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# Increased Delta as a Compensatory Strategy During Working Memory in High-Performing Patients with Schizophrenia

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Increased Delta as a Compensatory Strategy During Working  
Memory in High-Performing Patients with Schizophrenia

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B.A. Washington University in St. Louis, 2010

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# APPROVAL PAGE

Master of Science Thesis

## Increased Delta as a Compensatory Strategy During Working Memory in High-Performing Patients with Schizophrenia

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## **1. Introduction**

Schizophrenia (SZ) is a chronic and severe mental illness that impacts approximately 1% of the general population (Hirsch & Weinberge, 2003). Cognitive deficits are a core feature in the presentation of SZ and have been linked to functional outcomes in the disorder, over and above the presence of negative or positive symptoms (Heinrichs, Miles, Ammari, & Muharib, 2013). Impairments in working memory (WM) are a core neuropsychological deficit in SZ (Bowie & Harvey, 2005; Silver, Feldman, Bilker, & Gur, 2003). Patients with SZ frequently demonstrate impairments in encoding and early maintenance periods of transiently stored information, beginning in the prodromal period (Cannon et al., 2005; Lee & Park, 2005; Simon et al., 2007), particularly visual WM (Haenschel & Linden, 2011). However, there is a large degree of heterogeneity in WM performance in SZ, with some patients demonstrating intact WM performance (Bowie & Harvey, 2006; Haenschel, Linden, Bittner, Singer, & Hanslmayr, 2010; Kurtz & Wexler, 2006). Given the ineffectiveness of standard psychopharmacological interventions for treating cognitive impairments, increased understanding of the mechanisms of intact and impaired cognition is likely to be key in improving functional outcomes in SZ. Specifically, "high-performing" patients may be a key group to reveal potential compensatory mechanisms that can be targets for augmentation in patients with impaired cognition.

To identify potential compensatory mechanisms during a WM task in high-performing patients, it is first important to understand the dysfunctional and functional mechanisms in patients with impaired performance and healthy participants, respectively. In patients with impaired performance, electroencephalography (EEG) studies have demonstrated dysfunction in oscillatory activity across the range of

frequencies in gamma (Chen et al., 2014; Gandala, Edgarb, Klooka, & Siegel, 2012; Hirano et al., 2015; Uhlhaas & Singer, 2013), beta (Haenschel et al., 2009), alpha (Barr et al., 2010; Haenschel et al., 2009), and theta (Schack, Vath, Petsche, Geissler, & Möller, 2002). Gamma dysfunction has been hypothesized to be a trait marker in the disorder (Woo, Spencer, & McCarley, 2010), with some suggesting that patients may enhance beta oscillation to compensate for gamma dysfunction (Spencer et al., 2004). However, less is known about the relation of delta dysfunction and WM deficits in SZ, with very few studies examining delta oscillations during WM in SZ. An EEG study by Barr and colleagues (2010) showed intact delta activity, while a magnetoencephalography (MEG) study by Ince et al. (2009) showed patients had less frontal delta power during the encoding stage than controls. In healthy participants, neurophysiological studies of WM have demonstrated the importance of coordinated networks of brain regions (Gregoriou, Gotts, Zhou, & Desimone, 2009; Linden et al., 2003; Yoon, Curtis, & D'Esposito, 2006). Specifically, several studies have demonstrated interactions in alpha and theta as well as functional connectivity in visual WM tasks in the frontal-occipital network (Gregoriou et al., 2009; Huang et al., 2013; Palva, Monto, Kulashekhar, & Palva, 2010). WM impairment in SZ may result from dysfunction in the distributed networks, which may be reflected by impaired oscillatory activity within and between the involved regions (Deserno, Sterzer, Wustenberg, Heinz, & Schlagenhauf, 2012; Micheloyannis et al., 2006; Tan et al., 2006). There is some evidence for disruption of the connections between frontal and occipital locations during visual WM tasks in patients with impaired performance (Kang, Sponheim, Chafee, & MacDonald, 2011; Yoon et al., 2006).

There has been little done examining the role of occipital locations as candidates for compensatory recruitment in patients with preserved performance during visual WM tasks and very few hypotheses have been proposed as compensatory mechanisms in those patients. Haenschel and Linden (2011) proposed alpha phase-locking during encoding as a candidate compensatory mechanism given the findings that patients with preserved performance demonstrated increased alpha phase-locking during encoding relative to controls and non-performing patients (De Vico Fallani et al., 2010; Haenschel et al., 2010). Other studies have suggested that patients are able to perform by overactivating the prefrontal cortex in comparison to controls, which may represent a less efficient, compensatory strategy (MacDonald et al., 2005; Manoach, 2003; Manoach et al., 1999; Tan et al., 2006); patients with preserved performance show increased activation in ventrolateral prefrontal cortex to compensate for dysfunction in the DLPFC (MacDonald et al., 2005; Tan et al., 2006).

There is little consensus in the literature as to the frequency, timing, or location of the compensatory mechanisms in high-performing SZ patients. To address this question, we examined neural oscillatory activity across conventionally defined frequency bands in high-performing patients with SZ who performed at the level of healthy participants on a modified Sternberg WM task (containing clear WM stages, encoding, retention, and retrieval) with two difficulty levels at frontal, central, and occipital locations. Neural oscillatory activity was examined in time units of one second across the task, providing more precise timing than traditional analyses to examine when potential compensation might occur. We hypothesized that: High-performing patients have (1) increased frontal beta oscillatory activity, compensating their



decreased frontal gamma oscillations, and (2) increased occipital low frequency oscillatory activity, representing increased visual cortical recruitment. (3) These compensatory oscillatory activities occur in the encoding or early retention periods of the WM task.

## **2. Methods**

### **2.1 Participants**

The study was approved by the Institutional Review Boards of the New York State Psychiatric Institute (NYSPI) and Columbia University Medical Center. Seven patients with a clinical diagnosis of SZ (one female and 6 males, ages 21-49; mean = 33, SD = 12.8) were recruited for participation after voluntary admission to a research unit (Schizophrenia Research Unit, NYSPI) or its associated outpatient research clinic (Lieber Schizophrenia Research Clinic, NYSPI). Diagnosis was confirmed via the Diagnostic Interview for Genetic Studies assessed by a trained rater (Nurnberger et al., 1994). Inclusion criteria for patients were as follows: (i) no other DSM-IV Axis-I diagnosis, (ii) age 18-60, (iii) no lifetime history of alcohol or substance abuse or dependence, (iv) no concomitant or past severe medical conditions, including head trauma, (v) not pregnant, (vi) no metallic or other material in the body that would preclude safe exposure to MRI, and (vii) ability to provide informed consent. With the exception of one, all patients were receiving a clinically determined dose of a second-generation antipsychotic for at least four weeks prior to participation. The patient not on medication was stable without medication.

Nine controls (four females and five males, ages 24-46; mean = 32, SD = 8.0)

were recruited from the New York Metropolitan area. Controls did not differ from patients in age (independent-samples t-test:  $p = 0.810$ ) or gender ratios (chi-squared test,  $p = 0.197$ ). All participants were right-handed. Inclusion criteria for controls were as follows: (i) no DSM-IV Axis-I diagnosis, (ii) age 18-60, (iii) no lifetime history of alcohol or substance abuse or dependence, (iv) no concomitant or past severe medical conditions, including head trauma, (v) not pregnant, (vi) no metallic or other material in the body that would preclude safe exposure to MRI, and (vii) ability to provide informed consent. Criterion (i) was assessed in controls using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) non-patient version (First, Spitzer, Gibbon & Williams, 2002) by a trained rater.

Inclusion and exclusion criteria were assessed using structured interviews, medical and psychiatric history, review of systems, physical and neurological examination, routine blood tests (including pregnancy tests for females), urine toxicology, and electrocardiogram. Capacity to give informed consent was assessed by a clinician who was not otherwise associated with this study.

## **2.2 Procedure**

All participants completed a modified Sternberg WM task (Luber et al., 2007) while scalp EEG was recorded in a dimly lit, sound attenuated, and electronically shielded room. Individuals were excluded who performed below 50% on the six-letter set difficulty level.

### **2.2.1 Working Memory Task.**

The modified Sternberg WM task (see Figure 1) lasted a total of 34 minutes. Stimuli were presented on a screen placed approximately 80 cm from the participant's head. Each trial consisted of three stages: 1) encoding stage, an array of one of two possible set sizes (one or six uppercase letters) was presented for 3 seconds; 2) retention stage, a blank screen was presented for 7 seconds and participants were asked to fixate on the center of the screen; 3) probe stage, a test stimulus (a single lowercase letter) appeared for 3 seconds at the center of the screen. During the probe stage, participants were asked to identify whether the probe letter matched one of the letters in the array previously presented and then to respond by a button press as quickly and as accurately as possible. Each condition had 64 trials (total = 128 trials). For individual trials, set size and positive or negative probe was pseudorandom, with the criteria that there be 16 true positive and 16 true negative probes out of the 64 total trials for each set size.

### **2.2.2 EEG Recording.**

EEG was recorded using a 66-channel system with direct current BrainAmp MR amplifiers (Brain Product GmbH, Gilching, Germany). The EEG signal was recorded from 64 electrodes, positioned using an electrode cap placed according to the extended 10/20 international system. The EEG electrodes were referenced to the FCz electrode. Two electrooculography (EOG) channels were recorded from during EEG acquisition to obtain information about eye movements, blinks, and micro-saccade artifact that could be corrected for. Channels were hardware-filtered between 0.1 and 1000 Hz, and sampled at 1000 Hz with a 60 Hz notch filter (with a bandwidth of 5 Hz, symmetric

around 60 Hz with the edge rise of 24 dB/octave). All EEG data were re-referenced to average reference offline.

## **2.3 Data Analysis**

### **2.3.1 Working memory performance**

Participants' performance was assessed using reaction time to probe, accuracy, rate of hit, and rate of correct reject in both one and six letter-set conditions. Two-tailed independent-samples *t*-tests were performed. For comparisons that did not pass Levene's test for homogeneity of variance, adjusted degrees of freedom are reported.

### **2.3.2 Oscillatory activity**

The task was divided into four stages (one second of pre-trial baseline, encoding, retention, and probe). Task-induced amplitudes were computed for the gamma, beta, alpha, theta, and delta frequency bands for three midline electrodes (Fz, Cz, and Oz). Averaged amplitudes were then computed in 14 one-second steps across the task for each participant as follows: 1) raw EEG data were corrected for artifact of eye movements, blinks, and saccades. 2) Only correct (as measured by response to probe), artifact-free EEG trials were analyzed. 3) Instantaneous amplitude information was extracted by Morlet wavelet decomposition on 98 scales from 0.5 Hz to 100 Hz using MATLAB (The MathWorks, Inc., Natick, MA). Complex Morlet's wavelets  $w(t, f_0)$  have a Gaussian shape both in the time domain (SD  $\sigma_t$ ) and in the frequency domain (SD  $\sigma_f$ ) around its central frequency  $f_0$ :  $w(t, f_0) = A \cdot \exp(-t^2/2\sigma_t^2) \times \exp(2i\pi f_0 t)$ , with  $\sigma_f = 1/(2\pi\sigma_t)$  (Grossmann, Kronland-Martinet, & Morlet, 1989). A wavelet family is characterized by a constant ratio ( $f_0/\sigma_f$ ), which should be chosen in practice greater than  $\sim 5$  (Grossmann et

al., 1989). The wavelet family we used was defined by  $f_0/\sigma_f = 6$ , with  $f_0$  ranging from 0.5 to 100 Hz. At 2 Hz, this leads to a wavelet duration ( $2\sigma_t$ ) of 955 msec with spectral bandwidth ( $2\sigma_f$ ) of 0.67Hz, and at 30 Hz, to a wavelet duration of 63.7 msec and spectral bandwidth of 10 Hz. The time resolution of this method increases with frequency, while the frequency resolution decreases. The gamma frequency range from 30-56 HZ was used (avoiding 60 Hz artifact) to compute task-induced gamma power, consistent with the literature in WM and SZ (Basar-Eroglu et al., 2007; Schmiecht, Brand, Hildebrandt & Basar-Eroglu, 2005). The frequency ranges for the other bands were as follows: beta =14-28 Hz, alpha =8-12 Hz, theta = 4-8 Hz, and delta = .5-4 Hz. 4). For each trial, frequency band amplitude was summed across the band range and the time window in question to yield one value for power. Trials were excluded from analysis if either the power at that electrode or reaction time values were more than 2.5 standard deviations above the participant's mean.

To allow for increased temporal specificity, we subdivided the task phases in to one-second time windows. For each electrode of interest, the average power of each frequency band during each one-second (baseline: 1 second; encoding: 1-3 seconds; retention: 1-7 second; probe: 1-3 seconds) step was calculated by averaging power information across all correct one and six letter set trials separately, and then computing a weighted average of the one and six letter sets average power information. Average power was also computed by stage as above. Oscillatory activity was investigated by conducting repeated measures ANOVA with second, set size, and electrode as within subjects factors and group membership as a between subjects factor. Separate ANOVAs were conducted for each frequency band. Values in the delta band were log

transformed to correct for violation of homogeneity of variance. After transformation, four one-second periods (i.e., retention 2 and 3, and probe 1 and 3) were excluded for further analysis due to continued violation of the assumption. Given the low power of the above analyses to detect effects, additional ANOVAs were conducted for each frequency band using power by stage (See appendix B). In all frequency bands, effects were adjusted for violation of sphericity by correcting degrees of freedom according to Greenhouse–Geisser corrections where necessary.

### **3. Results**

#### **3.1 Behavioral Data**

Behavioral data is reported in Table 1. As expected by the design of recruiting high-performing patients with schizophrenia, the patient and control groups did not differ in reaction time, accuracy, hit rate, or correct reject rate at either the six or one letter sets ( $p > 0.05$ ).

#### **3.2 Oscillatory EEG Data**

Summaries of statistical results of the oscillatory data are shown in Table 2.

##### **3.2.1 Delta Activity**

Repeated measures ANOVA revealed a group x electrode x second interaction effect ( $F(2.34, 32.78) = 3.26, p = 0.044, \eta_p^2 = 0.19$ ) such that in patients delta power at Oz was significantly greater than delta power at Fz (paired-samples  $t = 3.79, df = 6, p = 0.009, d = -1.44$ ) and Cz ( $t = 6.99, df = 6, p < 0.001, d = -2.65$ ) across the task (see Figure 2). Additionally, delta power at Fz was significantly greater than at Cz ( $t = 2.64, df = 6, p = 0.039, d = 1.00$ ). In contrast, in the control group, while delta power at Fz and Oz was

still significantly greater than at Cz ( $t = 5.93$ ,  $df = 8$ ,  $p < 0.001$ ,  $d = 1.98$ ;  $t = 4.70$ ,  $df = 8$ ,  $p = 0.002$ ,  $d = -1.57$ ), delta power at Fz and Oz did not differ ( $t = -0.68$ ,  $df = 8$ ,  $p = 0.59$ ,  $d = -0.23$ ). Further exploration of this interaction revealed that patients showed greater delta power during the encoding stage of the task at Oz (independent samples  $t = -2.68$ ,  $df = 14$ ,  $p = 0.018$ ,  $d = -1.43$ ). Groups did not differ in power during retention (independent-samples  $t = 0.023$ ,  $df = 14$ ,  $p = 0.982$ ,  $d = 0.16$ ). Within group analysis revealed that patients showed greater occipital delta power at encoding (paired samples  $t = -3.57$ ,  $df = 6$ ,  $p = 0.012$ ,  $d = 0.06$ ) and retention (paired samples  $t = -3.54$ ,  $df = 6$ ,  $p = 0.012$ ,  $d = 0.04$ ).

### 3.2.2 Theta Activity

There was a significant main effect by electrode ( $F(1.63, 22.75) = 17.06$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.55$ ) (see Figure 3). Cz had significantly lower power than Fz ( $t = -5.04$ ,  $df = 15$ ,  $p < 0.001$ ,  $d = 1.48$ ) and Oz ( $t = -4.93$ ,  $df = 15$ ,  $p < 0.001$ ,  $d = -1.293$ ). Fz and Oz were not significantly different in power ( $t = 1.04$ ,  $df = 15$ ,  $p = 0.313$ ,  $d = 0.28$ ). No other effects were observed.

### 3.2.3 Alpha Activity

There was an electrode x second interaction ( $F(5.29, 74.01) = 2.92$ ,  $p = 0.017$ ,  $\eta_p^2 = 0.173$ ), which revealed greater power in Fz and Oz than Cz (see Figure 4). Post hoc analyses revealed that there was a significant increase in power from the first second of the encoding stage to the highest point in the retention stage at the occipital ( $t = -2.30$ ,  $df = 15$ ,  $p = .036$ ,  $d = -0.76$ ) and central electrodes ( $t = -2.19$ ,  $df = 15$ ,  $p = .045$ ,  $d = -0.914$ ) but not at the frontal electrode ( $t = -1.89$ ,  $df = 15$ ,  $p = .078$ ,  $d = -0.65$ ), suggesting suppression of occipital alpha band during encoding. Additionally, post-hoc contrasts

demonstrated that a fourth-order down-up-down polynomial best explained the pattern at the occipital electrode ( $F(1, 15) = 9.28, p = 0.008, \eta_p^2 = 0.38$ ). This pattern was not observed at the frontal ( $F(1, 15) = 8.33, p = 0.011, \eta_p^2 = 0.36$ ) and central ( $F(1, 15) = 6.09, p = 0.026, \eta_p^2 = 0.29$ ) electrodes. Thus, there appears to be greater modulation in Oz than in Fz across the task, which may be reflected by suppression of occipital alpha during encoding.

### 3.2.4 Beta Activity

Repeated measures ANOVA revealed a main effect of electrode ( $F(1.13, 15.81) = 4.39, p = 0.049, \eta_p^2 = 0.24$ ) (see Figure 5A). Cz had significantly lower power than Fz (paired-samples  $t = -3.57, df = 15, p = 0.003, d = -0.90$ ) and Oz ( $t = -2.52, df = 15, p = 0.024, d = -0.67$ ). Fz and Oz were not significantly different in power ( $t = -1.65, df = 15, p = 0.120, d = -0.44$ ). There was a set size x second interaction ( $F(3.51, 49.08) = 3.50, p = 0.017, \eta_p^2 = 0.20$ ), which revealed greater beta power in the one letter set at the end of encoding, reaching significance during the last second of encoding (paired-samples  $t = -2.46, df = 15, p = 0.027, d = 0.63$ ) (see Figure 5B).

### 3.2.5 Gamma Activity

There was a main effect of electrode ( $F(1.04, 14.54) = 5.110, p = .039, \eta_p^2 = 0.27$ ) (see Figure 6A). Significantly higher power was observed in Oz than Fz (paired-samples  $t = 2.30, df = 15, p = 0.036, d = -1.00$ ) and Cz ( $t = 2.50, df = 15, p = 0.025, d = -0.90$ ). Fz and Cz were not significantly different in power ( $t = 2.12, df = 15, p = 0.051, d = 0.54$ ). An interaction of set size x second was observed ( $F(2.51, 35.15) = 3.26, p = 0.040, \eta_p^2 = 0.189$ ) which revealed greater power during baseline and encoding with increased difficulty, though paired samples t-tests show that these differences do not reach



significance ( $p > 0.05$ ) (see Figure 6B). There were no effects of group.

#### **4. Discussion**

This study aimed to investigate the compensatory mechanisms in high-performing individuals with schizophrenia that allow preserved performance on a WM task by examining frontal, central, and occipital power across the frequency range during a modified Sternberg WM task. Individuals were only included for analysis who performed accurately at least at 50% of trials in the six letter set condition. We found no group differences in power in the gamma, beta, alpha, and theta bands. This is in contrast to the literature in patients with impaired WM performance which demonstrates dysfunctional activity in those bands (Haenschel et al., 2009; Link, Struening, Neese-Todd, Asmussen, & Phelan, 2001; Uhlhaas, Haenschel, Nikolić, & Singer, 2008; Uhlhaas & Singer, 2013). This suggests that high-performing patients preserved their higher frequency oscillation and in this way, may more closely resemble healthy controls than their SZ counterparts.

In the high frequency bands, gamma and beta, we found effects by set size such that during the encoding stage, the sample showed increased power in gamma at the six letter set and reduced beta power at the six letter set compared to the one letter set. Increases in gamma with increasing task difficulty is a common finding in the literature in epilepsy and general population (Basar-Eroglu et al., 2007; Meltzer et al., 2008). The reduction in beta activity during encoding is consistent with a study by Haenschel et al. (2009) in which increased WM load was associated with reduced beta activity in control subjects. Haenschel and colleagues found reductions in beta that were not associated with WM performance. In this way, our patient sample more closely follows the patterns

of controls than patient groups with impaired WM performance (Barr et al., 2010). Again, as stated above, this indicates the association between reduced beta and impaired WM performance. In the alpha band, we found an interaction of electrode and second such that both groups showed reductions in occipital alpha during encoding relative to frontal alpha. This is consistent with previous findings of posterior alpha suppression during WM (Klimesch, Sauseng, & Hanslmayr, 2007; Meltzer et al., 2008). In comparisons of power by electrode we found reduced power at the central electrode irrespective of time and frequency band. This may support the hypothesis that this task is highly reliant on frontal and occipital processes.

In the delta band, patients showed increased occipital power during encoding relative to controls. However, there were no between-group differences in power at the frontal electrode. This partially confirmed our prediction of increased low frequency power during encoding and early retention as potential compensatory strategies. Few studies have examined delta during WM in SZ, and those studies have not included high-performing patients. Barr et al. (2010) found no group differences in frontal delta during an N-back WM paradigm; in their study (24 patients and 24 controls), patients performed significantly below controls. However, the nature of the N-back task does not allow for distinction of the different stages of the WM task and may thus obscure findings that are specific to a given WM stage. Ince and colleagues (2009) used a modified Sternberg paradigm to examine MEG differences in patients with SZ and controls. They found that patients showed less delta power during the encoding stage and less frontal delta than controls. However, in their sample (15 patients and 23 controls) patients performed below the level of controls on a task with fewer WM

demands: Subjects were asked to encode and recall 5 letters with a delay of 2 seconds. In our sample of high-performing patients, we find equivalently preserved frontal power and greater occipital delta power during encoding. Thus, to perform this task at the level of controls, high-performing patients may be boosting frontal and occipital delta compared to patients with impaired performance. It should be noted that the Sternberg tasks were not identical in the current study and the study by Ince and colleagues: our task presented letters in an array, while Ince et al. presented five letters in serial sequence. Thus, comparisons of the effects observed in the encoding stages of the two studies should be done with caution. However, taken together, they suggest that delta may be an important under-examined feature is the performance of WM tasks in individuals with SZ.

Low frequency oscillations such as delta are thought to be involved in global processes that require the integration and coordination of diverse cortical sites (Nunez, 2000). The disconnection hypothesis of SZ states that cognitive deficits in the disorder may arise from disconnection between areas in the distributed neural networks required for the task (Uhlhaas & Singer, 2015). In a WM task such as the modified Sternberg paradigm used in this study, we might expect involvement of prefrontal, parietal, and occipital cortices (Deserno et al., 2012; Gregoriou et al., 2009). In this study, we see an increase in occipital delta in high-performing patients relative to controls with no other differences observed in neural oscillations. This increase in delta may represent a compensatory strategy in high-performing patients. As the increase in delta occurs largely during the encoding stage, it may represent greater recruitment of the visual cortex. Thus, high-performing patients may use a more visual encoding strategy on the

modified Sternberg, which is a task with visual, spatial, and verbal components. A study by Deserno et al. (2012) found reduced functional connectivity between frontal and precuneous locations in patients who performed at lower levels than controls during a numeric N-back task. Thus, increased activation of the occipital cortex may compensate for, or result from, disconnection between other cortical locations. Furthermore, delta has been linked to attention, motivation, and salience detection, all areas in which patients show dysfunction (Andreasen & Flaum, 1991; Knyazev, 2012). It may be that high-performing patients are using occipital recruitment to aid with attention and salience detection of the visually presented stimuli. This visual strategy may be required to counterbalance verbal difficulties (Ford, Gray, Faustman, Roach, & Mathalon, 2007). However, with the electrodes examined in this study, we cannot address the question of recruitment of other cortical locations, such as temporal or parietal areas. Although a more exploratory analysis was outside the scope of this study, we are currently investigating the hypotheses of cross-cortical area recruitments in a follow-up study.

This study is one of few studies to examine delta activation during WM performance in SZ. Delta may be important for understanding when patients perform below controls or show preserved performance. This study suggests occipital delta as a potential target or marker for future treatment of WM deficits in SZ that might otherwise have been missed in studies that only examine patients with impaired performance. Future studies should continue to explore the role of delta in WM performance in SZ as well as its potential to act as a compensatory mechanism in high-performing patients. As this study does not examine measures of functional connectivity such as phase-locking values between electrodes (Lachaux, Rodriguez, Martinerie, & Varela, 1999)

and cross-frequency couplings (Canolty et al., 2006), we cannot directly speak to how this increase in occipital delta during encoding might relate to other previously demonstrated compensatory mechanisms in high-performing patients, such as the increase in alpha phase-locking demonstrated by Haenschel et al. (2010). While we did not see differences between groups in power in gamma, beta, alpha, and theta, we cannot speak to the reductions in phase synchrony (e.g., inter-trial coherence) that have frequently been found in SZ (Gandala et al., 2012; Ghorashi & Spencer, 2015; Spencer et al., 2003; Uhlhaas & Singer, 2013). Furthermore, examining cross-frequency coupling between delta and other bands may be a potential area of interest. Specifically, several authors have proposed a reciprocal relationship between delta and alpha activity (Knyazev, 2012; Robinson, 2001). Given the findings implicating delta and alpha as compensatory mechanisms in high-performing patients, cross-frequency coupling in these bands may be an interesting area for future studies.

There are several limitations of this study that should be considered. One limitation is the small sample size. This study was designed to be part of a larger project that consisted of multiple visits and diverse methodologies, including magnetic resonance spectroscopy. Many participants did not complete the EEG recording part of the study. The small size was further reduced when we controlled participants who scored above 50% accuracy on the more difficult WM condition and only quality EEGs were included. It is possible that the high performance of this study relates to the fact that participants were required to complete intricate and lengthy experimental protocols. Thus, our results may not be generalizable to the greater SZ population. The small sample size also reduced our power to detect small effect sizes given the complexity of

our analyses. To address this concern, we ran repeated measures ANOVAs with power by stage (i.e., averaging second-level data to only four WM stages; baseline, encoding, retention, or retrieval stage) in each frequency band (See Appendix B); however, these analyses did not reveal any group effects, and in fact, they did not pick up on the group difference in delta described above. Thus, it may be that more detailed analyses of WM tasks in the second-by-second level should be considered in future studies.

Another limitation of this study is the lack of a patient group that performs below healthy individuals. This would be recommended to address the question of whether our findings in delta represents a compensatory mechanism that allows preserved WM performance, or whether increased occipital delta during encoding is present regardless of performance. As with most WM studies, the majority of patients were treated with antipsychotic medication. We cannot at this time distinguish between effects related to medication or to the disorder. In conjunction with this limitation, the lack of real resting state measures does not allow for the distinction between task-related effects and effects related to SZ more generally. The presence of elevated delta across the task, including the pre-task baseline second, suggests that this effect could be interpreted as a boost in attentional or motivational processes that allows for successful WM performance in this group. Finally, we interpreted the reduction in power at Cz to be indicative of the visual nature of this task. However, it should also be noted that the data was referenced to an average reference. As the most central electrode, Cz is also the most likely to be slightly correlated with other electrodes. As such we cannot discount the possibility that the observed reductions in Cz are related to processing effects rather than the nature of the task. However, these effects are greatest when a small surface of

the head is covered or when the number of electrodes is small (32 electrodes and below) (Junghofer, Elbert, Tucker, & Braun, 1999).

In summary, this study adds to the sparse literature on high-performing schizophrenia patients on working memory tasks. We found that high-performing patients show equivalent activity in gamma, beta, alpha and theta bands. However, we found increased occipital delta activity during the encoding stage in this specific subset of patients, suggesting a compensatory strategy for memory performance in high functioning individuals with schizophrenia. It may be that high-performing individuals with schizophrenia are utilizing greater recruitment of the visual cortex to perform a task with visual, spatial, and verbal components.

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## 6. Appendices

### 6.1 Appendix A: Tables and Figures

		Group				Group Comparisons	p value	Cohen's D
		HC (n=9)		SZ (n=7)				
		Mean	S.D.	Mean	S.D.			
Six letter Set								
	Mean RT (ms)	1187.7	405.56	1104.83	345.10	0.43	0.672	0.23
	Accuracy (%)	74.48	31.91	79.91	14.84	-0.41	0.685	-0.22
	Hit Rate (%)	87.96	11.25	66.07	32.60	1.89	0.079	1.01
	Correct Reject (%)	72.11	35.19	93.75	6.25	-1.81 <sup>#</sup>	0.105	-1.23
One Letter Set								
	Mean RT (ms)	905.0	337.96	856.03	189.07	0.34	0.737	0.18
	Accuracy (%)	80.27	32.32	92.63	5.39	-0.99	0.337	-0.53
	Hit Rate (%)	93.63	7.23	91.07	7.31	0.70	0.495	0.37
	Correct Reject (%)	78.01	34.20	94.20	7.53	-1.38 <sup>#</sup>	0.202	-0.92

**Table 1.** Descriptive data and between-group comparisons of behavioral indices for modified Sternberg Task. All participants' task performance was assessed by reaction time, overall accuracy, and rates of hit and correct rejection in one and six letter set conditions. Two-tailed independent-samples t -tests with an alpha level of 0.05 were performed to investigate performance differences between groups. No group differences were found.

<sup>#</sup> adjusted degrees of freedom used (*df* six correct reject = 8.64; *df* one correct reject = 8.98)

	Frequency Band				
	Gamma	Beta	Alpha	Theta	Delta#
Electrode	5.10*	4.39*	18.10***	17.06***	38.12***
Group	2.88	0.67	0.26	0.06	0.24
Group x Electrode	1.73	0.85	0.31	0.89	3.48*
Set Size	0.15	0.45	2.53	0.30	6.75*
Set Size x Electrode	0.97	1.37	1.90	1.90	0.42
Set Size x Group	0.18	0.40	0.03	1.64	3.89
Set Size x Group x Electrode	0.32	0.12	0.46	1.10	2.32
Second	3.07	3.50*	3.43	2.90	20.66***
Second x Electrode	2.25	2.25	2.92*	1.70	3.88**
Second x Group	1.01	1.06	0.13	0.68	3.08
Second x Set Size	3.26*	3.50*	2.30	2.00	9.52***
Second x Electrode x Group	0.56	0.67	1.11	2.03	2.81*
Second x Group x Set Size	0.92	1.77	0.64	1.08	0.96
Second x Electrode x Set Size	1.22	1.02	2.25	1.77	1.09
Second x Electrode x Group x Set Size	1.22	0.50	0.83	1.51	1.10

**Table 3.** Repeated measures ANOVA were performed separately for each frequency band. Statistics reported are F-ratios .

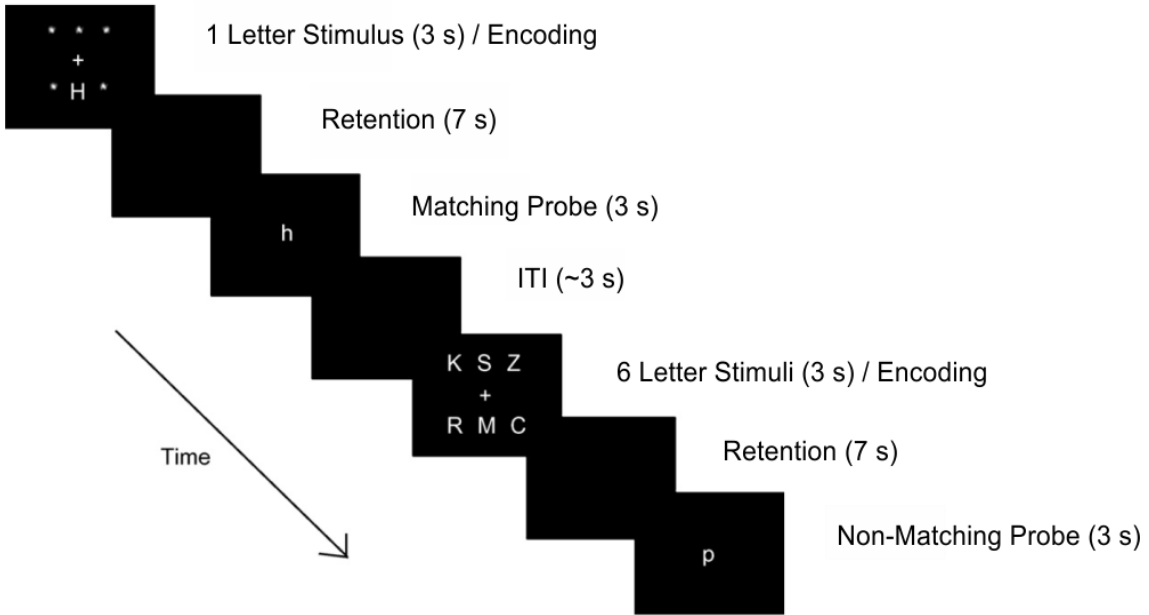
# The ANOVA in the delta band was performed on log-transformed scores and the following time points were excluded from analysis: Retention 2 & 3, Probe 1 & 3 due to violation of homogeneity.

\*  $p < 0.05$

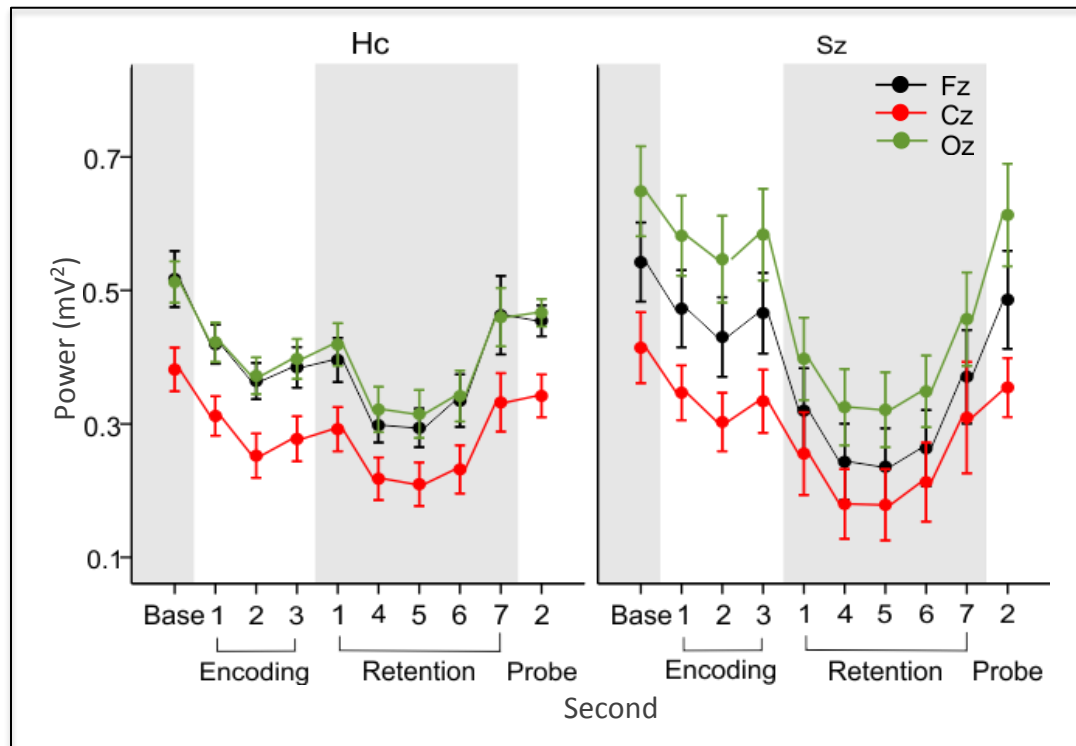
\*\*  $p < 0.01$

\*\*\*  $p < 0.001$

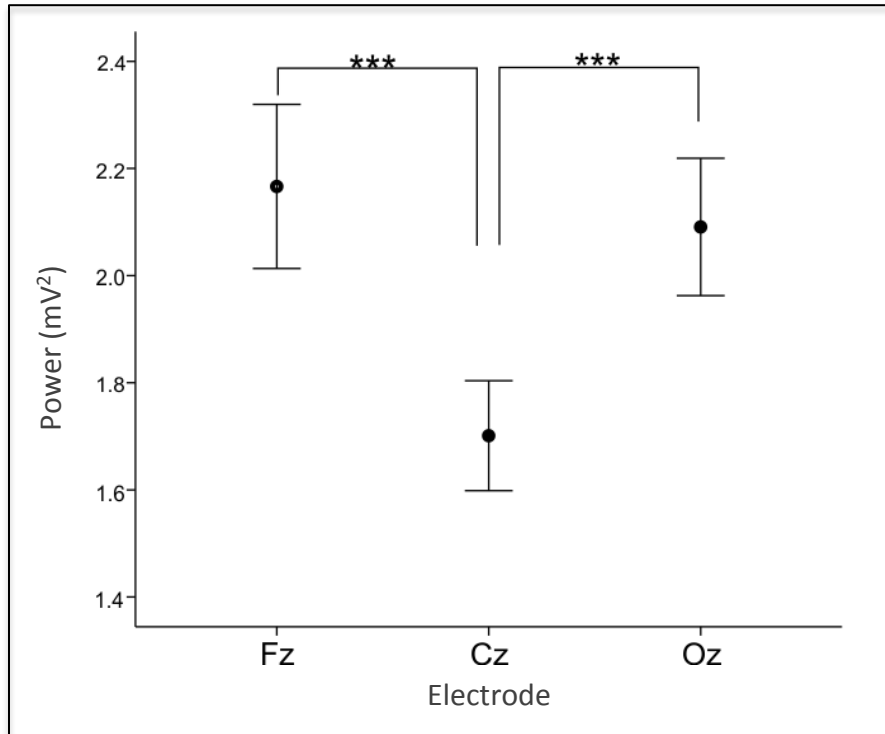




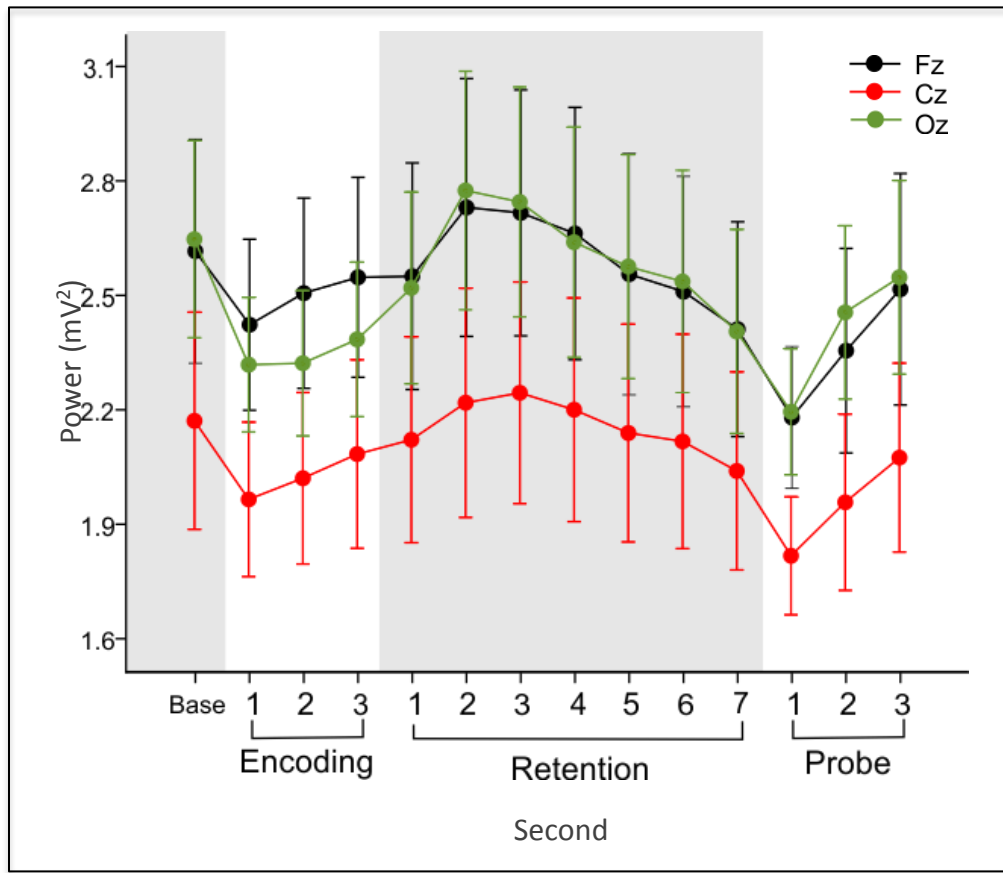
**Figure 1.** Schematic diagram of the Modified Sternberg Working Memory Task. Two trials are shown, the first with a set size of one and requiring a “yes” response, and the second with a set size of six and requiring a “no” response



**Figure 2.** Interaction of diagnosis x electrode x second in the delta band. Repeated-measures ANOVA was conducted on the delta band. Data was log-transformed and the following time points were excluded from analysis due to violation of homogeneity: retention 2 & 3, probe 1 & 3. Greenhouse-Geisser corrections were used to adjust degrees of freedom. There was a significant interaction of Diagnosis x Electrode x Second ( $F(2.34, 32.78) = 3.26, p = 0.044, \eta_p^2 = 0.19$ ). Patients showed greater delta power during the encoding stage of the task at Oz.

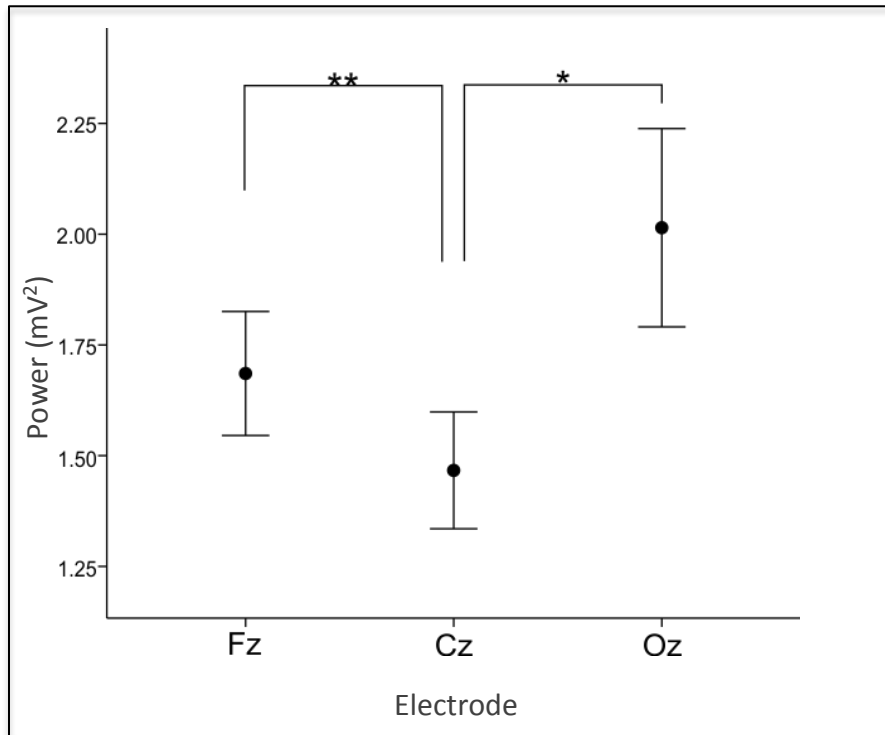


**Figure 3.** Main effect of electrode in the theta band. Repeated-measures ANOVA was conducted on the theta band. There was a significant main effect by electrode ( $F(1.63, 22.75) = 17.06, p < 0.001, \eta_p^2 = 0.55$ ). Cz had significantly lower power than Fz and Oz. Fz and Oz were not significantly different in power. No other effects were observed in the theta band.

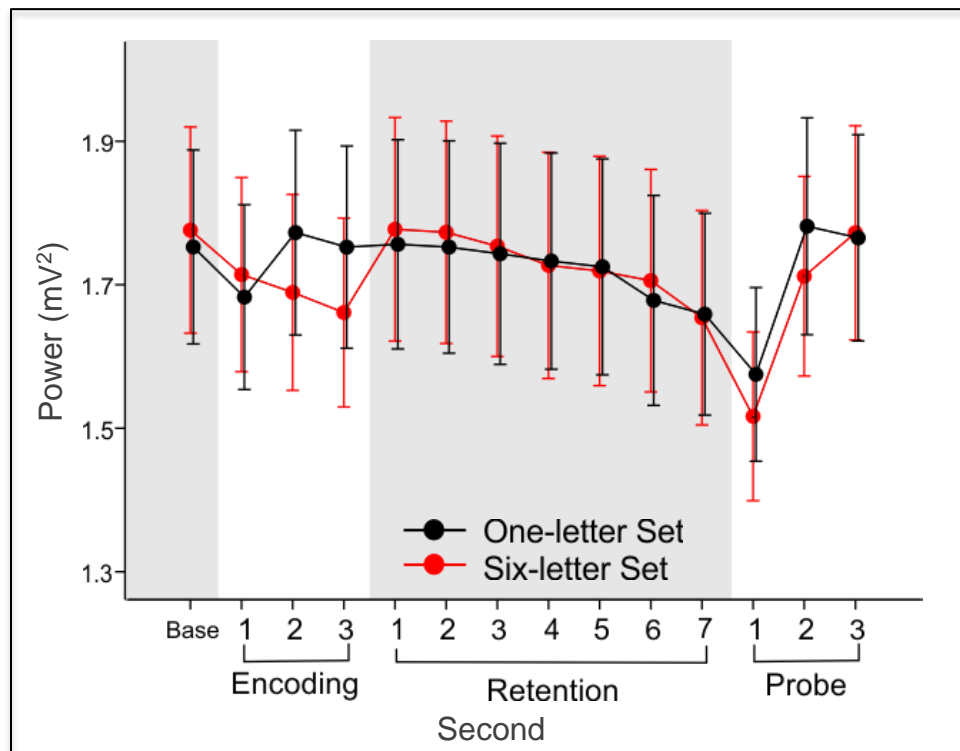


**Figure 4.** Interaction of electrode x second in the alpha band. A repeated-measures ANOVA was conducted on the alpha band. There was a significant electrode x second interaction ( $F(5.29, 74.01) = 2.92, p = 0.017, \eta_p^2 = 0.173$ ).

**Figure 5.** Repeated-measures ANOVA conducted on the beta band.

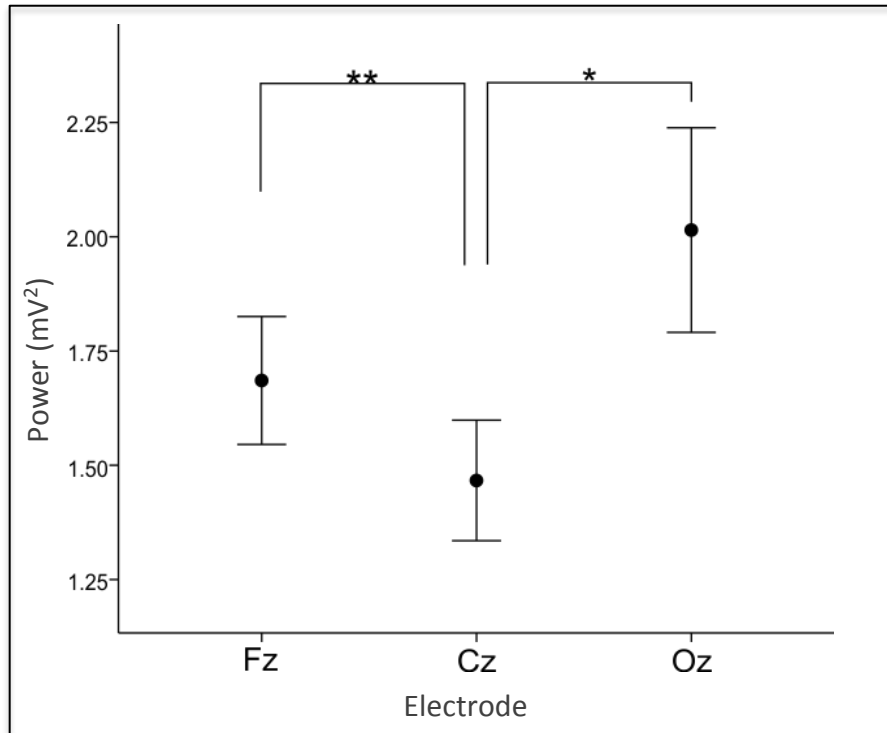


**A.** There was a significant main effect by electrode ( $F(1.13, 15.81) = 4.39, p = 0.049, \eta_p^2 = 0.24$ ). Cz had significantly lower power than Fz and Oz. Fz and Oz were not significantly different in power.

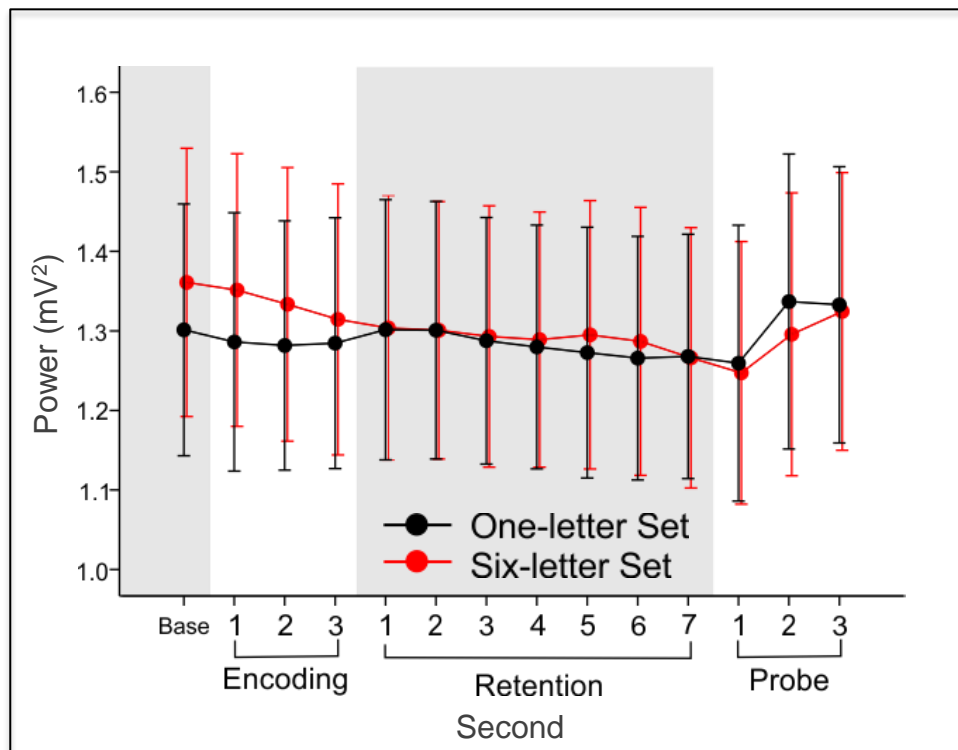


**B.** There was a set size x second interaction ( $F(3.51, 49.08) = 3.50, p = 0.017, \eta_p^2 = 0.20$ ), which revealed greater beta power in the one letter set at the end of encoding, reaching significance during the last second of encoding (paired-samples  $t = -2.46, df = 15, p = 0.027, d = 0.63$ ).

**Figure 6.** Repeated-measures ANOVA conducted on the gamma band.



**A.** There was a main effect of electrode ( $F(1.04, 14.54) = 5.110, p = .039, \eta_p^2 = 0.27$ ). Significantly higher power was observed in Oz than Fz and Cz. Fz and Cz were not significantly different in power.



**B.** There was a set size x second interaction ( $F(2.51, 35.15) = 3.26, p = 0.040, \eta_p^2 = 0.189$ ), which revealed greater power during baseline and encoding with increased difficulty, though paired samples t-tests show that these differences do not reach significance ( $p > 0.05$ ). There were no effects of group.



## 6.2 Appendix B: Supplemental Tables and Figures

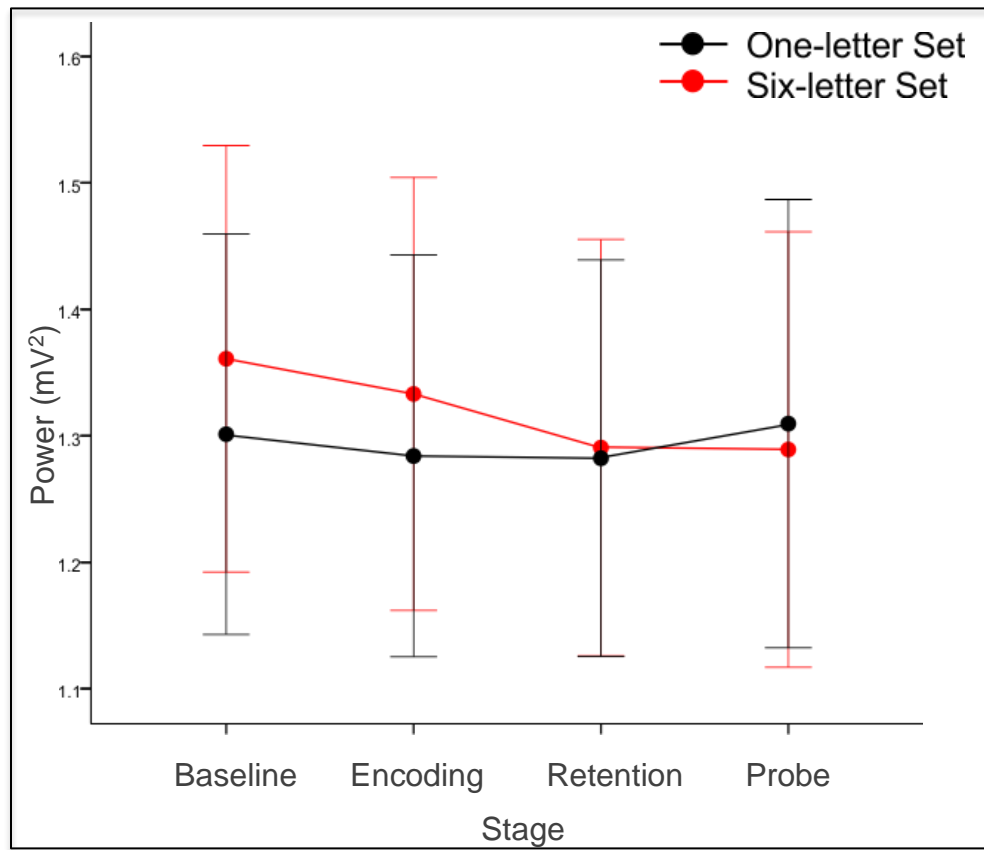
	Frequency Band				
	Gamma	Beta	Alpha	Theta	Delta#
Electrode	5.17*	4.40*	16.90***	19.26***	20.76***
Group	2.87	0.77	0.25	0.02	1.88
Group x Electrode	1.72	0.82	0.36	1.30	4.51*
Set Size	0.35	0.67	6.11*	1.84	6.91*
Set Size x Electrode	0.79	0.74	0.31	0.41	0.23
Set Size x Group	0.27	1.24	0.35	0.87	2.52
Set Size x Group x Electrode	0.31	0.10	0.19	0.43	1.32
Stage	3.50	1.72	4.11*	1.77	20.07***
Stage x Electrode	0.24	2.10	2.92*	2.61	5.43**
Stage x Group	0.43	1.25	0.06	0.78	2.71
Stage x Set Size	7.36*	3.76*	2.51	2.27	3.75*
Stage x Electrode x Group	0.56	0.40	0.78	1.97	3.22
Stage x Group x Set Size	2.03	3.02	0.86	1.55	0.56
Stage x Electrode x Set Size	1.99	0.85	3.45*	3.18*	0.69
Stage x Electrode x Group x Set Size	0.97	0.38	1.00	1.85	0.28

**Table 3.** Repeated measures ANOVA were performed separately for each frequency band. Statistics reported are F-ratios. # In the delta band the following violated the assumption of homogeneity of variance: At Cz six-letter set (baseline); at Oz one-letter set (baseline & encoding).

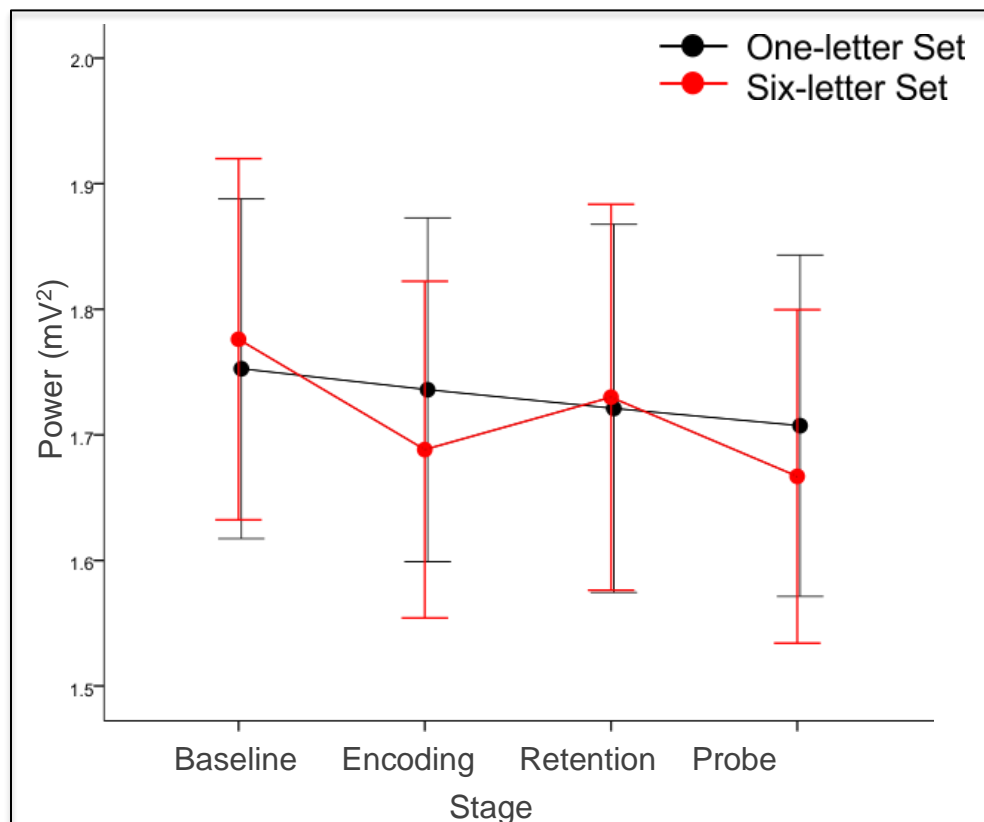
\*  $p < 0.05$

\*\*  $p < 0.01$

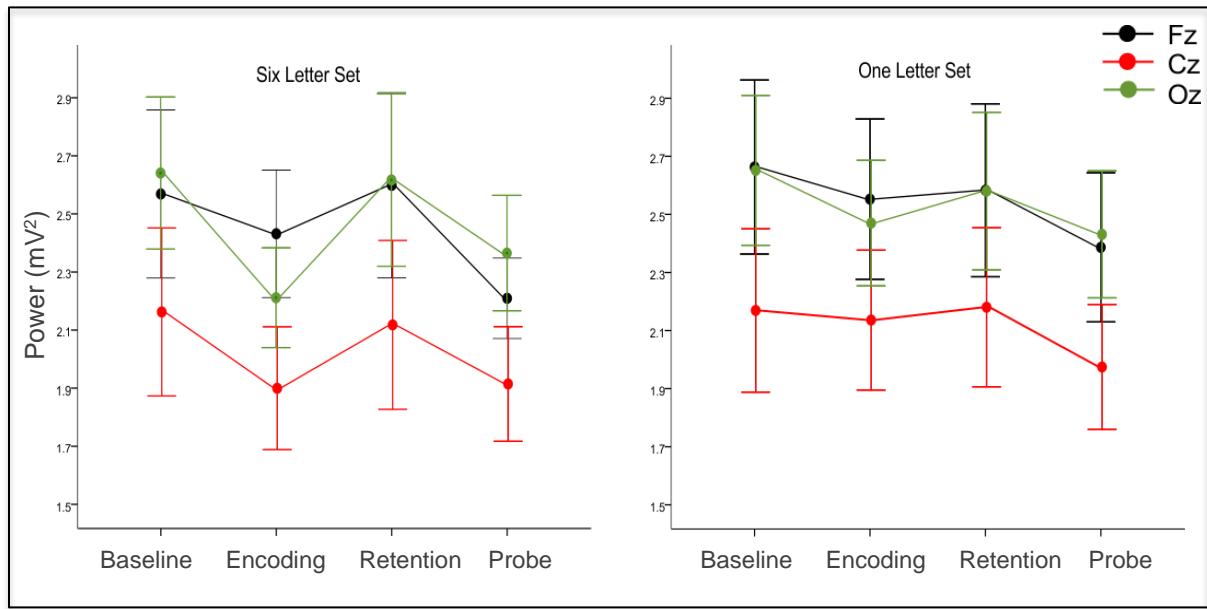
\*\*\*  $p < 0.001$



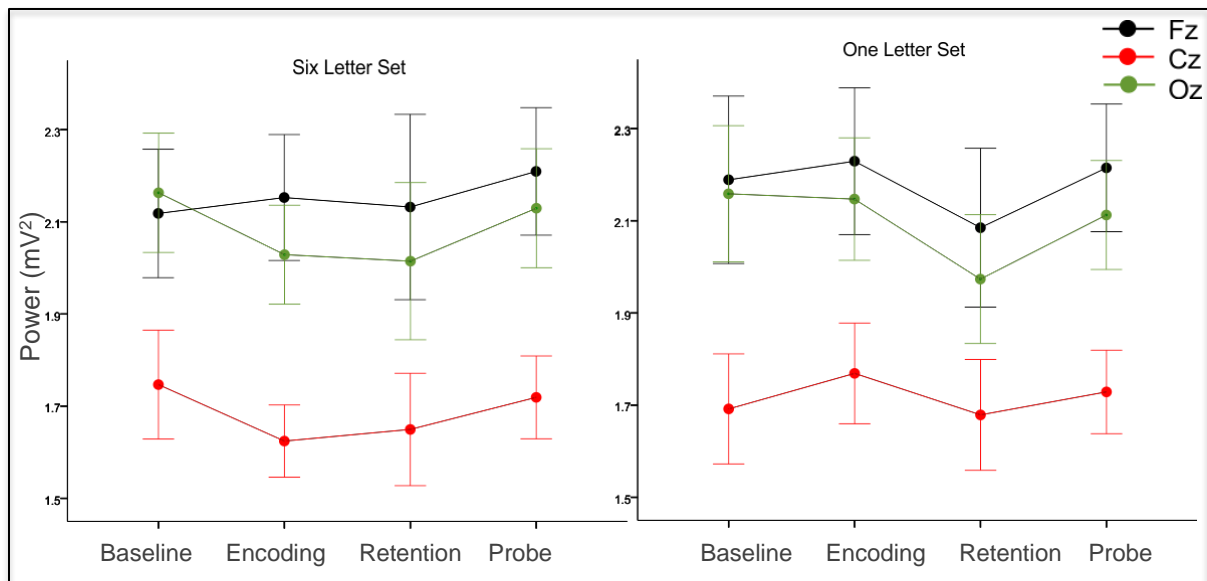
**Figure 8.** Interaction of set size x stage in the gamma band. A repeated-measures ANOVA was conducted on the gamma band. There was a significant set size x stage interaction such that greater power was observed in the baseline and encoding stages of the six letter set than the one letter set ( $F(2.377, 33.274) = 7.356$ ,  $p = 0.001$ ,  $\eta_p^2 = 0.344$ ). There were no effects of group.



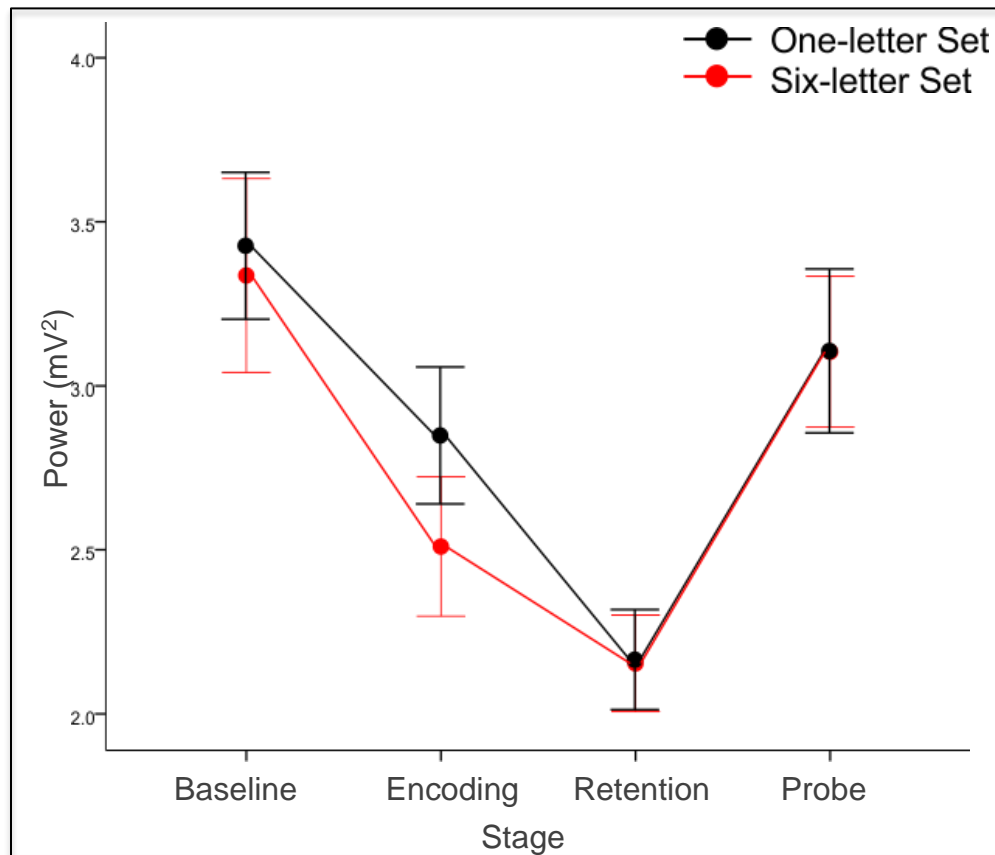
**Figure 9.** Interaction of set size x stage in the beta band. A repeated-measures ANOVA was conducted on the beta band. There was a significant set size x stage interaction ( $F(2.060, 28.836) = 3.760, p = 0.034, \eta_p^2 = 0.212$ ) such that there was greater power at the six letter set during the encoding stage. No group effects were observed.



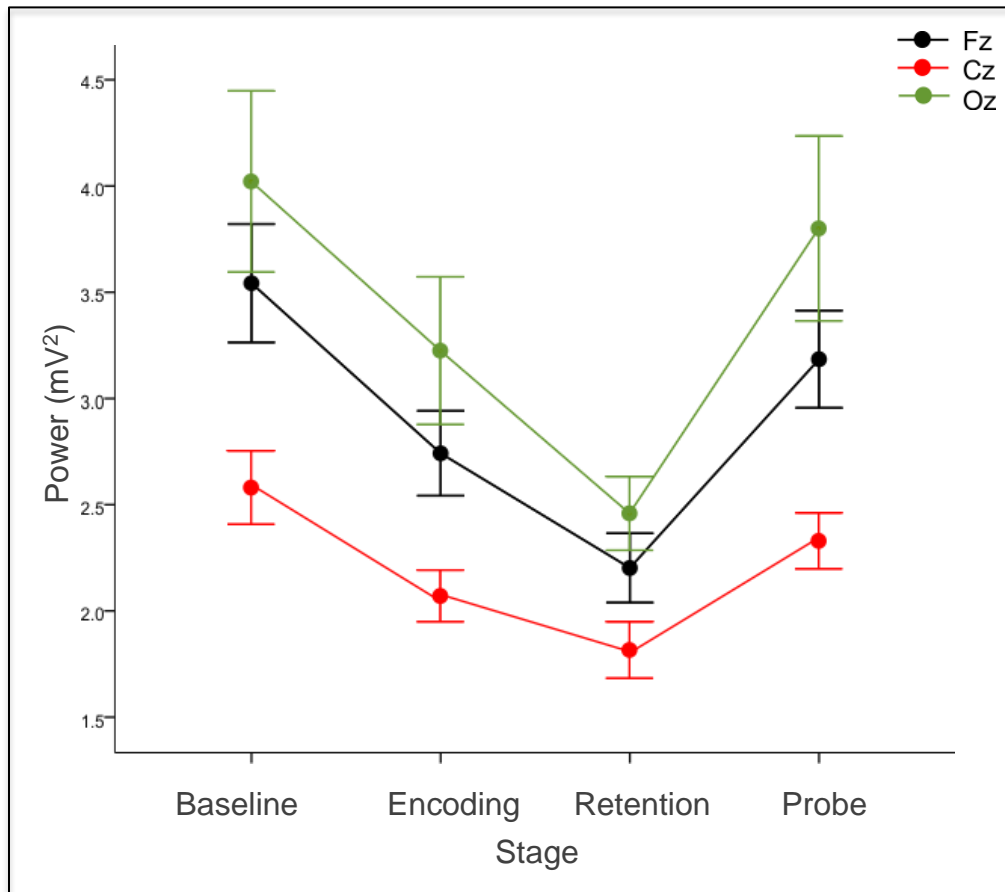
**Figure 10.** Interaction of electrode x set size x stage in the alpha band. A repeated-measures ANOVA was conducted on the alpha band. There was a significant electrode x set size x stage interaction ( $F(3.620, 50.679) = 3.453, p = 0.017, \eta_p^2 = 0.198$ ). No group effects were observed.



**Figure 11.** Interaction of electrode x set size x stage in the theta band. A repeated-measures ANOVA was conducted on the theta band. There was a significant electrode x set size x stage interaction ( $F(2.814, 39.392) = 3.180, p = 0.037, \eta_p^2 = 0.185$ ). No group effects were observed.



**Figure 12.** Interaction of set size x stage in the delta band. A repeated-measures ANOVA was conducted on the delta band. There was a significant set size x stage interaction ( $F(1.727, 24.173) = 3.748, p = 0.044, \eta_p^2 = 0.590$ ). No group effects were observed.



**Figure 13.** Interaction of electrode x stage in the delta band. A repeated-measures ANOVA was conducted on the delta band. There was a significant electrode x stage interaction ( $F(2.146, 30.047) = 5.432, p = 0.008, \eta_p^2 = 0.826$ ). No group effects were observed.