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Neural Connectivity during Multisensory Episodic Memory in Schizophrenia

A dissertation submitted in partial satisfaction of the

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in Psychology

By

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ABSTRACT OF THE DISSERTATION

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Evidence suggests that the core cognitive features of schizophrenia (SZ) include impairments in auditory and visual memory systems and that each of these deficits individually correlates with functional impairment. However, recent basic research suggests that numerous levels of cognitive processing, from perception to learning, optimally function under multisensory conditions, i.e., with multiple sensory modalities engaged at the same time by the same stimulus. Growing evidence points to the possibility that multisensory learning facilitates neuroplasticity beyond what is possible in unisensory modalities, and, what is more, multisensory information has increasingly been found to rely upon neural communication both within specific cortical modules and also across broad neural networks. In the area of SZ research, recent formulations of the disorder suggest that it is precisely in the domain of neural communication, or connectivity and plasticity, that patients are characteristically impaired. Yet, in the extant literature, one finds very few investigations of memory or other processes in which the more ecologically valid, multisensory stimuli were employed. Furthermore, while the

dysconnection model of SZ is promising theoretically and supported by neurological data, very few studies seek instantiations of these effects behaviorally or the emergent properties of their biomarkers. The current study examined SZ patients' capacity to benefit from multisensory encoding of auditory memoranda relative to healthy controls. It further sought to delineate the electrophysiological substrates predictive of behavioral performance within the framework of a neuroconnectivity-based model of episodic memory function. In addition to replicating pilot data findings of benefits to auditory recognition from multisensory encoding in controls, the data also demonstrated a capacity for SZ patients to capitalize upon this same process for improvement of auditory memory deficits. In keeping with the theoretical model, results revealed that recognition of unisensory-encoded sounds were predicted by low frequency connectivity across a broad, hippocampally-centered network. Auditory memory deficits in patients were statistically mediated by impairments in the operation of this system and several measures of SZ symptomatology were associated with those same biomarkers. Increases in memory for multisensory-encoded sounds appeared to be predicted by both low- and high-frequency posterior connectivity for which no group differences were found.

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PUBLICATIONS AND PRESENTATIONS

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Neural Connectivity during Multisensory Episodic Memory in Schizophrenia

1 INTRODUCTION

1.1 Neural dysconnectivity in schizophrenia

Our understanding of schizophrenia (SZ) etiology and pathogenesis has long been limited by a relative scarcity of empirically supported, theory-driven accounts of the disorder. However, recent conceptualization of the disorder as the manifestation of abnormalities in the connections between neurons and neuronal populations, resulting in disrupted coordination of cognitive processes, has garnered increasing support (Andreasen et al., 1999; Stephan et al., 2009), including: histological evidence of reduced dendritic arborization (Glantz & Lewis, 2000); large-scale reductions in gray matter (Zipursky et al., 1992); reduction of white matter integrity (Davis et al., 2003); disruptions in functional communication between task-relevant brain areas (McGuire & Frith, 1996; Ford et al., 2002); and aberrant function of neurotransmitter systems mediating synaptic plasticity (Stephan et al., 2006; Steullet et al., 2006).

Consistent with this model, SZ-related abnormalities have been documented in domains including early perceptual processes, as well as more complex, higher-order functions. Visual system findings in SZ include impaired visuo-spatial feature recognition (O'Donnell et al., 1996), impaired electrophysiological response to magnocellular-biased stimuli (Butler et al., 2001) and gestalt-based clusters of stimuli (Spencer et al., 2004), and visual masking deficits (Green et al., 2009). In the auditory modality, impaired speech perception (Bull & Venables, 1974), tone matching (Javitt et al., 2000), and top-down perceptual organization (Silverstein et al., 1996) have also been documented.

1.2 Multisensory episodic memory

Among findings of impaired higher-level processing in SZ, disruptions in declarative memory are prominent. Meta-analysis shows that memory impairments are severe, pervading most subtypes of memory in a manner that is stable, medication refractory, and generally unrelated to duration of illness (Aleman et al., 1999; Cirillo & Seidman, 2003). There is

considerable evidence of impaired short- and long-term declarative memory in individuals diagnosed with SZ (Cannon et al., 2000; van Erp et al., 2008). Patients are particularly impaired in the capacity to encode contextual information, including information associated incidentally with target memoranda, and/or in the capacity to retrieve target information with the help of contextual information (Aleman et al., 1999).

This ability to bind features together as a coherent object is critical to memory performance and therefore has been included as an integral part of numerous influential cognitive models of both short- and long-term memory (Buckner et al., 1999; Vogel et al., 2001; Wheeler & Treisman, 2002; Allen et al., 2006). The neural mechanisms supporting this feature binding process are open to further specification, but evidence suggests that a prefrontal-hippocampal circuit directs the binding of features processed in disparate sensory cortices into synchronously active, coherent, episodic representations (Wagner et al., 1998; Buckner et al., 1999). Importantly, these same anatomical loci, and their interconnecting pathways, are among the most affected neural structures in SZ patients (see Ranganath et al., 2008). Thus, declarative memory may require optimal orchestration of multiple scales of cortical communication – a process of neural integration which is degraded by the structural and functional abnormalities of SZ.

Of particular interest from this standpoint is memory for multisensory stimuli which, by its very nature, requires the binding of contextual features which are initially perceived and processed in disparate areas of the brain. Basic multisensory research reveals that not only does learning occur far more rapidly when memoranda are presented as part of a multisensory set, but that this multisensory facilitation involves storage and retrieval via networks connected across all relevant sensory cortices (see Shams & Seitz, 2008 for a review). Seitz and colleagues (2006) found that accuracy on a visual perceptual learning task not only increased more rapidly when stimuli were presented as part of a congruent bisensory pair (i.e., stimuli

matched in a way consistent with one's experience of sensory pairing in nature), but these performance gains were also more stable across several days.

While the neural mechanisms for this multisensory benefit (MSB) are not well-defined, several studies point to the action of a distributed sensory network enlisted at encoding which is reinstated in whole upon reactivation of its unisensory parts (also known as "redintegration", Horrowitz & Prytulak, 1969; Shams & Seitz, 2008; Hipp et al., 2011), thus creating a larger signal-to-noise ratio, or greater object fidelity, in recognition. This MSB is enhanced dramatically when the visual and audio components of the pair are semantically congruent (e.g., a picture of a bird presented with a chirping sound)(Lehmann & Murray, 2005).

1.3 Multisensory integration in schizophrenia

While the dysconnectivity conceptualization of SZ rests primarily on structural anatomical evidence, it requires greater elaboration with respect to its mechanisms and functional consequences. It may therefore be surprising that very little published research has examined multisensory processing in SZ, despite: 1) the great demands multisensory experience places on functional connectivity, 2) its more ecologically valid relation to real-world phenomena (Shams & Seitz, 2008), and 3) that SZ has been linked to basal deficits in the neural signal-to-noise ratio (Winterer et al., 2000) thought to be a key mechanism of MSB. Moreover, no prior study has addressed multisensory memory specifically.

1.3.1 Multisensory integration in schizophrenia: Behavioral data

The earliest behavioral investigations of multisensory integration in SZ focused specifically on audio-visual perceptions of speech (de Gelder et al., 2003). Here, study participants engaged in three experimental conditions: 1) listening to monosyllabic utterances played through speakers (e.g., "aba", "ada"); 2) viewing the lips of those speaking these utterances in the absence of sounds; and 3) listening to the utterances combined with similar but incongruently matched lips (e.g., the sound of "aba" paired with a silent video of "ada" or the sound of "ana" paired with a video of "ama"). In each task, the participant was instructed simply

to “repeat what the speaker said.” Results indicated that controls’ tendency in the audio-visual condition, relative to patients, was towards an increased visual-biasing of their report. That is, controls’ perception of the phoneme spoken conflated auditory information with that of lip-reading more frequently than did the patients, who relied more upon the audio information alone. The authors interpreted these findings as support for a reduced integration across different sensory modalities in patients.

A similar study performed by Ross and colleagues (2007), using more ecologically valid words rather than syllables, showed no benefit on the part of SZ patients to speech comprehension when audio streams were presented with congruent visual lip movement, a condition more conducive to task accuracy in controls, despite intact comprehension of speech alone. Later studies from de Gelder and colleagues demonstrated a similar deficit on the part of SZ patients in using the integration of facial and vocal cues for the perception of emotion (de Gelder et al., 2005; de Jong et al., 2009).

Recent work has further suggested impaired MSB in SZ in the form of slowed reaction time in a target identification task (Williams et al., 2010a). In healthy individuals, MSB is inferred in the form of faster target detection (i.e., decreased reaction time, Hershenson, 1962) when responding to an audio-visual pair than to either stimulus presented independently (e.g., a tone and an “X” presented visually). However, when performing the same task, patients were found to exhibit a decreased MSB in reaction time compared to healthy controls. Importantly, this impairment existed even when performance for unisensory conditions was controlled statistically. Furthermore, the impairment was found to be both greater for patients who have experienced hallucinations in more than one sensory modality and was also associated with negative symptom severity. Thus, reduced capacity for multisensory integration may be an important marker for unique elements of SZ symptomatology.

What is perhaps most compelling as evidence of impaired neuroconnectivity in the disorder are data in which patients’ performance on tasks thought to elicit neuroconnectivity-

based perceptual anomalies is actually more veridical than controls: namely, in multisensory illusions. In these tasks perceptual experience in one sensory modality is affected by task-irrelevant information from other sensory modalities. It is thought that projections between canonically unisensory cortices play a role in the interference of one sensory modality with the perceptual function of another (e.g., Bolognini et al., 2011). However, given that efficient multisensory integration requires precisely timed and directed neural coordination, it follows that SZ patients ought to exhibit reduced susceptibility to audio-visual illusions that result from automatic, temporally synchronized, multisensory integration.

For instance, in a weight-discrimination task, Williams and colleagues (2010b) found increased (i.e., more veridical) performance among SZ patients during conditions under which healthy individuals typically experience the "size-weight illusion." That is, when a participant is presented with two objects of identical mass but different sizes, he or she often reports that the smaller of the two items feels heavier when compared. In health, this effect is thought to reflect interplay between visual and sensorimotor cortices, the former contributing to the production of a sensorimotor expectation prior to information processing in the latter (Wolpert, 1997; Wolpert & Kawato, 1998). Thus, more accurate performance among patients for this task is interpreted as a breakdown of this communicative process.

1.3.2 Multisensory integration in schizophrenia: Physiological data

Only two studies have thus far appeared examining the physiological substrates of multisensory processing in SZ patients (Magnee et al., 2009; Szycik et al., 2009); an additional study is in preparation (Moran et al, in preparation). Seeking to uncover neural correlates of poor audiovisual integration of speech in SZ, Szycik and colleagues (2009) implemented fMRI recording during the presentation of speech (audio) plus either congruent or incongruent video (i.e., lips match the audio vs. mismatch) of a talking face. Imaging revealed a broadly distributed cluster of diverging activity (including the pars opercularis, middle frontal sulcus, and superior temporal gyrus of the right hemisphere, and the fusiform gyrus and nucleus accumbens

bilaterally) such that patients showed increased activation during the congruent, relative to incongruent, condition and controls showed the opposite pattern. The authors interpret this as impairment in right-hemisphere speech motor system contributing to deficits in audiovisual integration during speech perception.

Using ERP, Magnee et al. (2009) implemented a modified version of the traditional P50 paradigm to investigate the effects of multisensory stimuli on sensory gating in SZ. The auditory P50 paradigm involves presenting two identical stimuli ("S1" and "S2"), spaced 500 ms apart. By computing a ratio score of P50 to S2/S1, the magnitude of P50 suppression of S2 relative to S1 allows for inferences regarding the success of inhibitory processes, with better suppression/inhibition reflected by lower ratio scores. Impaired P50 suppression is well established among patients (Bramon, 2004; Heinrichs, 2004). Here, the authors altered this task by replacing S1 with a 15ms white oval visual stimulus followed by the traditional auditory S2. Using this modified S1 stimulus, thus creating an audiovisual version of the paradigm, they found impaired suppression of the P50 ERP in SZ for audiovisual conditions above and beyond impairments in the traditional paradigm.

Unfortunately, none of these physiological investigations includes the inferential support of a concurrent behavioral task, nor does either published study test specific, connectivity-based hypotheses crucial to contemporary conceptualization of the disorder. Most importantly, none of these studies examines physiological activity during each of the unisensory conditions separately, a contrast crucial for disambiguation of whether impairments in multisensory integration are independent of, or secondary to, impairments within a single modality. Indeed, basic research in the area of multisensory integration supports the idea that benefits in processing of multimodal stimuli are frequently super-additive, or above and beyond what would be expected through the addition of performance for each modality separately (i.e., multisensory processing can be more than the sum of its parts)(see Stein & Stanford, 2008). However, given the widespread deficits in low-level unisensory perceptual processes in SZ (see above), an

important step in the delineation of multisensory pathophysiology in biological studies will be in the demonstration of deficits in multisensory integration per se, beyond those of its constituent unisensory components.

In an unpublished study (Moran et al., in preparation), preliminary data from a small sample of subjects (N=16) reveals a trend for more veridical performance among patients on the "fusion" version of the sound-induced flash illusion. In this paradigm, participants sometimes report seeing a single flash of light when presented with two flashes simultaneous with one auditory beep, despite very high accuracy in detecting separate flashes when presented alone (Shams et al., 2005; Watkins et al., 2007; Wozny et al., 2008). This version of the task is contrasted to the original, "fission" version in which subjects report seeing two flashes when one flash is simultaneous with two beeps – an illusion found typically to be stronger than fusion (Shams et al., 2000; Wozny et al., 2008).

Though performing similarly to controls in fission-illusion conditions, early–onset SZ and schizoaffective patients exhibit a trend towards reduced susceptibility to the fusion-illusion condition. Furthermore, this increase in performance is associated with reduced gamma band (30-50hz) EEG coherence between midline occipital and parietal sites. Given gamma's putative role in sensory feature binding (Varela et al., 2001; Fries et al., 2007) and the use of cross-channel coherence as a measure of regional connectivity of the cortex (Roach & Mathalon, 2008), these findings may represent initial evidence of abnormal multisensory integration in SZ associated with a specific biological substrate; namely, the breakdown of coordinated neural communication across parietal-occipital cortex.

1.3.3 Multisensory integration in schizophrenia: Summary

Behavioral studies point to an impaired capacity for SZ patients to make use of the rich information accessible by multisensory presentation. Particularly convincing are studies revealing more veridical performance in patients using illusory paradigms thought to exploit the strong, automatic, normative connection between different sensory cortices. However, very few

of these studies have investigated biological mechanisms for these differences. Those that have used physiological measurement are suggestive of reduced or abnormal activity in basic multisensory neurocognitive processes, but have not been able to disentangle MSB deficits from impairments in unisensory processing.

Furthermore, perhaps surprisingly, no work to our knowledge has yet examined multisensory memory in SZ. Given the preponderance of gamma band activation concurrent with multisensory processing (Sakowitz et al., 2001; Senkowski et al., 2007,2008) and feature binding (Gray et al., 1989; Frien et al., 1994; Kreiter & Singer, 1996), and considering that it is the associative/feature binding element of memory that is thought to be most disrupted by SZ (see Ranganath et al., 2008, for a review), the simultaneous study of deficits in multisensory integration and in memory encoding and retrieval in SZ should shed light on the pathophysiology of memory dysfunction in SZ.

1.4 Electrophysiological model of episodic memory

A recently presented model for the physiological functioning of episodic memory, specified in terms of electrophysiological connectivity and synchrony, provides a framework against which experimental results in clinical and non-clinical populations may be interpreted (Nyhus & Curran, 2010). As an electrophysiological adaptation of Teyler and DiScenna's Hippocampal Memory Indexing Theory (1986), this model outlines circuitry between the hippocampus and disparate regions of sensory cortex, but further posits that they are linked via the individual and coupled activity of low- and high-frequency electrical oscillation. That is, in healthy individuals, representation and storage of the sensory building blocks of a memory are associated with gamma band (30-70 Hz) binding at distributed regions of the cortex. Within these areas, the process of long term potentiation (LTP) is uniquely supported by the time course of gamma activity which is suitable to the molecular requirements of spike-timing-dependent plasticity.

Within the hippocampus and posterior regions, the presence and strength of LTP is closely linked to, and possibly dependent upon, the presence of theta band (3-4 Hz) activity (Winson, 1978; Staubli & Xu, 1995; Olvera-Cortez et al., 2002). Regions of sensory cortex are then functionally linked by the hippocampus via theta band communication. The overarching orchestration of this process is achieved by the co-occurring function of each of these frequency bands in concert, and in particular by coupling of the two frequency bands through gamma activation at preferential moments of theta phase.

For later recollection of episodic memoranda, this same pattern of hippocampal-cortical communication is reinstated either by reactivation of the index-linked sensory cortices or by top-down signaling from the prefrontal cortex. The model is highly consistent with independently-gathered evidence of theta's role in hippocampal-to-sensory-cortex connectivity (von Stein & Sarnthein, 2000), including in the context of episodic memory (Klimesch, 1999), and also with evidence of gamma's role in perceptual and episodic feature binding (Varela et al., 2001; Fries et al., 2007) and coordination within highly local networks (von Stein & Sarnthein, 2000; Siegel et al., 2012).

1.5 The present study

The present study used a paradigm that would remedy the above-mentioned shortcomings in multisensory research in SZ through the study of multisensory episodic memory tested against the Nyhus & Curran model. It sought not only to measure behavioral effects during a task which requires extensive cross-modal neural communication, but also employed time-frequency analyses of the EEG, which is believed to be uniquely representative of fluctuations in functional connectivity supporting different aspects of task performance (Roach & Mathalon, 2008).

The processing of multisensory stimuli requires a heightened neural synchrony in order to support simultaneous activation of multiple sensory representations. This synchrony will be well captured by the extreme temporal sensitivity of EEG. For instance, while measures such

as cross-channel coherence (see row 3 of table 1, Electrophysiological Dependent Variables) directly examine the phase consistency between electrode pairs as a means to index regional connectivity of the cortex (Roach & Mathalon, 2008), spectral amplitude of single locations (see row 1 of table 1) is also thought to reflect communication between both local and long-range networks depending on the temporal precision and frequency of the activity (von Stein & Sarnthein, 2000; Siegel et al., 2012). Relevant to the binding of different stimuli within a particular sensory modality, SZ patients show dysregulation in high-frequency bands (see Uhlhaas & Singer, 2010, for a review), including both reduced gamma during an auditory steady-state task (Kwon et al., 1999) and reduced beta phase synchrony associated with deficits in gestalt image perception (Uhlhaas et al., 2006). In the low frequency ranges, memory-related processing abnormalities have been found including reductions in theta band activity during the performance of working memory tasks (Schmiedt et al., 2005).

1.5.1 The present study: The task and pilot data

This protocol was adapted from Murray, Foxe & Wylie (2005) to incorporate a test of episodic memory for unisensory (auditory) versus multisensory (audio-visual) stimuli. Work from the Murray group has shown enhanced memory for pictures presented as an audio-visual pair, but no studies have examined the effect of picture presentation on memory for audio stimuli. Thus, behavioral data were collected from a group of subjects recruited through the UCLA Introduction to Psychology Subject Pool (Moran et al., in preparation) in order to test both visual (i.e., comparable to Murray's design) and auditory (i.e., auditory recognition facilitated by pictures) versions of the task.

Interestingly, the data did not replicate the multisensory benefit of sound presentation for the recognition of either grayscale (N = 10) or color (N = 11) pictures. However, it showed large effect sizes in the improvement of recognition for sounds when presented with either grayscale (N = 10, Cohen's d = 0.77) or color pictures (N = 11, Cohen's d = 1.47; effect size calculations included correction for dependence between paired measures, Morris & DeShon, 2002). There

may be several reasons for the non-replication of findings using pictures as the primary memoranda, including both slight variations in visual stimuli (grayscale rather than pure black and white line drawings) and methodological changes to the protocol (e.g., requiring that all pictures included had at least the possibility of having an associated sound, excluding, e.g., vegetables). However, the present study opted to test only the auditory version of the task (i.e., sounds as primary memoranda) which was demonstrated the strongest MSB in these pilot analyses for comparison between SZ patients and controls.

1.5.2 The present study: Behavioral and electrophysiological predictions

First, in terms of the behavioral data, it was predicted that:

1. Although patients would show reduced memory for sounds compared with controls, they would also demonstrate a smaller MSB in memory performance (i.e., multi- relative to unisensory).

Second, it was expected that reduced episodic memory function would be associated with abnormalities in several spectral EEG markers in SZ patients. Theta band activity associated with memory encoding and indexing was measured at central and frontal sites where this signal has been found to be strongest (Klimesch et al., 1996; see row 1 of table 1). Thus, it was predicted that:

2. Reduced central and frontal theta power among patients serves as a marker of disruption in memory processes in general (across conditions).

Similarly, measures of gamma amplitude over more localized regions of sensory cortex would highlight feature binding demands, and quantification of the power-to-phase coupling of gamma to theta, respectively, would then yield insight into function of the organization of both large- and small-scale processes in concert (see row 4 of table 1). Given evidence of reductions in SZ patients' ability to utilize contextual information in the service of memory, it was predicted that:

3. Reduced event-related gamma power over task-modality-specific regions of cortex in patients relative to controls would result from an uncoupling of gamma amplitude from theta phase.

The unique examination of multisensory neural processing allowed for insight into connectivity during conditions requiring particularly intense demands in that domain - conditions which are more representative of real-world scenarios than the unisensory experience. Provided the evidence for the role of high frequency, beta (see Hipp et al., 2011) and gamma activity in multisensory integration in non-ill participants, it was expected that:

4. Patients would show reduced beta and gamma power and phase coherence between central, visual and auditory areas as a marker of impaired multisensory memory and communication between sensory cortices.

Similarly, in highlighting the benefit of multisensory integration to episodic memory, it was predicted that:

5. EEG beta and gamma power and phase coherence between these areas would correlate with behavioral MSB and account for group differences.

2 MATERIALS AND METHODS

2.1 Participants

Fifteen individuals diagnosed with DSM-IV schizophrenia or schizoaffective disorder-depressive type (14 schizophrenia and 1 schizoaffective) and 14 healthy controls participated in this study. While most were drawn from a pool maintained by the Consortium for Neuropsychiatric Phenomics (CNP) at UCLA (http://www.phenomics.ucla.edu, NIMH #: 5UL1DE019580-03), four controls responded to advertisements placed in the UCLA campus area. Use of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV; First et al., 1997) and the Family Interview for Genetic Studies (Maxwell, 1992) ensured that controls and their first-degree relatives were free of schizophrenia, or any other psychosis-spectrum disorder. No subject had been diagnosed with neurological disorders, failed to surpass the 8th grade (or

equivalent), or endorsed instances of substance abuse within the 3 months preceding assessment. Groups did not differ significantly in age (patient: M = 43.67, SD = 9.24; control: M = 36.93, SD = 12.65, $p > 0.1$) or gender (patient: 11 males, 4 females; control: 8 males, 6 females, Chi-square (n=29), = 0.84, $p > 0.1$).

Of the 15 SZ patients, 13 were receiving treatment using atypical (i.e., second-generation) antipsychotic medication and one with a traditional antipsychotic. Medication data was unavailable for one patient. Chlorpromazine equivalents were available for 12 patients, indicating an average Chlorpromazine equivalent of 359.5 mg (SD = 265.4; Woods, 2003). SZ patients also were assessed for psychotic symptomatology using the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984). The mean sum value of SAPS global scores (i.e., the sum of "Hallucinations," "Delusions," "Bizarre Behavior," "Thought Disorder," and "Inappropriate Affect" global scores) was 8.87 (SD = 3.5). The mean sum value of SANS global scores (i.e., the sum of "Flat Affect," "Alogia," "Avolition," "Anhedonia," and "Attention" global scores) was 11.56 (SD = 6.4). Clinical data were not available for two patients.

2.2 Task and procedure

A previous non-clinical episodic memory experiment (Moran et al., in preparation) revealed an accuracy advantage when sounds are learned as part of a multisensory set. To examine whether this effect holds true in SZ, this task was used in the present study of auditory versus visually-facilitated auditory recognition in patients (Figure 1).

In this task, participants heard a series of sounds of common objects, presented in a pseudorandom order, each of which were presented twice within this series. They were asked to identify whether each sound was novel or a repeat of an earlier sound. At initial presentation, half of the sounds were presented alone ("A" condition) while the other half were presented as a sound plus a congruent picture (e.g., a bird chirping coupled with a picture of a bird– "AV" condition). Repeated presentation of sounds always occurred as an auditory stimulus alone,

but corresponded to a stimulus which was presented either as a sound alone initially ("A-" condition) or an audio-visual pair initially ("A+" condition).

The participant's task was to identify with a button push, as quickly and accurately as possible, whether each sound presented was "new" or "old" (i.e., novel or repeated). Because all repeated stimuli were sounds alone, the picture stimuli were considered task-irrelevant and participants were instructed not to report on anything picture-related. No participants reported awareness of solely unisensory recognition trials.

2.4 Stimuli and presentation

Audio stimuli consisted of 168 meaningful sounds drawn from a collection of online databases and played on either side of a computer monitor. Visual stimuli were drawn from a set of 250 line drawings similar to those in Figure 1 ("Snodgrass-and-Vanderwart-Like Objects", Rossion & Pourtois, 2004). An additional 86 images were also drawn from online databases edited to be stylistically similar with Adobe Photoshop Elements, version 8.0 (Adobe Systems; Mountain View, CA). Sounds were presented through speakers placed on either side of a computer monitor approximately one meter away from participants. Images (in the case of AV pairs) were presented on the center of the monitor, an LCD computer screen, subtending about 5 deg in horizontal and vertical directions with participants. The sounds and pictures were played for 500ms, followed by an inter-trial interval (ITI) of between 1700-2000 ms. This ITI of 700 ms longer than the original Murray et al. task was used in order to provide a longer time window for event-related EEG required for the accurate estimation of low-frequency EEG activity. To minimize any possible item-specific effects, we randomly assigned each sound to either the A or AV condition, maintaining equal numbers of items from different object categories within each condition (e.g., tools, household objects, vehicles, animals, etc.).

Stimuli were presented in 4 blocks of 84 trials each with sounds repeated only once within each block, and the average number of stimuli between initial and repeated presentation of a stimulus was 17. This longer average number of intervening stimuli (relative to the original

Murray et al. task which used an average of 13) was employed as a means to avoid ceiling effects. All stimulus presentation was done using MATLAB's psychophysics toolbox (http://psychtoolbox.org), with calibration of audio and visual stimuli using an oscilloscope to ensure less than 5ms difference between onset of paired pictures and sounds.

2.5 Equipment and data pre-processing

Collection of psychophysiological data was done using a 64-channel BioSemi Active II system with ActiView V.2 software. Data were referenced to the nose, offline, and filtered from 1 to 100 Hz before all analyses. All data were analyzed using MATLAB (http://www.mathworks.com) and the EEGLAB toolbox (Delorme & Makeig, 2004). It was visually inspected for gross artifact as well as being subjected to Independent Component Analysis (ICA) for removal of eye-movement and blink artifact (Jung et al., 1997).

Time-frequency decompositions (TFD) were computed from 3 to 50 Hz for each encoding data epoch (i.e., initial stimulus exposure, conditions A and AV) from select electrode sites. Given previous work showing theta's strongest signal to be over central and frontal EEG sites (Klimesch et al., 1996), we selected Cz and AFz for TFD as well as C3 and POz to be representative of sensory modality-specific regions of cortex (Lenz et al., 2007; Osipova et al., 2006; see figure 2 for diagram of electrode locations on the scalp). TFDs included a wavelet-based, log-normalized comparison of pre-stimulus (baseline) spectral amplitude (drawn from a period of 250 ms pre-stimulus) with that of the 2000 ms post-stimulus period, i.e., event-related spectral perturbation (ERSP). Phase synchrony was also computed from these decompositions between electrode pairs selected for anatomical correspondence to the model of section 1.4. Additional TFDs were computed in which no baseline normalization was implemented in order to draw estimates of absolute power during the 250 ms pre-stimulus time window. Recent studies have shown heightened levels of both low and high frequency spectral activity in SZ patients – differences which, as has been shown for evoked gamma activity, may actually lead to spurious reports of decreased post-stimulus power in patients when using traditional

baseline-normalized methods (Winterer et al., 2000; Spencer, 2012). Therefore, this additional TFD was of particular importance for use both as a covariate for analysis of post-stimulus activity and for exploration of differences in tonic (i.e., non-event-related/non-phasic, pre-stimulus) spectral power between groups as well.

2.6 Analytic methods: Behavioral data

Analysis of behavioral data included measures of accuracy via recognition hit rates for both sounds that were presented alone (A-) and with a picture (A+) as dependent variables. MSB was measured as recognition hit rate in the A+ (i.e., multisensory) condition minus percent correct in the A- (i.e., unisensory) condition.

Thus, global analysis of differences in recognition and MSB involved the use of a repeated-measures ANOVA using group (SZ vs. control) as between-subject factor and condition (unisensory vs. multisensory) as a within-subject factor. A main effect of group was predicted such that SZ patients would show an overall reduction in memory across both conditions, consistent with past literature showing large and widespread memory deficits in this group. A group X condition interaction was also further anticipated such that controls would show larger increases in accuracy to A+ condition relative to A- condition (i.e., MSB) compared to patients. As exploratory measures, similar ANOVAs were conducted examining median reaction time and encoding hit rate as dependent variables as well.

In the event of uncovering differences in MSB, measures were planned to ensure that the influence of impairments in unimodal task performance on the multisensory task would be fully quantified by using hierarchical multiple regression analyses to examine group-wise differences in multisensory memory accuracy above and beyond the effects of unisensory accuracy. That is, regression equations were planned in which accuracy in the unisensory condition would predict accuracy in multisensory condition, followed by a test of r-squared change upon inclusion of the group factor in a subsequent step. Thus, the r-squared test of the resultant regression coefficient for the group factor would reveal the amount of variability in

accuracy for multisensory recognition accounted for by the group factor above and beyond that accounted for by unisensory performance. This approach yields greater sensitivity in measuring deficits of multisensory integration itself apart from the breakdown of task-primary sensory modalities.

Further correlations were used to investigate the hypothesis that reduced MSB is associated with increased levels of symptomatology, and hierarchical mediation analyses to examine whether reduced MSB is accounted for by disruptions of the time-frequency indices described below.

2.7 Analytic methods: Electrophysiological data

Table 1 outlines a summary of electrophysiological dependent variables, while section 1.5.2 above highlights specific predictions of the electrophysiological model. Using these variables, series of analyses directed specifically at testing the electrophysiological model of episodic memory posited in section 1.4 was designed. In particular, group differences in that model which account for impairments in patients' behavioral performance were examined.

Examination of ERSP and cross-channel coherence began with the selection of relevant time windows for further analyses. Here, a data-driven approach was implemented by drawing from times most predictive of behavioral recognition performance. Thus, for these TFDs, a series of plots were developed visualizing the magnitude of association between a given electrophysiology measure and behavioral performance, as a function of time. Each plot contained 318 correlations across time (each correlation of N=29) spanning from stimulus onset to 600ms post stimulus, wherein each correlation examined the relationship between approximately 1.9 ms of spectral power or coherence and global behavioral performance across the 29 subjects. This 600 ms window was selected in order to minimize the overall number of comparisons while maximizing focus on encoding period activity occurring prior to behavioral response.

Because of this high temporal resolution, and therefore large number of correlations, a standardized procedure for controlling false discovery rate (FDR) under conditions of non-independent tests, such as a time series, was implemented (Benjamini & Yekutieli, 2001). Using this method, common in fMRI methodology, adjusted p-values were examined dependent upon the standard specification of a false discovery rate (or q-value) of 0.05. To be additionally conservative, an additional requirement was specified that significant segments of the correlation time series contain at least 50 ms of sequential points. In the event that 75% or more of all points in the time series were significant, an effect was considered to be non-phasic, or tonic, and resulted in examination of pre-stimulus, baseline period activity for further analyses. In the event of multiple significant segments, but fewer than 75%, the longest contiguous set of points was selected in order to minimize collinearity in subsequent regression analyses.

Finally, windows of significant gamma activity were used to guide the investigation of theta and gamma band coupling at sites C3 and POz. Consistent with a growing body of methodology in this field (see Penny et al., 2008), raw EEG data from these channels was

decomposed using bandpass filters (4-8 Hz for theta and 30-50 Hz for gamma) and Hilbert transforms for extraction of phase angle and amplitude modulus. Using the circular statistic c-linear association, the theta phase angle signal was correlated with gamma amplitude modulus signal across the specified time window using the formula below (Zar, 2010), where θ_t denotes theta phase angle at timepoint t and X_t denotes gamma amplitude at time t, and:

1. r1= Pearson correlation (X_t, $\sin(\theta_t)$)
2. r2= Pearson correlation (X_t, $\cos(\theta_t)$)
3. r3= Pearson correlation ($\sin(\theta_t)$, $\cos(\theta_t)$)
4. C-linear Rho = square root ((r1^2 + r2^2 – 2*r2*r1*r3) / (1 – r3^2))

This method allows for the correlation between linear and circular (sometimes referred to as azimuthal) data through the transformation of circular data by its sin and cosine. These values were then further transformed into approximately Gaussian variables with Fisher's z-transformation in keeping with previous frequency coupling studies (Penny et al., 2008).

Once select windows of ERSP, cross-channel coherence, and estimates of cross frequency coupling were derived, they were entered into 2X2 repeated-measures ANOVAs using condition (unisensory vs. multisensory encoding) as a repeated-measure variable and group (control vs. SZ patient) as a between-subject variable. Estimates of tonic activity, such as pre-stimulus power, were examined for group differences using independent samples t-tests. In the event of group differences in ERSP in conjunction with group differences in pre-stimulus power for that same frequency band, pre-stimulus power was added to the ERSP ANOVA as a covariate. Following the predictions outlined in 1.4.2, the following variables were considered to be of particular relevance: theta power at sites Cz and AFz (prediction # 2); gamma power at sites C3 and POz (prediction #3); C-linear association between theta phase and gamma power at sites C3 and POz (prediction #3); and Cz-POz cross channel coherence in the theta, beta, and gamma bands (prediction #4). Variables for which a significant group difference was found

were also examined for correlation with measures of psychotic symptomatology among SZ patients.

To specifically examine these variables' relationship to behavioral performance, they were next entered into two series of hierarchical regression models. Whereas the first attempted to account for variance in recognition of sounds encoded alone (i..e, $A-_{hit\_rate}$, or basic unisensory memory), the second attempted to account for variance in MSB (i.e., $A+_{hit\_rate}$ minus $A-_{hit\_rate}$). Each model used group and encoding physiology as predictors. For both models, variables were entered stepwise into the regression model using the enter method, beginning with the dummy-coded group variable at step one (i.e., group difference, SZ = 0 and Control = 1, positive correlations or regression coefficients indicate higher values in controls). In step two, those physiological encoding variables from the list above were entered which were found to have both significant zero-order correlation with behavior (i.e., FDR corrected time windows of physiology) and a significant group difference. Thus, from step two it was possible to acquire regression parameters required for formal tests of statistical mediation under the hypothesis that physiology at encoding statistically mediates, or accounts for, group differences in behavior (Barron & Kenny, 1986). Finally, step three included encoding physiology found to have significant zero-order correlation with behavior but no group differences (i.e., processes predictive of behavioral performance but spared, or intact, in SZ patients).

3 RESULTS

3.1 Behavioral results

Looking first to behavioral effects on recognition hit rate (prediction #1), there were significant effects of group (patient vs. control), $F(1, 27) = 6.39$, $p < 0.05$, and condition (uni- vs. multisensory encoding), $F(1, 27) = 32.29$, $p < 0.001$, with no significant group by condition interaction, $F(1, 27) = 1.18$, $p = 0.29$ (figure 3). Thus, patients had poorer recognition performance than controls for all sounds, and both groups showed improvement in recognition of sounds encoded with a picture to equivalent degrees. Recognition hit rate for sounds

encoded without pictures (i.e., $A-_{\text{hit rate}}$) was negatively correlated with the global SANS measure of attention in patients, $r(n = 14) = -0.55$, $p < 0.05$, indicating an association between poorer memory and more severe attentional impairments among patients. MSB (i.e., $A+_{\text{hit rate}}$ minus $A-_{\text{hit rate}}$) was not associated with any clinical measure.

The analysis examining median reaction times revealed significantly higher reaction time among patients relative to controls, $F(1, 27) = 4.88$, $p < 0.05$, but no condition effect or interaction.

3.2 Electrophysiological results: Predictions #2 and #3, unisensory recognition

Consistent with predictions, the first FDR-corrected correlation plot (figure 4) indicated a significant period of association between Cz theta ERSP at encoding in A and $A-_{\text{hit rate}}$ from approximately 175 ms to 325 ms. The repeated-measure ANOVA showed that the averaged Cz theta power from this window was significantly lower in patients relative to controls, $F(1, 27) = 19.58$, $p < 0.001$, significantly increased during the encoding of AV (i.e., multisensory) relative to A (i.e., auditory alone) stimuli, $F(1, 27) = 12.18$, $p < 0.01$, but with a larger increase from A to AV in controls than in patients (i.e., group X condition interaction), $F(1, 27) = 5.08$, $p < 0.05$ (figure 5). Phasic Cz theta power appeared to be more sensitive to a group X condition interaction than the behavioral data.

However, an independent samples t-test suggested relatively heightened pre-stimulus theta power among patients compared to controls, $t(df = 27) = 2.60$, $p < 0.05$, though this activity did not significantly correlate with $A-_{\text{hit rate}}$, $p > 0.1$. Consequently, while adding pre-stimulus Cz theta power as a covariate to the above ANOVA did not impact either the condition, $F(1, 26) = 10.63$, $p < 0.01$, or group, $F(1, 26) = 10.69$, $p < 0.01$ effects, it did render the group X condition interaction insignificant, $F(1, 26) = 0.86$, $p = 0.36$. Thus, while group and condition effects in Cz theta ERSP appear to be robust to pre-stimulus activity, group differences in theta power MSB (i.e., A+ minus A-) may be attributable, at least in part, to heightened tonic theta in patients.

Phasic Cz theta power was also found to be significantly negatively correlated with several measures of psychotic symptomatology in patients, i.e., larger central theta deficits were predictive of more severe global ratings on SANS and SAPS scales of: flattened affect ($r(n = 14) = -0.55$, $p < 0.05$); alogia ($r(n = 14) = -0.67$, $p < 0.01$); anhedonia ($r(n = 14) = -0.74$, $p < 0.01$); attention ($r(n = 14) = -0.79$, $p < 0.01$); and delusions ($r(n = 13) = -0.71$, $p < 0.01$). Each association remained significant when controlling for (using partial correlations) the effect of pre-stimulus theta power.

No FDR-corrected window of AFz theta ERSP at encoding in A was found to correlate significantly with $A-_{\text{hit rate}}$. However, using the time window established for Cz theta ERSP above revealed a trend-level raw correlation between AFz theta from 175 to 325 ms and $A-_{\text{hit rate}}$, $r(n = 29) = .32$, $p = 0.09$. In addition, as with site Cz, there was significantly lower AFz theta in patients relative to controls, $F(1, 27) = 30.67$, $p < 0.001$, increases in theta between encoding of AV relative to A condition stimuli, $F(1, 27) = 15.85$, $p < 0.001$, and an interaction such that theta increase from AV relative to A was less prominent in patients relative to controls, $F(1, 27) = 10.78$, $p < 0.01$ (see figure 6).

Also as with Cz, pre-stimulus AFz theta power was heightened in SZ patients, $t(df = 27) = 2.94$, $p < 0.01$. When pre-stimulus theta was added as a covariate to the theta ERSP ANOVA, group and condition effects remained unaltered, and, in contrast to site Cz, the group by condition interaction remained significant at a trend level, $F(1, 26) = 2.93$, $p = 0.09$. Thus, patient deficits in both the production of frontal theta power and the modulation thereof in response to multisensory encoding conditions may be independent of heightened tonic theta activation.

No FDR-corrected window of phasic C3 gamma ERSP was found to correlate significantly with $A-_{\text{hit rate}}$ (figure 7). Nonetheless, though pre-stimulus C3 gamma power did not differ between groups, $p > 0.1$, this variable did correlate significantly with $A-_{\text{hit rate}}$, $r (n = 29) = 0.55$, $p < 0.01$. This suggests not only that unisensory recognition appears to be predicted by

pre-stimulus gamma band power, but that this effect is of a non-phasic, tonic nature, and that this process appears to be intact in SZ patients.

Using the pre-stimulus time window found previously to be predictive of performance, an independent samples t-test did not uncover a group difference between measures of theta-gamma coupling (i.e., c-linear association) at site C3, nor did these values correlate with $A-_{hit\ rate}$, p's > 0.1. However, the average c-linear association across groups was of moderate to large effect size (Patient: M = 0.51, SD = 0.02; Control: M = 0.50, SD = 0.02) suggesting a possible relationship between pre-stimulus theta phase and pre-stimulus gamma amplitude at site C3. As a follow-up to this, there was a significant increase in theta-gamma coupling (c-linear association) between the baseline period and the encoding period found significant at Cz, 175 to 325 ms, $F(1, 27) = 831.0$, $p < 0.001$ (Patient: M = 0.67, SD = 0.02; Control: M = 0.67, SD = 0.03). However, it may be the case that a difference in this value could result purely from the number of time points used for calculation of the estimate, with larger numbers of points leading to reduced estimates of c-linear association. Indeed, when the baseline window itself was expanded to included 450 ms prior to stimulus onset, rather than 250 ms, c-linear association was reduced to an average of 0.39 across groups. Thus, a difference of 250 ms used for baseline calculation versus 150 used for the post-stimulus time point may account for the highly significant effect of time point above.

3.3 Electrophysiological results: Unisensory recognition regression model

Table 2 summarizes zero-order correlations between each significant variable of section 3.2 and $A-_{hit\ rate}$. Following the above, a hierarchical regression model was developed attempting to 1): predict unisensory recognition performance from Cz theta ERSP at encoding and baseline C3 gamma power, and 2) test for mediation of group differences in performance by variability in Cz theta ERSP (having been shown to also be reduced in SZ patients). Table 3 summarizes the raw regression coefficients for each variable and step of this model. In step

one, the dummy-coded variable for group membership replicated the above group difference in performance, yielding a significant model, $F(1, 27) = 5.53$, $p < 0.05$, with $R^2 = 0.17$.

In step two, Cz theta ERSP (175 to 325 ms) was added to the model which resulted in a significant increase in model fit, F change $(1, 26) = 6.34$, $p < 0.05$, and a new $R^2 = 0.33$. Importantly, it was noted that upon entering Cz theta ERSP, the group effect was no longer significant while the relationship between theta and recognition maintained significance indicating one of the necessary conditions of statistical mediation had been met (table 2). In order to complete the test for statistical mediation, under the hypothesis that the relationship between group and recognition can be accounted for by the indirect effect of central theta power, the following pieces of information were derived (Baron & Kenny, 1986): 1) raw regression coefficient for the association between group and theta power (coefficient = 0.978, standard error = 0.096), and 2) raw regression coefficient for the association between theta power and $A-_{\text{hit rate}}$ when group is also included in the model (coefficient = 0.09, standard error = 0.038). Using these coefficients, a Sobel test (Sobel, 1982; Baron and Kenny, 1986) indicated significant mediation, test statistic = 2.31, $p < 0.05$. Thus, the difference in auditory recognition performance between patients and controls appears to be accounted for by, or attributable to, deficits in the production of central theta power during a brief time window during stimulus encoding.

In step three, pre-stimulus C3 gamma power was added to the model, the variable having shown no group difference in prior analyses. This resulted in a significant increase in model fit, F change $(1, 25) = 11.25$, $p < 0.01$, and a final $R^2 = 0.54$. As shown in Table 3, though the group effect remained insignificant, both the coefficients for phasic central theta and baseline gamma power maintained significance suggesting that these variables each account for separate sources of variability in $A-_{\text{hit rate}}$ (i.e., they are not purely collinear).

3.4 Electrophysiological results: Predictions #3 and #4, multisensory benefit

Consistent with predictions, FDR-corrected correlation plots revealed significant association of the following encoding physiology variables in the AV condition with MSB (i.e., $A+_{\text{hit rate}}$ minus $A-_{\text{hit rate}}$): C3 beta ERSP (215 to 275 ms, 350 to 475 ms); Cz-POz theta coherence (>75% of epoch); and Cz-POz beta coherence (225 to 320 ms, 420 to 475 ms, 480 to 560 ms). Therefore, in keeping with the procedures outlined in section 2.7, the following variables were retained for further analysis: C3 beta ERSP (350 to 475 ms); Cz-POz baseline theta coherence; and Cz-POz beta coherence (225 to 320 ms; figures 8-10). Table 4 summarizes zero-order correlation between each of these variables and MSB. No FDR-corrected associations were found between the following encoding physiology (either pre- or post-stimulus) and MSB: C3 gamma ERSP; POz beta or gamma ERSP; Cz-POz gamma coherence. There were no group differences for these variables, nor was pre-stimulus theta-gamma coupling at site C3 (calculated in section 3.2) associated with MSB, p's > 0.1.

Repeated-measures ANOVAs for the significant variables above showed the following: larger decreases in C3 beta ERSP (350 to 475 ms) at AV compared to A encoding, $F(1, 27) = 5.14$, $p < 0.05$, but no group effect or interaction, p's > 0.1; significant increases in CzPOz beta coherence (225 to 320 ms) at AV compared to A encoding, $F(1, 27) = 12.03$, $p < 0.01$, but no group effect or interaction, p's > 0.1(figures 9 and 10); and no significant group difference in baseline CzPOz theta coherence, $p > 0.1$.

Though no significant FDR-corrected correlations were uncovered between phasic theta or gamma at POz and MSB as predicted, there were significant increases in POz theta during AV encoding for the time window found to be predictive of later recognition in Cz theta ERSP, 175 to 325 ms. However, this increase was present only for controls, i.e., a group by condition interaction, mirroring that found for Cz and AFz theta, $F(1, 27) = 8.09$, $p < 0.01$. Also as with Cz and AFz, patients were found to have overall reductions in POz theta, $F(1, 27) = 7.03$, $p < 0.05$ (figure 13). Unlike the Cz and AFz sites, there was no group difference in pre-stimulus theta

power, and the above group by condition interaction remained fully significant when controlling for this variable.

Looking at gamma ERSP for this same site and time window, there was a significant effect of condition unqualified by a group interaction. That is, both groups showed gamma decreases during A condition encoding relative to gamma increases during AV condition encoding, $F(1, 27) = 21.65$, $p < 0.001$ (figure 14).

3.5 Electrophysiological results: MSB regression model

Table 4 summarizes zero-order correlations between each FDR-corrected significant variable of section 3.4 and MSB. As was done in section 3.2, a regression model was developed attempting to predict behavioral performance from physiology, this time using MSB ($A+_{\text{hit rate}}$ minus $A-_{\text{hit rate}}$) as the dependent variable. However, because there was no significant group difference either in MSB or in any of the predictors, group was excluded from this model and each variable was entered in one step. As is summarized in Table 5, this model, including the encoding variables C3 beta ERSP (350 to 475 ms), baseline CzPOz theta coherence, and CzPOz beta coherence (225 to 320 ms), showed significant prediction of MSB, $F(1, 24) = 3.65$, $p < 0.05$, with $R^2 = 0.30$. Unlike the previous model, no regression coefficients of individual predictors was significantly associated with MSB above and beyond the effect of the other variables, though C3 beta ERSP showed trend-level effects ($B = 0.15$, Std. Error = 0.008, $p = 0.09$). This suggests that these variables are largely collinear except possibly for some unique variance described by C3 beta ERSP.

No variable was found to be significantly related to Chlorpromizine equivalent dosages of antipsychotic medication.

4 DISCUSSION

This study investigated recognition of sounds encoded both alone and in the presence of semantically-congruent pictures between SZ patients and healthy controls. It sought to delineate the electrophysiological substrates predictive of behavioral performance within the

framework of a neuroconnectivity-based model of episodic memory function. In addition to replicating pilot data findings of benefits to auditory recognition from multisensory encoding, the data also demonstrated a capacity for SZ patients to capitalize upon this same process for improvement of auditory memory deficits. Furthermore, results revealed theory-consistent biological predictors of sound recognition for both unisensory- and multisensory- encoded sounds and also of the former's impairment in SZ. Whereas recognition of unisensory-encoded sounds appeared to be predicted by connectivity across a broad, hippocampally-centered network which was impaired in SZ patients, increases in memory for multisensory-encoded sounds appeared to be predicted by posterior connectivity for which no group differences were found.

4.1 Auditory recognition and patient deficits

Consistent with previous research, SZ patients displayed significant impairments in the overall recognition of sounds (Aleman et al., 1999; Cirillo & Seidman, 2003). However, by examining this deficit alongside an emerging model for episodic memory in health, key areas of physiological dysregulation associated with, and indeed accounting for, behavioral performance were uncovered. Using tests of statistical mediation, this behavioral impairment was explained by deficiencies in theta power production at encoding both, 1) during a time window known to be sensitive to old/new effects both in the time-frequency domain (Klimesch et al., 1999; Klimesch et al., 2000) and in event-related potential (ERP) studies (i.e., the P200 and P300 ERPs; Curran & Dien, 2003), and 2) over a central topography consistent with hippocampal generation (Klimesch et al., 1999; Hanslmayr et al., 2011). Though other studies have localized theta generation to a number of additional sources including prefrontal cortex and anterior cingulate (Asada et al., 1999), it has not been in the context of a memory paradigm. Neither are those findings inconsistent with the existence of a broad, distributed theta network centered upon the hippocampus during memory encoding.

In cases of mediation, the relationship between two variables is shown to be attributable to the indirect effect of a third variable (i.e., the mediator). The mediator thus serves as a candidate mechanism for the process from which the relationship between independent and dependent variables emerges. Prior work has shown abnormal theta power among patients, both at rest and during working memory paradigms (Koenig et al., 2001; Schmiedt et al., 2005). However, this study is the first to provide a direct test of a mediation relationship between memory impairments in SZ and theta power.

Earlier research into the role of theta power provides a clear backdrop for insight into the nature of this mechanism. First, theta activity has been implicated in communication across relatively broad areas of cortex (von Stein & Sarnthein, 2000; Siegel et al., 2012), with frontal and central topographies showing strongest activation in the service of memory performance (Klimesch et al., 1996), both of which were impaired in patients in this study. Consistent with the model presented in section 1.4, the activity of frontal and central theta power associated with memory performance has been localized to medial temporal cortex/hippocampus in simultaneous EEG/fMRI research (Hanslmayr et al., 2011). Within the hippocampus, a growing body of studies in animals and humans suggests that it is theta-dependent neuronal firing which represents the temporal signature (or "indexing") of long-term potentiation (LTP), successful LTP being marked by theta's presence and its inhibition through pharmacological blockade of theta production (see Berry and Seager, 2001 for a review). Depending upon experience, postsynaptic neurons may fire along varying stages of an input signal's theta's phase cycle, with more experience marked by progressively earlier points of theta phase required for post-synaptic excitation (so called "phase precession," Axmacher et al., 2006). Returning to the present data, one could interpret reduced central theta along the lines of impairments in patients' capacity for time-ordered, hippocampal-theta-dependent LTP.

Beyond differentiating between groups, theta power deficits also appeared to be associated with a wide range of both positive and negative symptomatology. Though more

targeted studies will be required to determine the full significance of this finding, it begs the question of whether this impairment constitutes either a generalized marker of mental illness severity or a psychosis-specific biomarker. In either scenario, variability in this measure appeared to be closely related to illness severity. Furthermore, it was not found to be associated with antipsychotic dosage – an important finding given evidence of disruptions in memory associated with antipsychotic use (Castner et al., 2000). Thus, its use may be warranted as a monitor of illness progression or predictor of risk for the disorder.

The model in section 1.4 further specifies a role for the coordinated activity of hippocampal theta with cortically-distributed gamma activity in episodic memory. If theta oscillations are responsible for the temporal ordering of memory-related neuronal excitation, gamma band activity represents the distribution of sensory/perceptual feature processing and excitability itself, i.e., the perceptual referents of a memory index (Hanslmayr et al., 2009; Osipova et al., 2006). More broadly, gamma band activity has been associated with a wide range of perceptual, cognitive, and neural processes, including attention (Gruber et al., 1999; Jensen et al., 2007), object recognition (Gruber et al., 2002; Lenz et al., 2007), cortical excitability (Lakatos et al., 2005), and potentially consciousness (Llinas & Ribary, 1992). Interestingly, data from this study show correlation not between phasic changes in gamma band ERSP and memory, but pre-stimulus, baseline power, suggesting that it may be overall tonic levels of gamma activation, rather than change per se, which determines recognition of sounds. Although not what was predicted, this finding is in line with previous work showing effects of sustained gamma activity in the maintenance of responsive attention networks for performance, e.g., in visual search tasks (Ossandon et al., 2012) and bimodal reaction time paradigms (Kahlbrock et al., 2012). Additionally, in keeping with the above model, this may point to a benefit of temporal non-selectivity in ongoing perceptual processes which is ordered and prioritized through the top-down effect of temporally-coded theta band oscillations. Importantly, these data suggest that the auditory perceptual stages of memory encoding, reflected by

lateralized-central gamma band activity, in patients is intact (further discussion of this in section 4.3).

The model in 1.4 predicts that the mechanism by which theta and gamma oscillations coordinate is in the coupling of gamma amplitude with preferential moments of theta phase. While neither group differences in estimates of coupling between groups nor correlation with behavior were found, there were medium to large to effect sizes across groups for this measure, indicating a relationship between theta phase and gamma amplitude.

Importantly, this frequency-band coupling estimate appeared to be highly sensitive to the number of time points included for calculation, with larger numbers of data points yielding reduced measures of c-linear association. Given the novelty of this area of study, it is difficult to determine whether this phenomenon is biologically meaningful or mere statistical artifact. Support for the latter may be the lack of significant correlation with behavior, though lack of group differences in coupling metrics has recently been reported during the auditory steady-state paradigm (Kirihara et al., 2012). However, support for the former may actually be encapsulated by essential tenets of the model itself, which predicts that, by reason of theta phase precession, the coupling between theta phase and gamma amplitude would not constitute a static relationship (Nyhus & Curran, 2010). Rather, as experience modulates the points of theta phase preferred by gamma excitation, the coupling between the two would change over time. If so, this suggests that the coupling relationship between theta phase and gamma amplitude provide somewhat of a moving target, characterized by greater variability over longer windows of time. Indeed, the phenomenon may be ubiquitous, occurring both during pre- and post-stimulus time windows, with behavioral changes marked not by coupling itself but by qualitative dimensions of signal intermodulation. More research, including simulations and empirical studies, will be needed for clarification. For the present purposes, however, it is important to note that there was no evidence of group differences in this measure.

4.2 Multisensory benefit to recognition in controls and patients

Contrary to expectations, SZ patients showed unimpaired behavioral capacity for MSB as did controls. However, while behavioral results showed no group by condition interaction between recognition for sounds encoded with or without pictures, theta ERSP appeared to show greater sensitivity for such an effect reflected by blunted increases among patients, relative to controls, during the encoding of AV relative to A stimuli. In controls, the data show theta ERSP activation during unisensory encoding of sounds which was accentuated by the presence of a picture at both frontal and central topographies. At an occipital site, as might be expected, controls showed no fluctuation in theta ERSP in the absence of visual stimuli but increases during picture presentation. At each of these electrodes, significant effects were uncovered during a time window found to be associated with later recognition of sounds, though none correlated with MSB itself, perhaps implicating local theta power with memory-specific processing. Further, at each of these locations, patients showed diminished accentuation of theta ERSP during encoding of AV stimuli.

While this group by condition interaction may have been accounted for by heightened tonic theta power among patients at the central electrode site, the frontal theta interaction persisted when controlling for pre-stimulus theta power, at least at trend-level, while the occipital interaction retained full significance. Of itself, heightened tonic theta in patients has also been observed in the literature and may be a result of overall reductions in signal-to-noise ratio among schizophrenia patients (Winterer et al., 2000). Consistent with heightened pre-stimulus theta in the central and frontal, but not occipital site, this may be suggestive of overall decreased signal-to-noise ratio in the process of hippocampal indexing.

Regardless, that patients showed unimpaired MSB at the behavioral level despite physiological abnormalities in AV encoding will require further elucidation. On the one hand, this distinction may have resulted from less restricted range in the continuous measurement of electrophysiology relative to the coarser averaging of binary “old” versus “new” responses. Thus, on the level of measurement sensitivity, encoding physiology may simply have been more

powerful for the detection of an interaction than behavior. Similarly, “old/new” tests of recognition may rely more heavily upon familiarity-based- as opposed to recollection-based-processing (i.e., “know” vs. “remember”, respectively; Tulving, 1985). That the latter has been shown to be more sensitive in discrimination between SZ patients and controls could point to the presence of a group by condition behavioral interaction if testing conscious recall (Huron et al., 1995).

On the other hand, this discrepancy may suggest the possibility of a compensatory mechanism. While not in a position to definitively specify this mechanism, the present results nonetheless highlight candidates in showing the spared functioning among patients in several encoding physiological variables while pictures were presented with the sounds. Consistent with connectivity-based accounts of multisensory interaction, this study found evidence for the recruitment of occipital visual systems during the encoding of visually-augmented audio stimuli in both groups. Over the occipital region, in controls, the data confirmed hypothesized increases in event-related theta and gamma activity during the window of encoding found relevant to unisensory recognition. As expected, this increase was present during the AV condition alone, when pictures were present, whereas theta band stability and gamma band suppression were present during in the absence of pictures. Further, though patients showed impairments in production of event related theta power in this region, their production of gamma ERSP was intact. Looking to the model in 1.4, this may represent unimpaired sensory or perceptual feature binding in visual cortex contributing to the encoding of a distributed memory trace (Osipova et al., 2006).

Continuing with areas unaffected in patients, there were larger drops in beta power during the encoding of AV, relative to A, stimuli over a lateralized-central electrode. Beta decreases during memory formation have been reported from surface and intracranial EEG (Weiss & Rappelsberger, 2000; Sederberg et al., 2007; Hanslmayr et al., 2009) and have been shown to correspond to subsequent memory effects localizable to the left inferior prefrontal

cortex (PFC; Hanslmayr et al., 2011). This anatomical location, combined with an EEG study linking beta suppression to semantic encoding explicitly (Hanslmayr et al., 2009), supports an interpretation of this effect as a result of additive semantic richness derived from the coupling of sounds and pictures. Curiously, the present data also show a positive correlation between beta amplitude within AV condition encoding and MSB (i.e., smaller beta decreases associated with greater MSB). Though difficult to interpret, one might suggest the possibility of a degree of independence between semantic and multisensory processes which are subservient to memory functioning. If prefrontal beta suppression supports the processing of higher-order semantic features of a memory trace, it may be that an overlapping system, functioning along the same frequency band but from separate generators, supports the integration of information across multiple sensory modalities.

If independent processes at different levels of cognition are at play, one might expect to find further evidence of positive associations between sensory/perceptually-relevant beta signals and MSB. Returning to the present data, it was found that central-to-posterior beta coherence does indeed positively predict MSB. Similarly, Hipp and colleagues (2010) show the emergence of large-scale synchronization of cortical networks in the beta range predicting the integration of ambiguous audio and visual stimuli at the level of subject's perception. Anticipating the topography of the present results, synchronization in that study spanned a broad fronto-parieto-occipital network. Of particular relevance to the present study, Hipp and colleagues' data reveal a dissociation between long-range synchronization of beta oscillations and local beta power. That is, accompanying heightened long-range beta synchronization was significant suppression of localized measurements of beta power. Other studies have since replicated similar dissociations between local power and large-scale coherence, and it has been suggested that phase synchronization between populations of neurons, marked by coherence, may represent altogether different cognitive processes from the activity, or power, of the constituent, local populations themselves (Siegel et al., 2012). This finding lends additional

credence to the notion of multiple layers of spectral functioning, and may help to explain larger beta decreases during AV encoding but positive correlation between beta amplitude and MSB found in this study.

This dissociation may also lend itself to understanding the pattern of coherence between central and occipital theta oscillations which was positively associated with MSB. While local measurements of theta power across frontal, central, and occipital regions were reduced among patients, there was no group difference in production of central-occipital theta phase coherence predictive of MSB, also behaviorally unimpaired in patients. Granting the possibility of independence between the two, this initially surprising discrepancy may actually correspond to the impairment of functionally-specific connectivity in one domain versus intact connectivity in another. For instance, if reduced theta amplitude corresponds to decreased signal-to-noise in hippocampal indexing, impaired communication represented by localized theta activity within a broad cortical network may correspond to disruptions in memory-specific functioning. That central-occipital theta coherence predicted MSB, and was instead unimpaired in patients, may implicate this level of phase-synchronized communication specifically with the binding of multiple sensory signals perceptually. Furthermore, that theta coherence predictive of MSB appeared to be ubiquitous across time windows, or tonic, may support the plausibility of its overarching synchronization in the service of multisensory integration despite phasic, local impairments in memory-specific processing. Figure 15 provides a graphical representation of this possibility, where ongoing phase coherence represents the activity of perceptual multisensory processing and changes in localized amplitude, circled in red, represents memory-specific processing.

4.3 Summary: Implications for SZ pathophysiology and treatment

The term “schizophrenia” was originally coined as a representation of the behavioral and cognitive disjointedness (i.e., “schisms”) observed in patients suffering from the disorder (Blueler, 1911). Though not based on any directly neurological research, this observation

foreshadowed the modern conceptualization of SZ as a disorder of neural dysconnectivity. While the results of the present study support the dysconnectivity model of SZ, they also reflect a view of this model whereby the pattern of that dysconnectivity requires more subtle and nuanced specification than the widespread mental fragmentation originally suggested by Bleuler. Indeed, as Stephan and colleagues have argued (2006; 2009), use of the term "dysconnectivity" rather than "disconnectivity" has been deliberate in order to emphasize abnormal ("dys," meaning bad or ill) rather than necessarily reduced ("dis," meaning apart) connectivity. Though the Bleulerian notion of fragmented structural connections might be one example of this phenomenon, equally possible could be the presence of either altered structural connections or qualitative abnormalities in the functional properties (e.g., synaptic transmission) of those connections (Stephan et al., 2006). Thus, continued investigations of dysconnectivity in SZ may require equal focus upon reduced, altered, and normative patterns of neural connectivity for most accurate specification of the model. Furthermore, the results of the present study, combined with recent findings about the multiplicity of cognitive processes within ostensibly singular brain anatomy, may require the search for task-specific patterns of connectivity or dysconnectivity as well.

Turning first to neuro-connective reductions, the present study revealed significant impairment in the recognition of sounds among patients accompanied by impaired frontal, central, and occipital production of theta power during a mid-latency time window of encoding. Anatomically, this disruption may best be understood within the context of dysconnectivity in the function of a large, hippocampally-centered network, specifically in its capacity for time-ordered indexing of distributed cortical sensory inputs. It is consistent with work showing volumetric and functional deficits in the hippocampus in SZ (see Harrison, 2004 for a review) and known impairments in structural and functional connectivity across fronto-temporal networks of patients (Friston & Frith, 1995; Fletcher et al., 1999; Wolf et al., 2007). This study showed theta power to be associated not only with group status, but also with a range of different measures of

positive and negative symptomatology within patients. In addition to marking its potential for use as a biomarker or as a monitor of illness risk or progression, this finding may also be reflective of fundamental characteristics of SZ pathophysiology.

Interestingly, activity in the gamma band, hypothesized by the model of episodic memory described in section 1.4 to contribute to recognition, was found to be intact in patients. Neither baseline central gamma, uniquely predictive of later recognition, nor event-related occipital gamma increases during the presentation of pictures differed between groups. Putting these findings together may point to: 1) disruptions in communication between the hippocampal index and its distributed sensory referents, but 2) intact distributed cortical excitability required for the perceptual processing of the sensory referents themselves achieved through high frequency activation.

Complementarily, one might interpret this constellation within the context of abnormalities in the "top-down" organization or connectivity of sensory inputs (an example of task- or process-specific dysconnectivity) but relatively intact "bottom-up" connectivity associated with the initial perceptual processing of auditory stimuli (Kinchla & Wolf, 1979). For the purposes of these data, "bottom-up" is taken to refer to neural processing responding to lower-order stimuli characteristics (the number of which, as a preview of later discussion, presumably increases upon addition of extramodal stimuli) in contrast to higher-order organizational principles (such as temporal ordering). This view is consistent with findings of impaired top-down organization of auditory memoranda in SZ (Silverstein et al., 1996) and with the role of sustained gamma band activity, here unaffected in patients, in bottom-up control of attentional and perceptual resources (Buschman & Miller, 2007; Ossandon et al., 2012). Further support for this interpretation may be found in this study's regression model for unisensory recognition, in which central theta ERSP at encoding and sustained gamma power each described unique, non-shared pools of variance in their prediction of later recognition of sounds.

Given the significant attention paid to gamma deficits among SZ patients in the literature (e.g., Kwon et al., 1999; Gallinat et al., 2004; Hong et al., 2004), unimpaired gamma in the current study may seem surprising at first. However, recent work from Spencer (2012) has called into question the expectation of deficits in that range. First, biasing of gamma measurements resulting from common baseline-normalization methods may contribute to underestimations of gamma activation in patients, particularly given observations of higher pre-stimulus gamma levels in that group. Second, the prominent neurotransmitter theory upon which many gamma predictions rest states that N-methyl-D-aspartate (NMDA) receptor hypofunction reduces the excitation of parvalbumin-expressing, fast-spiking inhibitory interneurons, postulated to be chief regulators of cortical gamma oscillations (Traub et al., 2003; Sohal et al., 2009; Lewis et al., 2011). Therefore, rather than expecting gamma deficits among patients, down-regulation of inhibitory interneurons ought actually to be reflected by increased gamma band activity. Thus, finding no reductions in patient gamma is perhaps more consistent with extant theory and data. That patients did not show heightened baseline activity in this band may actually reflect equalization from increased sustained gamma among controls due to the attentional demands of a quickly-paced recognition task and attentional symptomatology among patients. Nonetheless, normality or even hyper-function of distributed, sensory cortical excitability may be a candidate mechanism for SZ patients' capacity to improve upon auditory recognition deficits through multisensory encoding.

Contrary to the small body of work showing reduced multisensory integration in SZ (see section 1.3), this study found behaviorally spared measures of MSB – that is, both controls and patients showed improved auditory recognition when sounds were encoded with a semantically-congruent picture. Physiologically, however, while controls exhibited an accentuation of frontal, central, and occipital theta power during sound encoding when pictures were present, patients did not. As discussed in section 4.2, there may be several explanations for this discrepancy, including the relative sensitivity of physiological versus behavioral measures of "old/new"

recognition paradigms. However, these findings may also provide candidates for compensatory circuitry at play among patients for the processing of multisensory stimuli. For instance, patients displayed comparable levels of beta power production to controls, suppression of which was found previously to be linked to semantic processing (Hanslmayr et al., 2009) and here found also to be positively associated with MSB. Indeed, though not statistically significant, the direction of results in this signal show the possibility, perhaps with added statistical power, of even larger beta suppression among patients during AV encoding than controls, giving the appearance of a compensatory over-reliance on this process (interaction $p = 0.24$; figure 11). Regardless, localization of this signal to inferior PFC is consistent with neuroimaging evidence of spared functioning in that region among patients during processing of task-related contextual information (Barch et al., 2001; Barch et al., 2003). Thus, another candidate compensatory mechanism in future studies of MSB in SZ could be the capacity for patients to capitalize on the increase in semantic richness which results from combined inputs of multiple sensory sources.

This study also implicates posterior cross-channel phase synchronization, an index of connectivity between central and occipital regions, with MSB among controls and patients alike. This finding seems surprising in light of previous work documenting parieto-occipital and prefrontal-hippocampus connectivity deficits in the synchronization of BOLD signal activation among patients during working memory (Henseler et al., 2010). However, several important considerations might reconcile this with the present study and further delineate the dysconnectivity model of SZ. First, it has been demonstrated that the activation of local neuronal ensembles (such as that measured by fMRI or local EEG power) may be dissociable from the cognitive processes marked by phase-coherent measures of network electrophysiological synchronization (Hipp et al., 2011; Siegel et al., 2012). Thus, while many fMRI studies show widespread reductions in synchronized activation of the BOLD signal (Schlosser et al., 2003; Liang et al., 2006; Zhou et al., 2007), the relatively few EEG and MEG investigations of phase-coherent connectivity point to potentially independent patterns of

abnormalities including regions of both hypo- and hyperconnectivity, depending on topography, task, and frequency band (Pachou et al., 2008; Hinkley et al., 2011).

Second, and similarly, a growing body of evidence supports the notion of task-specific patterns of functional connectivity present within the human cortex. For instance, it has been shown that laboratory-induced pain activates a rapidly-switching pattern of functional connectivity as measured by electrocorticography in non-psychotic individuals (Ohara et al., 2006). Specifically, beta phase-synchronization within a single network including primary somatosensory and parasylvian cortex fluctuate over time depending upon the attentional demands of the task at hand. Also, examining individuals diagnosed with dyslexia using fMRI, Pugh and colleages (2000) have shown disruptions of functional connectivity (i.e., BOLD covariance) surrounding the left angular gyrus confined only to tasks demanding increased phonological assembly. In translation, accurate specification of the dysconnectivity model of SZ may require not only precise anatomical mapping of neuroconnectivity, but also task- or process-specific functional mapping as well.

From this perspective, data from the present study support the notion not of ubiquitous dysconnectivity within specific anatomical regions of SZ patients, but rather of dysconnectivity within cortically-distributed top-down processes. Further, they are suggestive of intact connectivity within posterior networks during the bottom-up encoding of multisensory stimuli. While posterior functional connectivity during working memory may indeed be impaired under unisensory conditions, (Henseler et al., 2010) these results suggest that its function could be somewhat salvageable by mechanisms specific to multisensory processing. Such mechanisms might include, for instance, a shift toward more bottom-up processing required by perceptually-richer stimuli.

Nonetheless, and regardless of possible compensatory mechanisms, behaviorally-intact MSB may have very significant implications for treatment of the disorder. Indeed, an important finding of the current study, which ought not to be overlooked, is that of improvements in

auditory recognition for SZ patients achieved through multisensory encoding of those stimuli. Acknowledging the centrality of memory-related impairments in SZ, cognitive remediation is a novel treatment approach which has garnered increasing interest for improving cognitive performance among patients. It has been implemented both as a standalone augmentation to traditional pharmacotherapy and in conjunction with psychotherapy (see Wykes et al., 2011 for a review and meta-analysis).

One promising example of this approach, representative of those which have been effective (Wykes et al., 2011) involved intensive and iterative training on a range of auditory memory skills with patients, ranging from tasks of sound discrimination to more complicated memory for verbal story information (Fisher et al., 2009). After completing 40 hours of this training, the authors reported sizeable improvements to patients' performance on common, standardized neuropsychological measures of memory. Considering this in light of basic research pointing to the immense advantages of multisensory conditions and environments for the learning of stimuli (see Shams & Seitz, 2008 for a review), one might argue that the addition of multisensory stimuli or conditions to cognitive remediation protocols may allow for stronger therapeutic effects and reductions in the time required for achieving these effects. Also considering the significant associations found between cognitive performance and social and functional outcomes in SZ (Green, 1996; Green et al., 2000) it is hopeful that the translation of such effects to clinically-relevant outcomes among patients could be possible.

4.4 Limitations and future research

While these data add to our understanding of the pathophysiology of SZ in several important domains, they also pave the way for areas of future research. For instance, in the continued examination of the dysconnectivity model of the disorder, they echo previous research pointing to the need for exploration of both structural and functional measurements of normal and abnormal (beyond merely reduced) connectivity. They further expand this call to include investigations of task, context, or process-specific connectivity as well. This principle is

of paramount importance in the examination of connectivity during multisensory integration - a process thought to take place across broad regions of the brain and at multiple stages of both cortical and subcortical processing (Shams & Seitz, 2008). Complex interactions taking place across each of these levels of functioning could underlie varying neural manifestations of multisensory processes in health. Thus, characterization of affected versus unaffected connectivity during these processes in schizophrenia may require comparison across a large number of tasks and circumstances. However, at the multivariate or meta-analytic level, overarching phenotypic themes could provide valuable leverage in the search for genetic abnormalities in a highly heterogeneous disorder. This approach may also yield the benefit of allowing future treatments to capitalize upon areas of unaffected functioning for the strengthening of weaknesses having shared physiological substrates.

In addition, a number of limitations within the present report will be ameliorated through continued data collection on this project. Increasing the number of participants will add the statistical power necessary for the emergence of more subtle effects which may have been undetected, for instance, in FDR-corrected correlations between event-related gamma power and MSB. Similarly, a larger database of clinical data and symptom measures will allow for regression-based modeling of symptom profiles in the nature of those achieved presently for behavioral performance. Importantly, the lack of group difference in MSB reported here reflected an effect size d of 0.41, requiring a vastly larger sample size of 190 (95 participants per group) in order to reach statistical significance (assuming alpha = 0.05 and power = 0.8). Nonetheless, increased N will yield greater confidence in the representativeness of this sample of participants, as would replication of this study.

In testing patient EEG against a new electrophysiological model of episodic memory, this study sought to examine the most parsimonious collection of variables reflective of that model as possible. This first step included the use of a small, hypothesis-directed set of surface electrodes drawn from a 64-channel EEG cap and selected for their topographical and empirical

association with anatomy of interest. Though these data provide a strong foundation for interpretations of SZ deficits consistent with the model examined, follow-up analyses at the conclusion of this study using source-based methodology will augment those interpretations with more specific anatomical information. Similarly, future studies using simultaneous, or co-registered, EEG and fMRI will allow for maximal temporal resolution while minimizing the level of spatial uncertainty inherent to the localization of non-invasive scalp EEG generators (i.e., the so-called “inverse problem”). Despite these limitations, the present data provide a strong foundation for future investigations both of SZ pathophysiology and novel treatment approaches.

Tables

Dependent Variable	Description	Underlying Construct	Key References

Table 1. Electrophysiological Dependent Variables

1. Event-related Spectral Perturbation (ERSP)	Event-related changes in spectral amplitude (i.e., power) measured as a function of time during the experimental trial. Measured in units of dB. The present study proposes to focus on measurement of ERSP in the theta (3-7 Hz), beta (15-25 Hz), and gamma (30-50 Hz) bands.	Thought to reflect information processing within various cognitive domains depending upon the frequency range of the activity. For instance, different spatial ranges of cortical communication are thought to be associated with range (i.e., low vs. high) of signal frequency, with specific frequency bands also associated with the activity of unique cognitive processes or brain regions (e.g., theta has been associated with hippocampal memory processing and gamma associated with feature binding and attention).	Von Stein & Sarnthein, 2001; Makeig et al., 2004; Roach & Mathalon, 2008
2. Pre-stimulus baseline activity	Measurement of non-event-related, tonic spectral amplitude (i.e., power) in units of squared microvolts. Particularly relevant to this study is baseline activity in the gamma band.	Baseline gamma power has been posited to reflect tonic levels of cortical excitability, particularly that resulting from the activity of NMDA receptor-mediated inhibitory interneurons.	Homayoun & Moghaddam, 2007; Spencer, 2009; Spencer 2012.
3. Phase coherence	A relationship in which two signals - transformed to emphasize activity within a selected frequency band - maintain a fixed synchrony between their phase angles. When those signals are collected from two different sites, the metric is called cross-channel coherence. Values are real numbers ranging from 0 (asynchronous) to 1 (perfectly synchronized or coherent).	Cross-channel coherence: taken to be evidence of cortical communication between different cortical areas (i.e., functional connectivity).	Makeig et al., 2004; Tallon-Baudry et al., 2006; Roach & Mathalon, 2008
4. Cross-frequency coupling	Refers to measures of the statistical relationship between two signals of different frequencies. C-linear Association: The degree of association, in Pearson's R, between a sin- and cosine-transformed circular variable (here, EEG signal phase) and a traditionally linear variable (here, EEG signal amplitude).	Each measure of cross-frequency coupling is thought to reflect the process of modulating the excitability state of neuronal bodies via the phase or amplitude of another neural signal. This modulation, broadly, has been put forth as a candidate mechanism for generation of the temporal neural precision required for complex tasks such as memory, learning, and stimulus processing.	Lakatos et al., 2005; Canolty et al., 2006; Nyhus & Curran, 2010

Table 2. Zero-order correlations (Pearson R, p-value) of unisensory recognition model variables, N = 29. Group dummy codes are 0 = SZ, 1 = Control.

	A- $_{\text{hit rate}}$	Group	Cz Theta (175 to 325 ms)	C3 Gamma (Baseline)
A- $_{\text{hit rate}}$	--	0.41 (0.026)	0.57 (0.001)	0.51 (0.004)
Group	--	--	0.56 (0.002)	-0.04 (0.833)
Cz Theta (175 to 325 ms)	--	--	--	0.16 (0.398)

Table 3. Regression model output of unisensory recognition model

Model 1	$R^2 = 0.17$	$F(1, 27) = 5.53$	$p < 0.05$		
	Variable	B Coefficient	Std. Error	_t_	_p_
	Group	0.14	0.06	2.35	0.026
Model 2	$R^2 = 0.33$	$F(1, 26) = 6.48$	$p < 0.01$		
	Variable	B Coefficient	Std. Error	_t_	_p_
	Group	0.05	0.07	0.72	0.48
	Cz Theta	0.10	0.04	2.52	0.02
Model 3	$R^2 = 0.54$	$F(1, 25) = 9.78$	$p < 0.001$		
	Variable	B Coefficient	Std. Error	_t_	_p_
	Group	0.08	0.06	1.38	0.18
	Cz Theta	0.07	0.03	2.14	0.04
	C3 Tonic Gamma	0.03	0.01	3.35	0.003

Table 4. Zero-order correlations (Pearson R, p-value) of MSB model variables, N=29. Group dummy codes are 0 = SZ, 1= Control.

	MSB	C3 Beta ERSP (350 to 475 ms)	Baseline CzPOz Theta Coherence	CzPOz Beta Coherence (225 to 320 ms)
MSB	--	0.48 (0.009)	0.41 (0.026)	0.46 (0.012)
C3 Beta (350 to 475 ms)	--	--	0.35 (0.066)	0.47 (0.01)
Baseline CzPOz Theta Coherence	--	--	--	0.84 (<0.001)

Table 5. Regression model output of MSB model

Model 1	$R^2 = 0.30$	$F(1, 25) = 3.65$	$p < 0.05$		
	Variable	B Coefficient	Std. Error	_t_	_p_
	C3 Beta	0.02	0.01	1.79	0.09
	CzPOz Theta Coherence	0.06	0.13	0.44	0.66
	CzPOz Beta Coherence	0.09	0.16	0.57	0.56

FIGURES

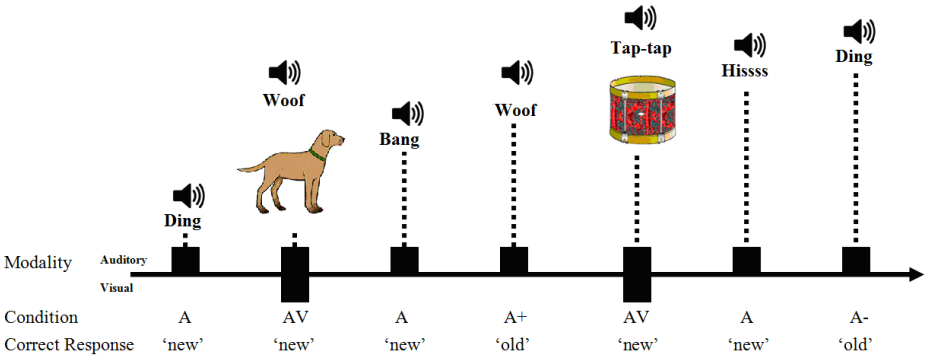

Figure 1. Experimental paradigm. Figure and task adapted from Lehmann & Murray, 2005.

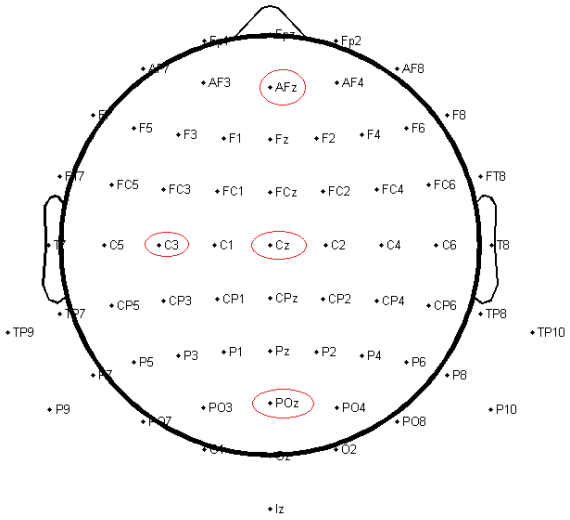

Figure 2. Electrode locations on the scalp. Those analyzed in the present study are circled in red.

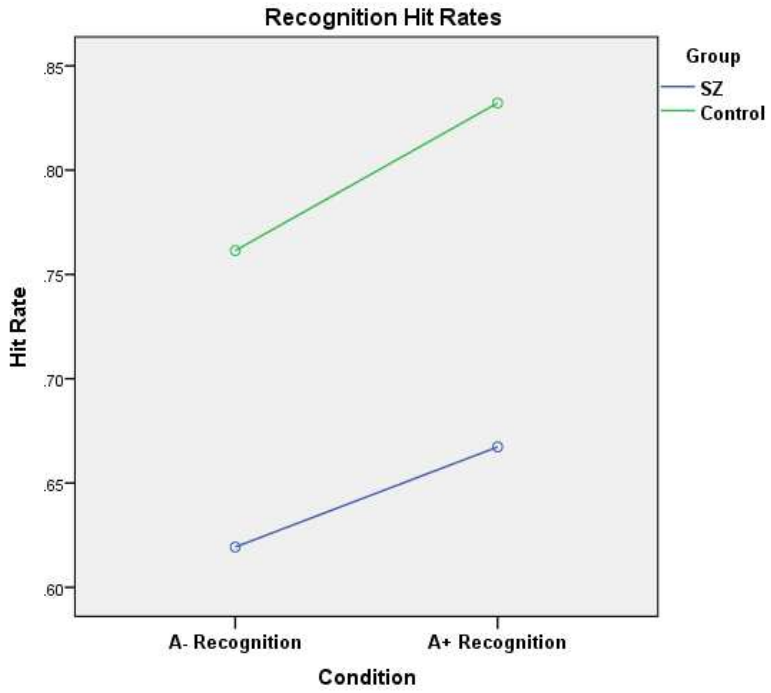

Figure 3. Behavioral results, recognition hit rates, reveal impaired recognition in SZ patients but overall improvements to memory (MSB) resulting from multisensory encoding in both groups. Effects significant for group and condition variables.

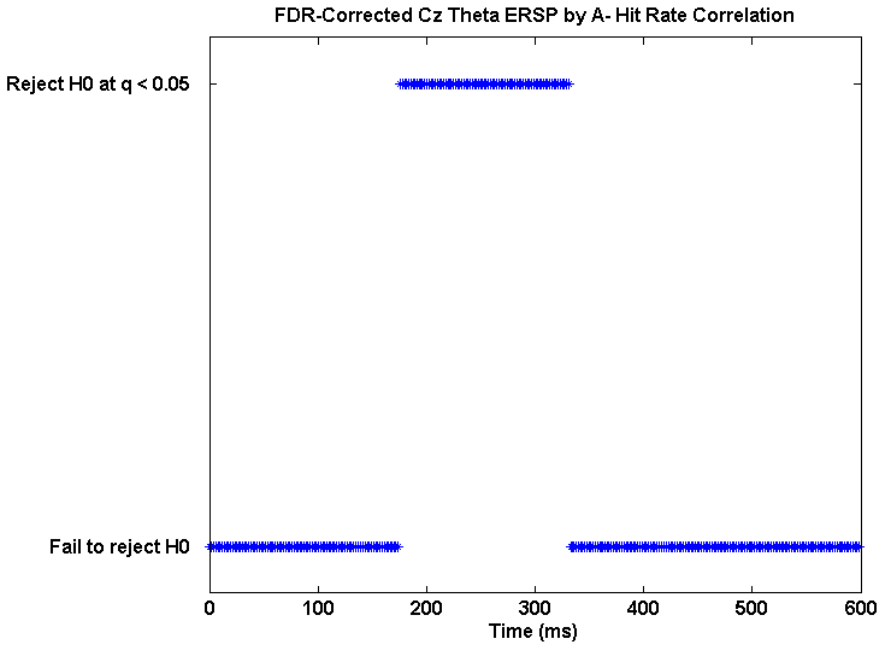

Figure 4. Cz theta ERSP by A- $_{\text{hit rate}}$ FDR-corrected correlation plot. Values of 1 indicate rejection of the null hypothesis that there is no relationship between variables at $q < 0.05$, whereas 0 indicates failure to reject the null hypothesis.

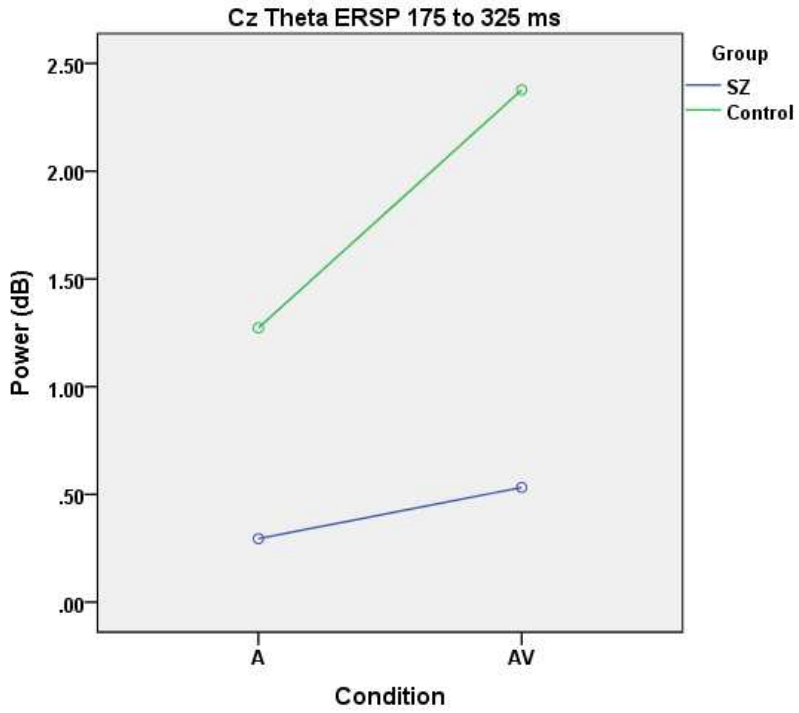

Figure 5. Cz theta ERSP from 175 to 325 ms ANOVA. Units indicate increases or decreases in spectral power, in dB, relative to 250 ms baseline preceding stimulus onset. Effects significant for group, condition, and group X condition interaction.

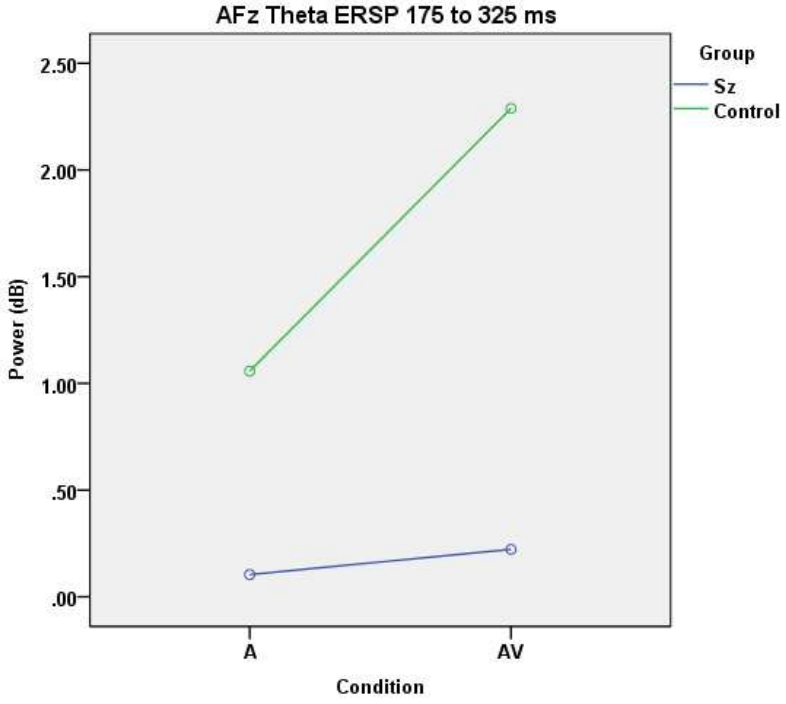

Figure 6. AFz theta ERSP from 175 to 325 ms ANOVA. Units indicate increases or decreases in spectral power, in dB, relative to 250 ms baseline preceding stimulus onset. Effects significant for group, condition, and group x condition interaction.

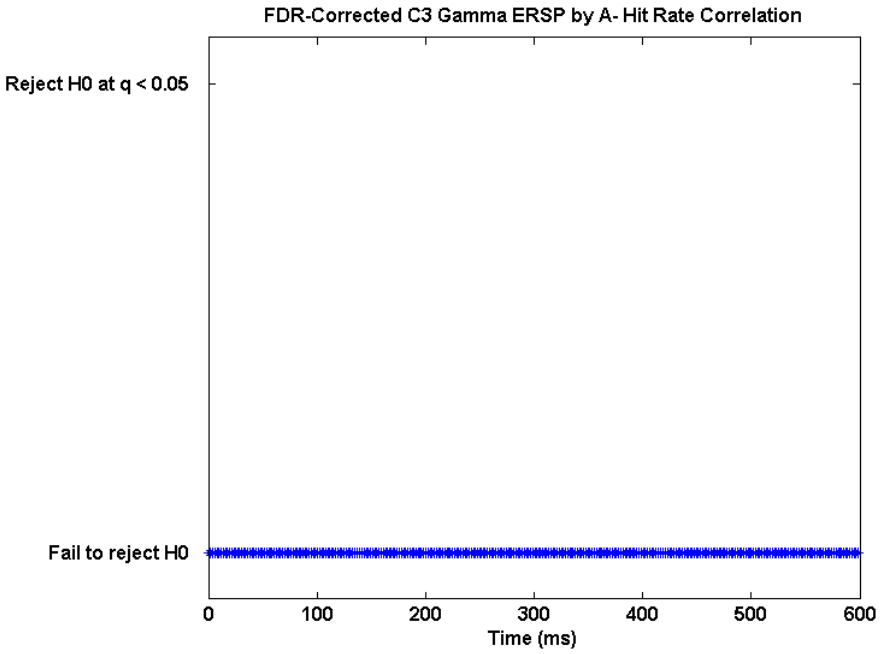

Figure 7.C3 gamma ERSP by A- $_{\text{hit rate}}$ FDR-corrected correlation plot. No significant periods of post-stimulus activity were found to correlate with behavior.

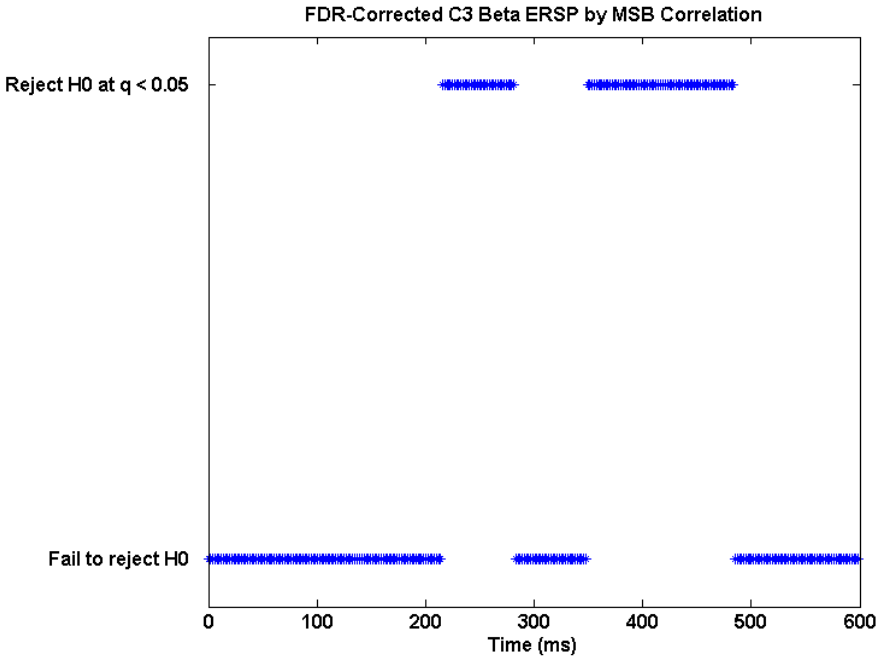

Figure 8. C3 beta ERSP by MSB FDR-corrected correlation plot. Values of 1 indicate rejection of the null hypothesis that there is no relationship between variables at $q < 0.05$, whereas 0 indicates failure to reject the null hypothesis.

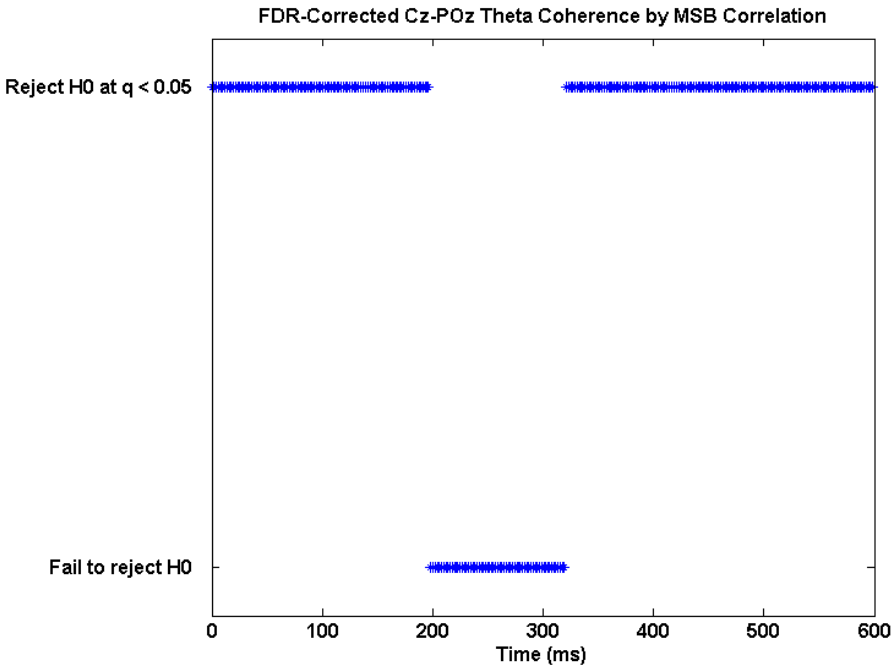

Figure 9. Cz-POz theta coherence by MSB FDR-corrected correlation plot. Values of 1 indicate rejection of the null hypothesis that there is no relationship between variables at $q < 0.05$, whereas 0 indicates failure to reject the null hypothesis.

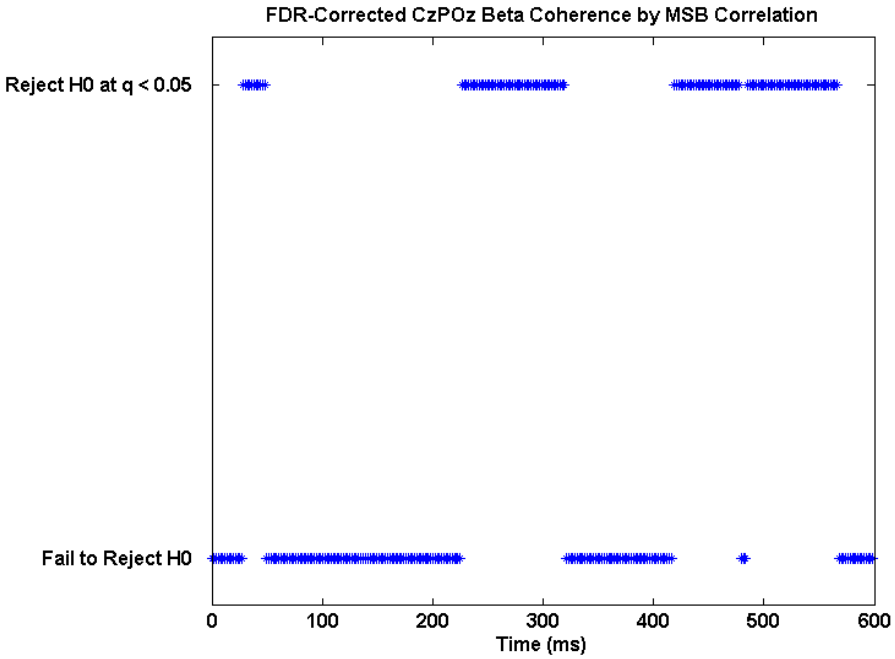

Figure 10. Cz-POz beta coherence by MSB FDR-corrected correlation plot. Values of 1 indicate rejection of the null hypothesis that there is no relationship between variables at $q < 0.05$, whereas 0 indicates failure to reject the null hypothesis.

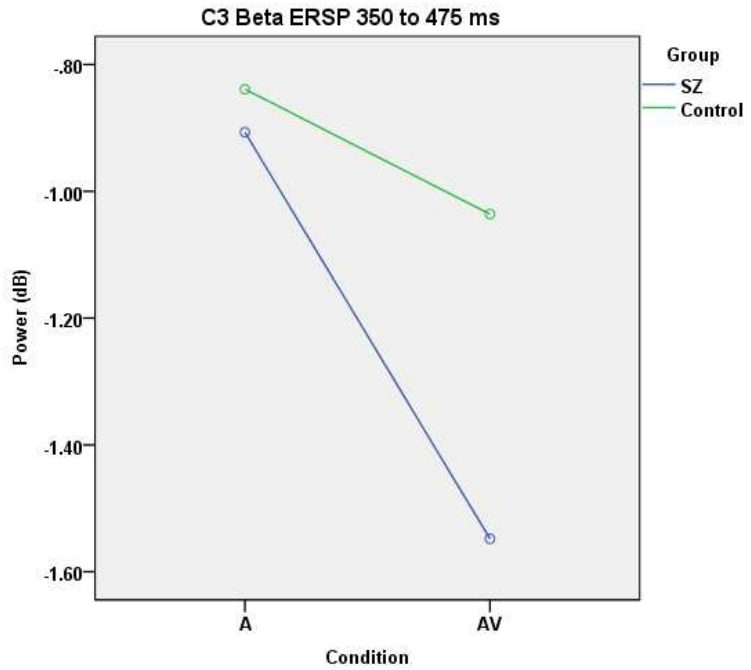

Figure 11. C3 beta ERSP from 350 to 475 ms ANOVA. Units indicate increases or decreases in spectral power, in dB, relative to 250 ms baseline preceding stimulus onset. Effect significant for condition variable.

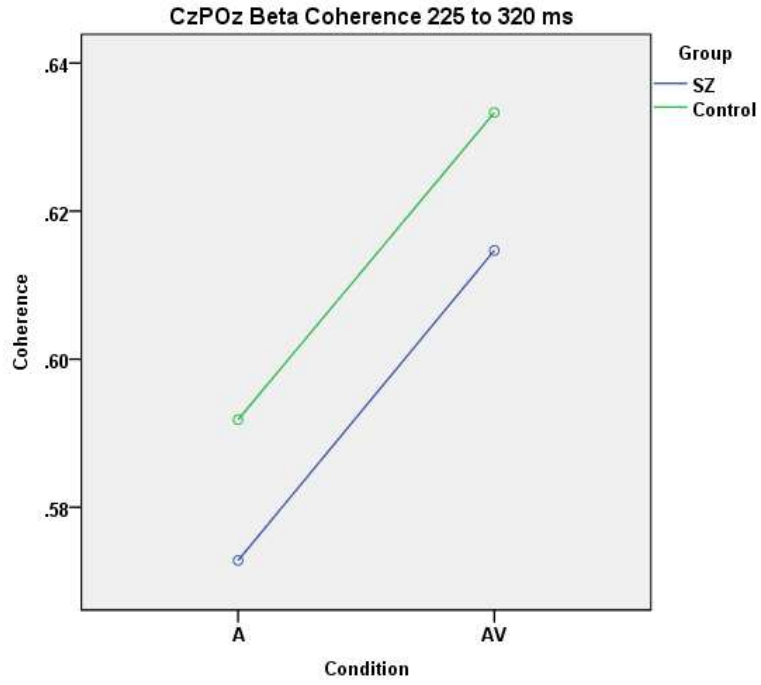

Figure 12. CzPOz beta coherence from 225 to 320 ms ANOVA. Units indicate degree of synchrony between beta phase at site Cz and that of site POz, with 1 indicating perfect synchrony and 0 indicating complete asynchrony. Effect significant for condition variable.

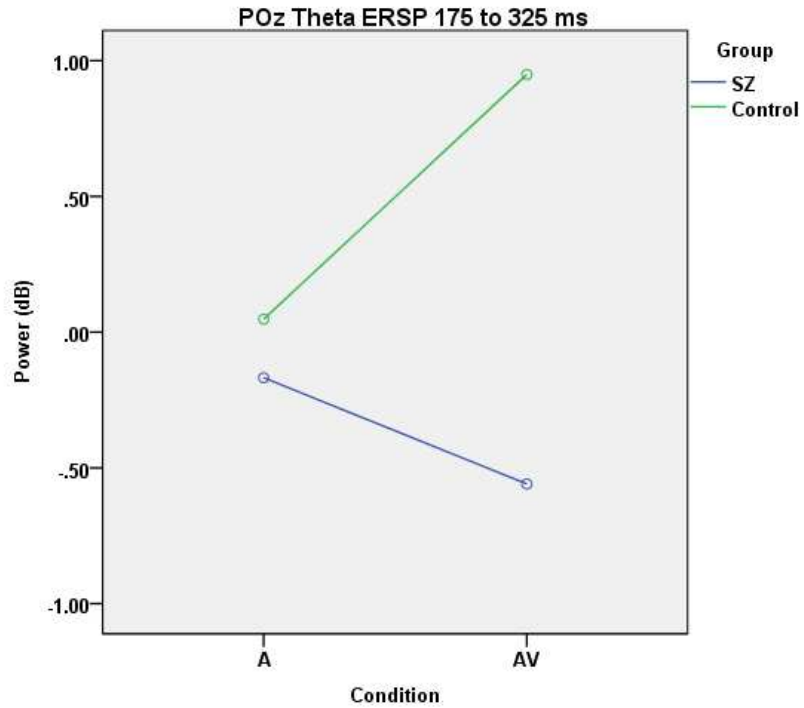

Figure 13. POz theta ERSP from 175 to 325 ms ANOVA. Units indicate increases or decreases in spectral power, in dB, relative to 250 ms baseline preceding stimulus onset. Effects significant for group and group x condition interaction.

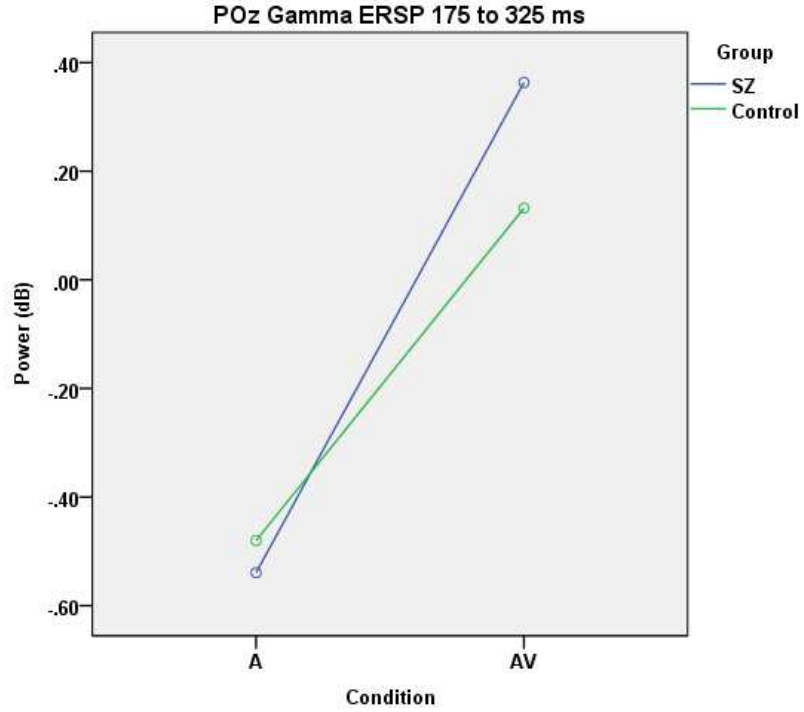

Figure 14. POz gamma ERSP from 175 to 325 ms ANOVA. Units indicate increases or decreases in spectral power, in dB, relative to 250 ms baseline. Effect significant for group variable.

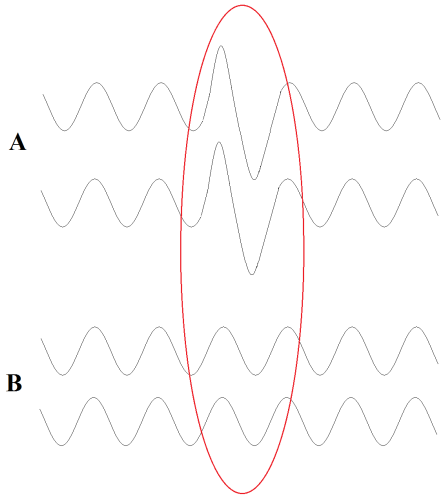

Figure 15. Graphical depiction of dissociation between coherence and local amplitude. Note the discrepancy in amplitudes between the signals of A and B, marked by the red circle, despite equivalent coherence within the two signals of both. With respect to the present study, one might consider the two signals to represent the theta activity of Cz and POz during AV encoding, with that of A corresponding to controls and that of B corresponding to patients.

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