 20673874, **PMCID:** PMC2943005

Henseler, I., Falkai, P., & Gruber, O. (2010). Disturbed functional connectivity within brain networks subserving domain-specific subcomponents of working memory in schizophrenia: Relation to performance and clinical symptoms. *Journal of Psychiatric Research*, *44*, 364–372. **DOI:** https://doi.org/10.1016/j.jpsychires.2009.09.003, **PMID:** 19837416

Howard, M. W., Rizzuto, D. S., Caplan, J. B., Madsen, J. R., Lisman, J., Aschenbrenner-Scheibe, R., et al. (2003). Gamma oscillations correlate with working memory load in humans. *Cerebral Cortex*, *13*, 1369–1374. **DOI:** https://doi.org/10.1093/cercor/bhg084, **PMID:** 14615302

Hsieh, L.-T., Ekstrom, A. D., & Ranganath, C. (2011). Neural oscillations associated with item and temporal order maintenance in working memory. *Journal of Neuroscience*, *31*, 10803–10810. **DOI:** https://doi.org/10.1523/JNEUROSCI.0828-11.2011, **PMID:** 21795532, **PMCID:** PMC3164584

Hsieh, L.-T., & Ranganath, C. (2014). Frontal midline theta oscillations during working memory maintenance and episodic encoding and retrieval. *Neuroimage*, *85*, 721–729. **DOI:** https://doi.org/10.1016/j.neuroimage.2013.08.003, **PMID:** 23933041, **PMCID:** PMC3859771

Hyvärinen, A., & Oja, E. (2000). Independent component analysis: Algorithms and applications. *Neural Networks*, *13*, 411–430. **DOI:** https://doi.org/10.1016/S0893-6080(00)00026-5

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., et al. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*, *167*, 748–751. **DOI:** https://doi.org/10.1176/appi.ajp.2010.09091379, **PMID:** 20595427

Jensen, O., Gelfand, J., Kounios, J., & Lisman, J. E. (2002). Oscillations in the alpha band (9–12 Hz) increase with memory load during retention in a short-term memory task. *Cerebral Cortex*, *12*, 877–882. **DOI:** https://doi.org/10.1093/cercor/12.8.877, **PMID:** 12122036

Johnson, J. S., Sutterer, D. W., Acheson, D. J., Lewis-Peacock, J. A., & Postle, B. R. (2011). Increased alpha-band power during the retention of shapes and shape–location associations in visual short-term memory. *Frontiers in Psychology*, *2*, 128. **DOI:** https://doi.org/10.3389/fpsyg.2011.00128, **PMID:** 21713012, **PMCID:** PMC3114253

Kayser, J., & Tenke, C. E. (2006a). Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: I. Evaluation with auditory oddball tasks. *Clinical Neurophysiology*, *117*, 348–368. **DOI:** https://doi.org/10.1016/j.clinph.2005.08.034, **PMID:** 16356767

Kayser, J., & Tenke, C. E. (2006b). Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: II. Adequacy of low-density estimates. *Clinical Neurophysiology*, *117*, 369–380. **DOI:** https://doi.org/10.1016/j.clinph.2005.08.033, **PMID:** 16356768

Klem, G. H., Lüders, H. O., Jasper, H. H., & Elger, C. (1999). The ten–twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology. *Electroencephalography and Clinical Neurophysiology*, *52(Suppl.)*, 3–6.

Kraguljac, N. V., Srivastava, A., & Lahti, A. C. (2013). Memory deficits in schizophrenia: A selective review of functional magnetic resonance imaging (fMRI) studies. *Behavioral Sciences*, *3*, 330–347. **DOI:** https://doi.org/10.3390/bs3030330, **PMID:** 25379242, **PMCID:** PMC4217593

Lisman, J., & Buzsáki, G. (2008). A neural coding scheme formed by the combined function of gamma and theta oscillations. *Schizophrenia Bulletin*, *34*, 974–980. **DOI:** https://doi.org/10.1093/schbul/sbn060, **PMID:** 18559405, **PMCID:** PMC2518638

Lisman, J. E., & Grace, A. A. (2005). The hippocampal–VTA loop: Controlling the entry of information into long-term memory. *Neuron*, *46*, 703–713. **DOI:** https://doi.org/10.1016/j.neuron.2005.05.002, **PMID:** 15924857

Manza, P., Hau, C. L. V., & Leung, H.-C. (2014). Alpha power gates relevant information during working memory updating. *Journal of Neuroscience*, *34*, 5998–6002. **DOI:** https://doi.org/10.1523/JNEUROSCI.4641-13.2014, **PMID:** 24760858, **PMCID:** PMC6608286

Miller, E. K., Lundqvist, M., & Bastos, A. M. (2018). Working memory 2.0. *Neuron*, *100*, 463–475. **DOI:** https://doi.org/10.1016/j.neuron.2018.09.023, **PMID:** 30359609

Min, B.-K., & Park, H.-J. (2010). Task-related modulation of anterior theta and posterior alpha EEG reflects top–down preparation. *BMC Neuroscience*, *11*, 79. **DOI:** https://doi.org/10.1186/1471-2202-11-79, **PMID:** 20584297, **PMCID:** PMC2906487

Nenert, R., Viswanathan, S., Dubuc, D. M., & Visscher, K. M. (2012). Modulations of ongoing alpha oscillations predict successful short-term visual memory encoding. *Frontiers in Human Neuroscience*, *6*, 127. **DOI:** https://doi.org/10.3389/fnhum.2012.00127, **PMID:** 22586390, **PMCID:** PMC3347628

O'Connell, R. G., Dockree, P. M., Robertson, I. H., Bellgrove, M. A., Foxe, J. J., & Kelly, S. P. (2009). Uncovering the neural signature of lapsing attention: Electrophysiological signals predict errors up to 20 s before they occur. *Journal of Neuroscience*, *29*, 8604–8611. **DOI:** https://doi.org/10.1523/JNEUROSCI.5967-08.2009, **PMID:** 19571151, **PMCID:** PMC6665670

Park, S., Holzman, P. S., & Goldman-Rakic, P. S. (1995). Spatial working memory deficits in the relatives of schizophrenic patients. *Archives of General Psychiatry*, *52*, 821–828. **DOI:** https://doi.org/10.1001/archpsyc.1995.03950220031007, **PMID:** 7575101

Park, S., Püschel, J., Sauter, B. H., Rentsch, M., & Hell, D. (1999). Spatial working memory deficits and clinical symptoms in schizophrenia: A 4-month follow-up study. *Biological Psychiatry*, *46*, 392–400. **DOI:** https://doi.org/10.1016/S0006-3223(98)00370-9

Perlstein, W. M., Carter, C. S., Noll, D. C., & Cohen, J. D. (2001). Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. *American Journal of Psychiatry*, *158*, 1105–1113. **DOI:** https://doi.org/10.1176/appi.ajp.158.7.1105, **PMID:** 11431233

Raghavachari, S., Kahana, M. J., Rizzuto, D. S., Caplan, J. B., Kirschen, M. P., Bourgeois, B., et al. (2001). Gating of human theta oscillations by a working memory task. *Journal of Neuroscience*, *21*, 3175–3183. **DOI:** https://doi.org/10.1523/JNEUROSCI.21-09-03175.2001, **PMID:** 11312302, **PMCID:** PMC6762557

Ragland, J. D., Blumenfeld, R. S., Ramsay, I. S., Yonelinas, A., Yoon, J., Solomon, M., et al. (2012). Neural correlates of relational and item-specific encoding during working and long-term memory in schizophrenia. *Neuroimage*, *59*, 1719–1726. **DOI:** https://doi.org/10.1016/j.neuroimage.2011.08.055, **PMID:** 21907293, **PMCID:** PMC3230711

Ragland, J. D., Maddock, R. J., Hurtado, M. Y., Tanase, C., Lesh, T. A., Niendam, T. A., et al. (2020). Disrupted GABAergic facilitation of working memory performance in people with schizophrenia. *Neuroimage: Clinical*, *25*, 102127. **DOI:** https://doi.org/10.1016/j.nicl.2019.102127, **PMID:** 31864216, **PMCID:** PMC6928454

Ragland, J. D., Ranganath, C., Harms, M. P., Barch, D. M., Gold, J. M., Layher, E., et al. (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 Psychiatry*, *72*, 909–916. **DOI:** https://doi.org/10.1001/jamapsychiatry.2015.0276, **PMID:** 26200928, **PMCID:** PMC4558363

Ragland, J. D., Yoon, J., Minzenberg, M. J., & Carter, C. S. (2007). Neuroimaging of cognitive disability in schizophrenia: Search for a pathophysiological mechanism. *International Review of Psychiatry*, *19*, 417–427. **DOI:** https://doi.org/10.1080/09540260701486365, **PMID:** 17671874, **PMCID:** PMC4332575

Resnick, S. M. (1992). Matching for education in studies of schizophrenia. *Archives of General Psychiatry*, *49*, 246. **DOI:** https://doi.org/10.1001/archpsyc.1992.01820030078011, **PMID:** 1567279

Roach, B. J., & Mathalon, D. H. (2008). Event-related EEG time–frequency analysis: An overview of measures and an analysis of early gamma band phase locking in schizophrenia. *Schizophrenia Bulletin*, *34*, 907–926. **DOI:** https://doi.org/10.1093/schbul/sbn093, **PMID:** 18684772, **PMCID:** PMC2632478

Roberts, B. M., Hsieh, L.-T., & Ranganath, C. (2013). Oscillatory activity during maintenance of spatial and temporal information in working memory. *Neuropsychologia*, *51*, 349–357. **DOI:** https://doi.org/10.1016/j.neuropsychologia.2012.10.009, **PMID:** 23084981, **PMCID:** PMC3546228

Roux, F., & Uhlhaas, P. J. (2014). Working memory and neural oscillations: α–γ versus θ–γ codes for distinct WM information? *Trends in Cognitive Sciences*, *18*, 16–25. **DOI:** https://doi.org/10.1016/j.tics.2013.10.010, **PMID:** 24268290

Tenke, C. E., & Kayser, J. (2015). Surface Laplacians (SL) and phase properties of EEG rhythms: Simulated generators in a volume-conduction model. *International Journal of Psychophysiology*, *97*, 285–298. **DOI:** https://doi.org/10.1016/j.ijpsycho.2015.05.008, **PMID:** 26004020, **PMCID:** PMC4537832

Unsworth, N., & Engle, R. W. (2007). The nature of individual differences in working memory capacity: Active maintenance in primary memory and controlled search from secondary memory. *Psychological Review*, *114*, 104–132. **DOI:** https://doi.org/10.1037/0033-295X.114.1.104, **PMID:** 17227183

van Vugt, M. K., Schulze-Bonhage, A., Litt, B., Brandt, A., & Kahana, M. J. (2010). Hippocampal gamma oscillations increase with memory load. *Journal of Neuroscience*, *30*, 2694–2699. **DOI:** https://doi.org/10.1523/JNEUROSCI.0567-09.2010, **PMID:** 20164353, **PMCID:** PMC2835496

Ventura, J., Lukoff, D., Nuechterlein, K. H., Liberman, R. P., Green, M. F., & Shaner, A. (1993). Brief Psychiatric Rating Scale (BPRS) expanded version (4.0): Scales, anchor points, and administration manual. *International Journal of Methods in Psychiatric Research*, *3*, 227–243.

Vogel, E. K., & Machizawa, M. G. (2004). Neural activity predicts individual differences in visual working memory capacity. *Nature*, *428*, 748–751. **DOI:** https://doi.org/10.1038/nature02447, **PMID:** 15085132

Voytek, B., Kayser, A. S., Badre, D., Fegen, D., Chang, E. F., Crone, N. E., et al. (2015). Oscillatory dynamics coordinating human frontal networks in support of goal maintenance. *Nature Neuroscience*, *18*, 1318–1324. **DOI:** https://doi.org/10.1038/nn.4071, **PMID:** 26214371, **PMCID:** PMC4551604

Williams, L. E., Must, A., Avery, S., Woolard, A., Woodward, N. D., Cohen, N. J., et al. (2010). Eye-movement behavior reveals relational memory impairment in schizophrenia. *Biological Psychiatry*, *68*, 617–624. **DOI:** https://doi.org/10.1016/j.biopsych.2010.05.035, **PMID:** 20655509, **PMCID:** PMC3184178