

EARLY SENSORY PROCESSING DEFICITS IN SCHIZOPHRENIA

by

VICTORIA M. LEAVITT

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of
the requirements for the degree of Doctor of Philosophy, The City University of New
York

2009

© 2009

VICTORIA M. LEAVITT

All Rights Reserved

This manuscript has been read and accepted by the
Graduate Faculty in Psychology in satisfaction of the
dissertation requirement for the degree of Doctor of Philosophy.

Date

John J. Foxe, Chair of Examining Committee

Date

Maureen O'Connor, Executive Officer

Hilary Gomes, Ph.D.

Jeffrey Halperin, Ph.D.

Sophie Molholm, Ph.D.

Dean Salisbury, Ph.D.

Supervision Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

EARLY SENSORY PROCESSING DEFICITS IN SCHIZOPHRENIA

by

Victoria M. Leavitt

Advisor: Professor John J. Foxe

Sensory processing deficits have been found in individuals with schizophrenia across sensory modalities, including auditory, visual, somatosensory, and olfactory systems. These deficits have been identified at very early stages of cortical, and subcortical processing. It remains to be seen whether or not these deficits have implications for higher order cognitive processes and the positive and negative symptoms of schizophrenia. Before we can begin to understand the role they play in the etiology and manifestation of the disease, the deficits themselves must be fully characterized. Three high-density (168-channel) electrophysiological investigations are detailed herein, the first two of which are concerned with the auditory system, and the final, the visual system. First, we present an investigation of the middle latency auditory evoked potentials, a processing period which has not previously been explicated in the schizophrenia literature, and one which represents the transition from brainstem-level processing to late-latency cortical processes. Next, we present a normative investigation of the ventral and dorsal ('what' and 'where') auditory pathways which employed functionally distinct behavioral tasks in an attempt to characterize the evoked componentry within each of the respective pathways. On the basis of the notion that

dorsal and ventral pathways show differential impairment in individuals with schizophrenia, the paradigm was then applied to a group of patients to determine whether the pattern of processing within the two pathways differed from that observed in healthy controls. Finally, we present a visual experiment that employed a monocular deprivation challenge as a means of amplifying known early visual processing deficits in schizophrenia, namely the visual P1 deficit which was recently identified as an endophenotypic marker for schizophrenia. Taken together, the deficits that were identified and characterized within each of these sensory modalities may contribute to an overarching model of sensory processing deficits in schizophrenia wherein the contributions of many decrements, taken together across sensory modalities, result in a profile common to individuals with schizophrenia.

Without the help and support of so many wonderful colleagues in the Cognitive Neurophysiology Laboratory at the Nathan Kline Institute with whom I have had the privilege to learn and discover over the past years, this work would not have been possible.

My thanks to John Foxe, for many, many late nights, early mornings, and all opportunities in between that he spent helping me. His unflagging enthusiasm and excitement kept me going when the going got tough; his passion for science is contagious to all who are fortunate to work with him.

Most of all, I thank my supportive and infinitely patient husband and friend, Benny Koonyevsky, and our daughters, Galia and Neve. Without their unconditional love over the years, I may have achieved this more quickly, but with much less happiness in my life.

TABLE OF CONTENTS

I.	Chapter 1- Introduction.....	1
	References.....	14
II.	Chapter 2- Auditory processing in schizophrenia during the middle latency period (10-50 milliseconds): High-density electrical mapping and source-analysis reveal subcortical antecedents to early cortical deficits.....	19
	References.....	62
III.	Chapter 3-“What” and “Where” in auditory sensory processing I: A high-density electrophysiological investigation of distinct neural processes underlying sound object recognition and sound localization.....	71
	References.....	111
IV.	Chapter 4- “What” and “Where” in auditory sensory processing II: A high-density electrophysiological investigation of distinct neural processes underlying sound object recognition and sound localization in patients with schizophrenia.....	116
	References.....	135
V.	Chapter 5- The binocular effect: Brief monocular deprivation as an assay of short-term plasticity of visual sensory processing in patients with schizophrenia.....	137
	References.....	171
VI.	Chapter 6-Conclusion.....	175
	References.....	180

CHAPTER 1

Introduction

Cognitive dysfunction is the most obviously debilitating aspect of schizophrenia (Harvey, Docherty, Serper, & Rasmussen, 1990; Kay & Murrill, 1990). Whereas much research has been devoted to higher order cognitive functioning- the delusions, hallucinations and thought disorder that often signify disease onset- a large amount of current investigation also focuses on impairment of elementary sensory processing under the reasonable assumption that deficits originating in lower tier processing might ultimately be a contributing factor to higher order deficits. Examination of basic sensory processes has revealed surprisingly early deficits across sensory modalities. For example, schizophrenia patients show impairment in basic visual functions, such as motion detection and smooth pursuit eye movements (Chen et al., 1999; Holzman, 1975). The goal of this dissertation is to investigate deficits in the auditory and visual systems that may impact on more complex cognitive impairment seen in schizophrenia.

As early as 1893 in Praecox and Paraphrenia (Kraepelin, English translation 1919), Kraepelin described the disruption of attention in patients with schizophrenia as a hallmark of the disease. Increasingly, evidence suggests that disturbances attributed to a breakdown of attentional processes may actually be due to basic sensory processing deficits. The event-related potential (ERP) known as mismatch negativity (MMN) serves as an index of pre-attentive processing of stimulus deviation, and is elicited when a deviant tone is interjected into a sequence of repetitive standard stimuli. Numerous studies have found the MMN to both duration and frequency deviants to be highly attenuated in schizophrenia patients (Javitt, Doneshka, Grochowski, & Ritter, 1995; Javitt, Strous, Grochowski, Ritter, & Cowan, 1997; Oades, Dittmann-Balcar, Zerbin, & Grzella, 1997), and this attenuation has been correlated with behavioral outcomes such as subsequent deficits in attention-dependent processing (Javitt, 2000). One study found that lack of left hemisphere lateralization of the MMN in patients was

associated with positive symptoms (as reviewed by Ford & Roth, 2004). Baldeweg and colleagues (2004) found MMN amplitude to be significantly correlated with cognitive impairment in patients. This suggests that early sensory processing deficits may lead to disrupted higher order processes. Further evidence to support the assertion that higher order processing is impaired subsequent to deficits in basic sensory processing comes from a number of studies done in our laboratory, such as those showing that impairments in affective prosody are secondary to basic auditory deficits (Leitman, 2005).

Auditory processing deficits in schizophrenia

There is a substantial literature describing effects on later-latency auditory evoked potentials (AEPs) (>50 ms) of patients with schizophrenia, and deficits in these components (e.g. P1, N1, MMN) have been consistently documented (Javitt, Jayachandra, Lindsley, Specht, & Schroeder, 2000; Michie, 2001; Valkonen-Korhonen et al., 2003). Likewise, investigations of very early subcortical responses, so-called auditory brainstem responses (ABRs) are abundant, although findings from these studies have been somewhat equivocal. For example, Lindstrom and colleagues published two studies (Lindstrom, Klockhoff, Svedberg, & Bergstrom, 1987; Lindstrom, Wieselgren, Klockhoff, & Svedberg, 1990), with the first reporting abnormal ABRs in 10 of 20 patients, and the second reporting fewer than half of the patients (15 of 39) showing abnormal ABRs. Four studies by other groups also found significant latency delays in ABRs of patients (Grillon, Ameli, & Glazer, 1990; Harell, Englender, Demer, Kimhi, & Zohar, 1986; Hayashida et al., 1986; Kimhi, Englender, Zohar, & Harell, 1987), while four other studies found no differences at all between the ABRs of patients and controls (Brecher & Begleiter, 1985; McKay, Headlam, & Copolov, 2000; Pfefferbaum, Horvath, Roth, Tinklenberg, & Kopell, 1980; Szelenberger, 1983). While our understanding of ABRs in schizophrenia clearly remains somewhat incomplete, these studies do appear to suggest that auditory processing deficits may

well occur before initial afference of primary auditory cortex (i.e. subcortically). Unfortunately, the next time period of auditory processing that has been the focus of significant research efforts begins with the auditory P1 component, some 45 ms after the end of the ABR. The intervening middle latency response (MLR) potentials have been largely skipped over, despite the fact that they demarcate a key period in sensory processing in that they bracket the point of initial afference of primary auditory cortex.

With regard to the P1, unlike the ABR responses, there is widespread agreement in the literature pointing to patient deficits (e.g. Boutros, Korzyukov, Jansen, Feingold, & Bell, 2004; Clementz, Blumenfeld, & Cobb, 1997; Clementz, Geyer, & Braff, 1998; Erwin, Mawhinney-Hee, Gur, & Gur, 1991; Erwin, Shtasel, & Gur, 1994; Freedman et al., 1987). This component is most often studied in the context of a gating paradigm that involves presentation of a tone (S1) followed by a short inter-stimulus-interval (200-500 ms) before presentation of a second tone (S2) (e.g. Adler, Waldo, & Freedman, 1985; Braff, 1993; Clementz et al., 1997; Freedman et al., 1987; Nagamoto, Adler, Waldo, & Freedman, 1989). What is typically done is that the amplitude of the P1 evoked by the second of these tones (S2) is measured as a function of the amplitude of the P1 evoked by the first tone (S1). Control subjects show a clearly attenuated P1 to S2, presumably due to sensory gating. This attenuation is frequently found to be decreased in patients (Braff, 1993; Clementz et al., 1997; Clementz et al., 1998; Freedman et al., 1987; Nagamoto et al., 1989). More importantly for this study, it has been shown that this effect is in large part a consequence of an attenuated P1 to the first S1 stimulus (Clementz & Blumenfeld, 2001). But if in fact the point of divergence between the auditory evoked response of patients and healthy individuals comes at a much earlier point, this finding will help bridge our knowledge about subcortical versus cortical deficits in schizophrenia.

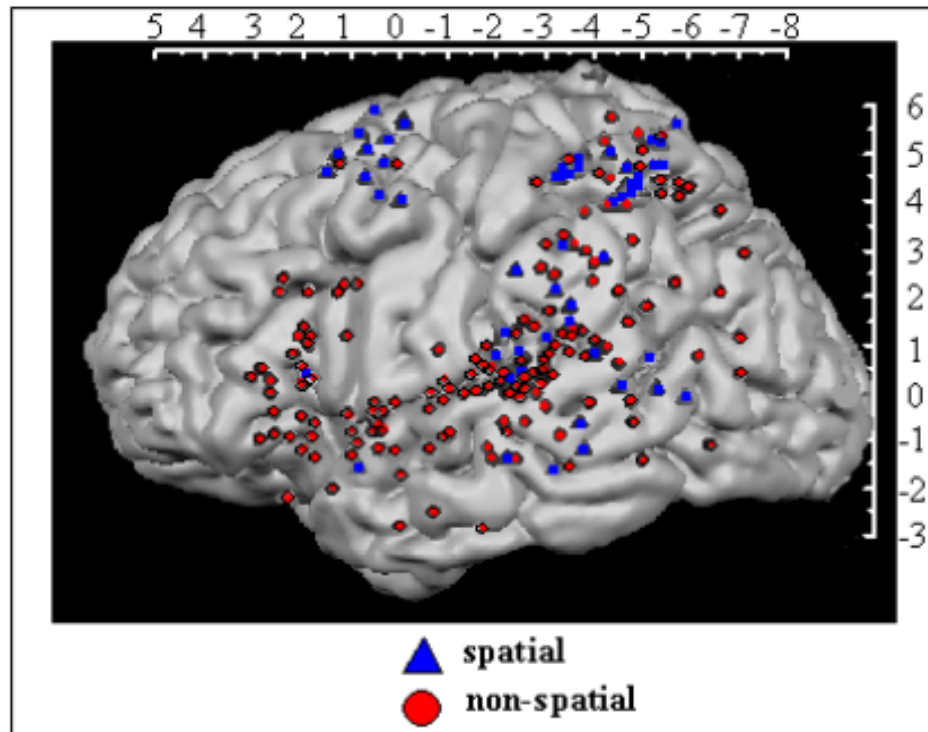
What vs. Where: Dorsal and ventral auditory pathways

There is now clear growing evidence for functionally distinct auditory pathways, with findings in non-human primates (Rauschecker & Tian, 2000; Romanski et al., 1999; Tian, Reser, Durham, Kustov, & Rauschecker, 2001) and humans (Anourova et al., 2001; Clarke, Bellmann, Meuli, Assal, & Steck, 2000; Clarke et al., 2002; Poremba et al., 2003; Weeks et al., 1999; Zatorre, Bouffard, Ahad, & Belin, 2002), pointing to a what/where distinction analogous to that seen in the visual system (Mishkin, Lewis, & Ungerleider, 1982). Namely, the dorsal pathway is thought to primarily process information regarding spatial localization of sound ('where'), while it is posited that the ventral pathway is processing specific features of a signal such as spectral and temporal integration ('what'). At least two distinct auditory processing streams have been found in monkeys, identified as a spatial stream, coursing dorsally, and a pattern or object stream, coursing ventrally (Rauschecker & Tian, 2000; Romanski et al., 1999; Tian et al., 2001). Through tracing studies utilizing histochemical techniques, areas in the superior temporal gyrus (STG) of rhesus monkeys were found to be tonotopically arranged (Rauschecker & Tian, 2000; Tian et al., 2001). Using band-passed noise bursts, every neuron in the lateral belt of STG was characterized. Using digitized versions of monkey vocalizations, neurons in the anterolateral belt (projecting to the ventral auditory pathway) were found to respond maximally to monkey vocalizations. When a task of sound localization was performed, with an azimuth of speakers arranged around the animal and monkey calls played through the speakers, the neurons in the caudolateral belt (projecting to the dorsal auditory pathway) exhibited the greatest activation.

Some of the best evidence for functionally distinct auditory pathways in humans comes from lesion studies (Clarke et al., 2000; Clarke et al., 2002; Clarke & Thiran, 2004). A recent study of 15 patients with right focal hemispheric lesions showed that sound recognition and sound localization could be disrupted independently (Clarke et al., 2002). Patients with selective

sound localization deficits had lesions involving inferior parietal and frontal cortices, as well as superior temporal gyrus; patients with selective recognition deficits had lesions of the temporal pole, the anterior part of fusiform, inferior and middle temporal gyrus. This double dissociation supports independent processing of sound recognition and sound localization in humans, but very few electrophysiological investigations to delineate auditory pathways in healthy participants have been done. There is a paucity of literature detailing early componentry in terms of a what/where distinction in the auditory system. A meta-analysis of neuroimaging studies of the ventral and dorsal auditory pathways was done by Arnott and colleagues (2004). By reviewing 11 spatial studies and 27 nonspatial studies, these authors concluded that physiologically distinct areas for processing spatial and nonspatial sounds could be identified (see **Figure 1**). Spatial studies reported activation along the dorsal stream: inferior parietal lobule, areas posterior to primary auditory cortex, and superior frontal sulcus. Nonspatial studies reported processing primarily along the ventral stream, notably, inferior frontal areas. Currently, this type of meta-analysis is one resource available for determining appropriate electrode sites corresponding to dorsal and ventral pathways. Due to the lack of electrophysiological studies of auditory pathways, there is little in the literature to refer to in the way of electrodes that demarcate ventral and dorsal stream processing as can be done for visual ventral/dorsal function (see, for example, Doniger, Foxe, Murray, Higgins, & Javitt, 2002; Mishkin & Ungerleider, 1982). For our studies, we will choose gross regions to represent each of these pathways, respectively: central parietal and parietal scalp correspond to dorsal pathway and frontocentral and frontal scalp correspond to ventral pathway. This seems to represent a reasonable strategy based on what we know about the neuroanatomical projections of these pathways. Furthermore, as discussed in the Methods section, we will employ two methods to localize putative neural generators: source analysis techniques to localize intracranial generators

Figure 1. Schematic representation of auditory pathways as evidenced by a meta-analysis of 11 spatial (**dorsal**) and 27 non-spatial (**ventral**) studies. Regions showing greatest activation in each study are indicated. Adapted with permission from Arnott et al. 2004.



contributing to individual auditory evoked potentials, thereby informing us of dorsal and ventral trajectories that may be evident in the data (for details, see Source localization section in Methods) and the method of surface Laplacian transformation to ameliorate the limitations of using the topographic display of scalp potentials to posit putative underlying neural generators.

What vs. Where II: Dorsal and ventral auditory pathways in schizophrenia patients

In work done in our laboratory, we have seen consistent deficits of dorsal stream processing in the visual system of schizophrenia patients, relative to ventral stream processing: visual P1 amplitudes were significantly reduced to a much greater degree over dorsal scalp than ventral in a patient group in a study by Foxe and colleagues (Foxe, Doniger, & Javitt, 2001), a

finding that has since been replicated twice by our group in studies of dorsal/ventral visual stream interaction in schizophrenia (Doniger et al., 2002; Foxe, Murray, & Javitt, 2005). Further, Foxe and colleagues used inverse source-localization to confirm that the major sources of this deficit were in the dorsal stream – methods that will be similarly applied here. Thus far, the dorsal/ventral distinction has simply not been explored in the auditory system of schizophrenia patients. There is also evidence in the literature to suggest that pathology in the brains of patients is organized along the lines of a dorsal/ventral distinction. For example, Christensen and Bilder (Christensen & Bilder, 2000) provide justification for a dorsal/ventral framework of cortical dysfunction which they termed the “dual cytoarchitectonic trends theory.” They claim that evidence supports the notion that all cortical regions evolved from two primitive sources, the hippocampus (archicortex) and olfactory areas (paleocortex), and projections from these two cortical areas subsequently occupy dorsal and ventral regions of the brain. In their view, these dorsal and ventral distinctions exist across multiple cortical systems. Furthermore, they assert that the brains of patients with schizophrenia demonstrate deficits at all cytoarchitectonic levels of the “dorsal trend.” This normative investigation of dorsal and ventral auditory pathways will lay a solid foundation for the subsequent patient study of same.

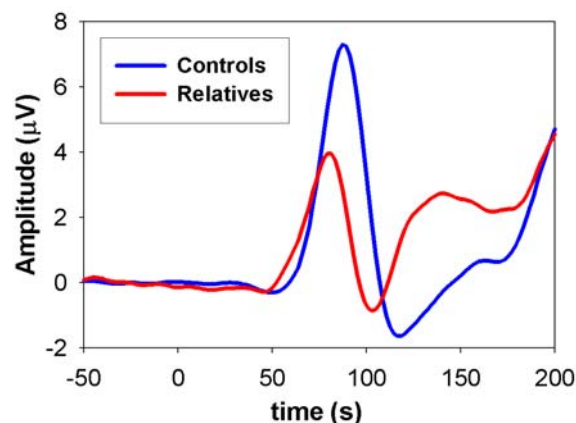
Deficits in the visual system of patients with schizophrenia

Several recent studies from our group have evaluated the integrity of early visual processing in schizophrenia; findings include dysfunction of magnocellular lower-level visual pathways (Butler et al., 2001), P1 deficits (Foxe et al., 2001), and impairment in perceptual closure (Doniger et al., 2002). Another recent study from our group found the visual P1 to be an endophenotypic marker (Yeap et al., 2006), showing significant attenuation in first-degree relatives with an effect size of 0.9. In **Figure 2** (adapted from Yeap et al., 2006), event-related potential (ERP) waveforms of controls (n=26) in blue and relatives (n=25) in red at a right

parieto-occipital scalp electrode (PO4) are plotted over a short-latency timeframe clearly showing the P1 component, which appears to strongly discriminate between groups. While this provides us with a critical marker for the disease, the variability amongst patients is such that there is great overlap between healthy controls and patients, thereby rendering this a measure that lacks diagnostic sensitivity. That is, an individual with schizophrenia may not be detected as having an abnormal P1 and therefore evade diagnosis (a Type-II error). Our goal here was to devise a visual paradigm that would sufficiently challenge patients such that the known P1 deficit would impair their performance, thereby providing us with a clinically useful test for diagnosis.

In 1977, Tyler and Kaitz (1977) determined that by covering one eye of healthy control subjects for several hours, it was possible to significantly increase the amplitude of the visual P1 evoked from the non-occluded eye. This effect was maximized after two to six hours of deprivation. There is also evidence in the literature of the nonlinear nature of binocular interactions in humans (Baith & Levi, 1988; Zemon, Pinkhasov, & Gordon, 1993)- that is, when

Figure 2. Waveforms for controls (blue) and first-degree relatives of patients with schizophrenia (red) from a representative electrode over right parieto-occipital scalp showing P1 deficit in the relatives (adapted with permission from Yeap et al., 2006).



we add the visual evoked potentials (VEPs) of each eye elicited from monocular viewing of stimuli, they sum to a greater value than VEPs obtained from binocular viewing of the same stimuli (Eye 1 alone + Eye 2 alone > Both eyes together). Accessing a second-order effect of this type may very well prove an effective way to uncover a substantial difference in basic sensory processing in patients that will provide us with a more sensitive diagnostic tool that can more reliably identify the possible presence of schizophrenia.

We created a shortened paradigm, which employs the collection of VEPs immediately after administering an eye patch. In this way, the entire experiment can be completed in less than 30 minutes. This type of modification is very important when working with a patient population with attentional limitations. By employing such a technique of monocular deprivation it is our hope that we will dramatically boost the effect size of the P1 deficit in patients. By increasing our sensitivity to the P1 deficit in a patient population, we hope to magnify the deficit, thereby providing us with a more reliable diagnostic tool for schizophrenia.

Clinical Relevance of Sensory Processing Deficits in Schizophrenia

It is anticipated that measures developed during the course of this research may be incorporated into future challenge studies. Such measures may serve as important therapeutic targets and as endophenotypes for etiological investigations of schizophrenia. A continuing goal of this project is to evaluate the hypothesis that sensory processing measures may serve as effective indices of non-dopaminergic pathology, particularly in patients who respond poorly to currently available medications (typically, those with a preponderance of negative symptoms). In studies done in our laboratory (Javitt, Shelley, Silipo, & Lieberman, 2000; Javitt et al., 1997; Rabinowicz, Silipo, Goldman, & Javitt, 2000; Strous, Cowan, Ritter, & Javitt, 1995) and similar studies performed by Wexler and colleagues (1998), sensory processing deficits were present disproportionately in chronic, poor outcome patients, and, when present, were associated with a

pattern of global cognitive impairment, in agreement with predictions of the phencyclidine (PCP)/NMDA model. Auditory evoked potentials such as P1 and N1 have been shown to be sensitive to NMDA dysfunction based upon challenge studies performed in humans (Umbricht et al., 2000) and non-human primates (Javitt, Jayachandra et al., 2000). Further characterization of these deficits in relation to negative symptoms may provide clues about the etiology of schizophrenia as well as new directions for clinical intervention.

The ultimate goal of the proposed studies is to permit new insights into the pathophysiology of schizophrenia. By exploring purported impairment of auditory and visual sensory modalities, we believe that we will elucidate organizing principles of dysfunction, which will ultimately allow for the development of even more specific diagnostic and therapeutic interventions.

Specific aims and hypotheses

Experiment 1: Auditory processing in schizophrenia during the middle latency period. To establish the onset of the earliest deficits in auditory processing, we will examine the time window demarcating the transition from subcortical to cortical processing: the period from 10-50 ms during the so-called middle latency responses (MLRs). These auditory evoked potentials (AEPs), insofar as they have not been adequately characterized in patients with schizophrenia, represent a critical link between the auditory brainstem responses and the later latency potentials that are well known to be generated in primary auditory cortex (i.e. from the P1 onwards). We hypothesize that auditory sensory dysfunction in patients with schizophrenia begins extremely early in processing and is evident during the timeframe of initial cortical afference. The implication is that well-established sensory processing deficits in schizophrenia are in fact secondary to earlier subcortical dysfunction.

Experiment 2a: *What and Where* in auditory sensory processing I: A high-density electrophysiological investigation of distinct neural processes underlying sound object recognition and sound localization. A study of sound localization (*where*), a function of dorsal processing, and sound object recognition (*what*), a function of ventral processing, will be conducted to determine the underlying physiology of function of these respective pathways. We hypothesize that a high-density investigation will enable us to better characterize separate physiological pathways that underlie these processes of *what* and *where* in auditory sensory processing. The overall goals of this study are to characterize neurophysiological differences between the processes of sound localization and sound object recognition. This normative study will enable us to elucidate the degree of dysfunction in these respective pathways in patients with schizophrenia.

Experiment 2b: *What and Where* in auditory sensory processing II: A high-density electrophysiological investigation of distinct neural processes underlying sound object recognition and sound localization in patients with schizophrenia. Pilot data will be collected from six patients with schizophrenia to determine the extent to which known early auditory processing dysfunction in patients is evident in their dorsal and ventral pathways. We hypothesize that, consistent with the dual trends theory of Christensen and Bilder (2000), we will see evidence of greater deficits in the AEPs that correspond to their dorsal pathway than ventral.

Experiment 3: The binocular effect: Brief monocular deprivation as an assay of short-term plasticity of visual sensory processing in patients with schizophrenia. It has been shown that brief monocular deprivation results in visual evoked potentials elicited in response to presentation of stimuli to each single eye that, when added together, sum non-linearly (Baith & Levi, 1988). That is, the sum of the two separate eyes is greater than the VEPs recorded when visual stimuli are viewed binocularly. By employing a method of forced plasticity with a patient sample (the

brief application of an eye patch over each eye, respectively), we hope to uncover a second-order effect that more clearly distinguishes patients from controls. We hypothesize that the non-linear nature of binocular interactions that has been shown for control subjects will be observed in patients with schizophrenia, but to a significantly lesser degree, enabling us to develop a clinically useful challenge test.

References

- Adler, L. E., Waldo, M. C., & Freedman, R. (1985). Neurophysiologic studies of sensory gating in schizophrenia: comparison of auditory and visual responses. *Biol Psychiatry*, 20(12), 1284-1296.
- Anourova, I., Nikouline, V. V., Ilmoniemi, R. J., Hotta, J., Aronen, H. J., & Carlson, S. (2001). Evidence for dissociation of spatial and nonspatial auditory information processing. *Neuroimage*, 14(6), 1268-1277.
- Arnott, S. R., Binns, M. A., Grady, C. L., & Alain, C. (2004). Assessing the auditory dual-pathway model in humans. *Neuroimage*, 22(1), 401-408.
- Baitch, L. W., & Levi, D. M. (1988). Evidence for nonlinear binocular interactions in human visual cortex. *Vision Res*, 28(10), 1139-1143.
- Baldeweg, T., Klugman, A., Gruzelier, J., & Hirsch, S. R. (2004). Mismatch negativity potentials and cognitive impairment in schizophrenia. *Schizophr Res*, 69(2-3), 203-217.
- Boutros, N. N., Korzyukov, O., Jansen, B., Feingold, A., & Bell, M. (2004). Sensory gating deficits during the mid-latency phase of information processing in medicated schizophrenia patients. *Psychiatry Res*, 126(3), 203-215.
- Braff, D. L. (1993). Information processing and attention dysfunctions in schizophrenia. *Schizophr Bull*, 19(2), 233-259.
- Brecher, M., & Begleiter, H. (1985). Brain stem auditory evoked potentials in unmedicated schizophrenic patients. *Biol Psychiatry*, 20(2), 199-202.
- Butler, P. D., Schechter, I., Zemon, V., Schwartz, S. G., Greenstein, V. C., Gordon, J., et al. (2001). Dysfunction of early-stage visual processing in schizophrenia. *Am J Psychiatry*, 158(7), 1126-1133.
- Chen, Y., Levy, D. L., Nakayama, K., Matthyse, S., Palafox, G., & Holzman, P. S. (1999). Dependence of impaired eye tracking on deficient velocity discrimination in schizophrenia. *Arch Gen Psychiatry*, 56(2), 155-161.
- Christensen, B. K., & Bilder, R. M. (2000). Dual cytoarchitectonic trends: an evolutionary model of frontal lobe functioning and its application to psychopathology. *Can J Psychiatry*, 45(3), 247-256.
- Clarke, S., Bellmann, A., Meuli, R. A., Assal, G., & Steck, A. J. (2000). Auditory agnosia and auditory spatial deficits following left hemispheric lesions: evidence for distinct processing pathways. *Neuropsychologia*, 38(6), 797-807.

- Clarke, S., Bellmann Thiran, A., Maeder, P., Adriani, M., Vernet, O., Regli, L., et al. (2002). What and where in human audition: selective deficits following focal hemispheric lesions. *Exp Brain Res*, 147(1), 8-15.
- Clarke, S., & Thiran, A. B. (2004). Auditory neglect: what and where in auditory space. *Cortex*, 40(2), 291-300.
- Clementz, B. A., & Blumenfeld, L. D. (2001). Multichannel electroencephalographic assessment of auditory evoked response suppression in schizophrenia. *Exp Brain Res*, 139(4), 377-390.
- Clementz, B. A., Blumenfeld, L. D., & Cobb, S. (1997). The gamma band response may account for poor P50 suppression in schizophrenia. *Neuroreport*, 8(18), 3889-3893.
- Clementz, B. A., Geyer, M. A., & Braff, D. L. (1998). Poor P50 suppression among schizophrenia patients and their first-degree biological relatives. *Am J Psychiatry*, 155(12), 1691-1694.
- Doniger, G. M., Foxe, J. J., Murray, M. M., Higgins, B. A., & Javitt, D. C. (2002). Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. *Arch Gen Psychiatry*, 59(11), 1011-1020.
- Erwin, R. J., Mawhinney-Hee, M., Gur, R. C., & Gur, R. E. (1991). Midlatency auditory evoked responses in schizophrenia. *Biol Psychiatry*, 30(5), 430-442.
- Erwin, R. J., Shtasel, D., & Gur, R. E. (1994). Effects of medication history on midlatency auditory evoked responses in schizophrenia. *Schizophr Res*, 11(3), 251-258.
- Ford, J. M., Roth, W.T. (2004). Deficient response modulation of event-related brain potentials in schizophrenia. *Current Opinion in Psychiatry*, 17, 91-96.
- Foxe, J. J., Doniger, G. M., & Javitt, D. C. (2001). Early visual processing deficits in schizophrenia: impaired P1 generation revealed by high-density electrical mapping. *Neuroreport*, 12(17), 3815-3820.
- Foxe, J. J., Murray, M. M., & Javitt, D. C. (2005). Filling-in in Schizophrenia: a High-density Electrical Mapping and Source-analysis Investigation of Illusory Contour Processing. *Cereb Cortex*.
- Freedman, R., Adler, L. E., Gerhardt, G. A., Waldo, M., Baker, N., Rose, G. M., et al. (1987). Neurobiological studies of sensory gating in schizophrenia. *Schizophr Bull*, 13(4), 669-678.
- Grillon, C., Ameli, R., & Glazer, W. M. (1990). Brainstem auditory-evoked potentials to different rates and intensities of stimulation in schizophrenics. *Biol Psychiatry*, 28(9), 819-823.
- Harell, M., Englender, M., Demer, M., Kimhi, R., & Zohar, M. (1986). Auditory brain stem responses in schizophrenic patients. *Laryngoscope*, 96(8), 908-910.

- Harvey, P. D., Docherty, N. M., Serper, M. R., & Rasmussen, M. (1990). Cognitive deficits and thought disorder: II. An 8-month followup study. *Schizophr Bull*, 16(1), 147-156.
- Hayashida, Y., Mitani, Y., Hosomi, H., Amemiya, M., Mifune, K., & Tomita, S. (1986). Auditory brain stem responses in relation to the clinical symptoms of schizophrenia. *Biol Psychiatry*, 21(2), 177-188.
- Holzman, P. S. (1975). Smooth-pursuit eye movements in schizophrenia: recent findings. *Res Publ Assoc Res Nerv Ment Dis*, 54, 217-231.
- Javitt, D. C. (2000). Intracortical mechanisms of mismatch negativity dysfunction in schizophrenia. *Audiol Neurotol*, 5(3-4), 207-215.
- Javitt, D. C., Doneshka, P., Grochowski, S., & Ritter, W. (1995). Impaired mismatch negativity generation reflects widespread dysfunction of working memory in schizophrenia. *Arch Gen Psychiatry*, 52(7), 550-558.
- Javitt, D. C., Jayachandra, M., Lindsley, R. W., Specht, C. M., & Schroeder, C. E. (2000). Schizophrenia-like deficits in auditory P1 and N1 refractoriness induced by the psychomimetic agent phencyclidine (PCP). *Clin Neurophysiol*, 111(5), 833-836.
- Javitt, D. C., Shelley, A. M., Silipo, G., & Lieberman, J. A. (2000). Deficits in auditory and visual context-dependent processing in schizophrenia: defining the pattern. *Arch Gen Psychiatry*, 57(12), 1131-1137.
- Javitt, D. C., Strous, R. D., Grochowski, S., Ritter, W., & Cowan, N. (1997). Impaired precision, but normal retention, of auditory sensory ("echoic") memory information in schizophrenia. *J Abnorm Psychol*, 106(2), 315-324.
- Kay, S. R., & Murrill, L. M. (1990). Predicting outcome of schizophrenia: significance of symptom profiles and outcome dimensions. *Compr Psychiatry*, 31(2), 91-102.
- Kimhi, R., Englender, M., Zohar, M., & Harell, M. (1987). Brainstem auditory evoked responses in hospitalized unmedicated schizophrenic patients. *Isr J Psychiatry Relat Sci*, 24(4), 289-294.
- Kraepelin, E. (1919). Dementia Praecox and Paraphrenia (translated by R.M. Barclay). In *Edinburgh: E. & S. Livingstone, 1919.*
- Leitman, D. I., Foxe, J.J., Butler, P.D., Saperstein, A., Javitt, D.C. (2005). Do affective speech recognition deficits in schizophrenia have early cortical antecedents? *Biol Psychiatry*.
- Lindstrom, L., Klockhoff, I., Svedberg, A., & Bergstrom, K. (1987). Abnormal auditory brain-stem responses in hallucinating schizophrenic patients. *Br J Psychiatry*, 151, 9-14.
- Lindstrom, L. H., Wieselgren, I. M., Klockhoff, I., & Svedberg, A. (1990). Relationship between abnormal brainstem auditory-evoked potentials and subnormal CSF levels of HVA and 5-HIAA in first-episode schizophrenic patients. *Biol Psychiatry*, 28(5), 435-442.

- Loeb, P. A. (1996). ILS: Independent Living Scales Manual. *The Psychological Corporation, Harcourt Race Jovanovich, Inc.*
- McKay, C. M., Headlam, D. M., & Copolov, D. L. (2000). Central auditory processing in patients with auditory hallucinations. *Am J Psychiatry*, 157(5), 759-766.
- Michie, P. T. (2001). What has MMN revealed about the auditory system in schizophrenia? *Int J Psychophysiol*, 42(2), 177-194.
- Mishkin, M., Lewis, M. E., & Ungerleider, L. G. (1982). Equivalence of parieto-preoccipital subareas for visuospatial ability in monkeys. *Behav Brain Res*, 6(1), 41-55.
- Mishkin, M., & Ungerleider, L. G. (1982). Contribution of striate inputs to the visuospatial functions of parieto-preoccipital cortex in monkeys. *Behav Brain Res*, 6(1), 57-77.
- Nagamoto, H. T., Adler, L. E., Waldo, M. C., & Freedman, R. (1989). Sensory gating in schizophrenics and normal controls: effects of changing stimulation interval. *Biol Psychiatry*, 25(5), 549-561.
- Oades, R. D., Dittmann-Balcar, A., Zerbin, D., & Grzella, I. (1997). Impaired attention-dependent augmentation of MMN in nonparanoid vs paranoid schizophrenic patients: a comparison with obsessive-compulsive disorder and healthy subjects. *Biol Psychiatry*, 41(12), 1196-1210.
- Pfefferbaum, A., Horvath, T. B., Roth, W. T., Tinklenberg, J. R., & Kopell, B. S. (1980). Auditory brain stem and cortical evoked potentials in schizophrenia. *Biol Psychiatry*, 15(2), 209-223.
- Poremba, A., Saunders, R. C., Crane, A. M., Cook, M., Sokoloff, L., & Mishkin, M. (2003). Functional mapping of the primate auditory system. *Science*, 299(5606), 568-572.
- Rabinowicz, E. F., Silipo, G., Goldman, R., & Javitt, D. C. (2000). Auditory sensory dysfunction in schizophrenia: imprecision or distractibility? *Arch Gen Psychiatry*, 57(12), 1149-1155.
- Rauschecker, J. P., & Tian, B. (2000). Mechanisms and streams for processing of "what" and "where" in auditory cortex. *Proc Natl Acad Sci U S A*, 97(22), 11800-11806.
- Romanski, L. M., Tian, B., Fritz, J., Mishkin, M., Goldman-Rakic, P. S., & Rauschecker, J. P. (1999). Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. *Nat Neurosci*, 2(12), 1131-1136.
- Strous, R. D., Cowan, N., Ritter, W., & Javitt, D. C. (1995). Auditory sensory ("echoic") memory dysfunction in schizophrenia. *Am J Psychiatry*, 152(10), 1517-1519.
- Szelenberger, W. (1983). Brain stem auditory evoked potentials and personality. *Biol Psychiatry*, 18(2), 157-174.
- Tian, B., Reser, D., Durham, A., Kustov, A., & Rauschecker, J. P. (2001). Functional specialization in rhesus monkey auditory cortex. *Science*, 292(5515), 290-293.

- Tyler, C. W., & Kaitz, M. F. (1977). Binocular interactions in the human visual evoked potential after short-term occlusion and anisometropia. *Invest Ophthalmol Vis Sci*, 16(11), 1070-1073.
- Umbricht, D., Schmid, L., Koller, R., Vollenweider, F. X., Hell, D., & Javitt, D. C. (2000). Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. *Arch Gen Psychiatry*, 57(12), 1139-1147.
- Valkonen-Korhonen, M., Purhonen, M., Tarkka, I. M., Sipila, P., Partanen, J., Karhu, J., et al. (2003). Altered auditory processing in acutely psychotic never-medicated first-episode patients. *Brain Res Cogn Brain Res*, 17(3), 747-758.
- Weeks, R. A., Aziz-Sultan, A., Bushara, K. O., Tian, B., Wessinger, C. M., Dang, N., et al. (1999). A PET study of human auditory spatial processing. *Neurosci Lett*, 262(3), 155-158.
- Wexler, B. E., Stevens, A. A., Bowers, A. A., Sernyak, M. J., & Goldman-Rakic, P. S. (1998). Word and tone working memory deficits in schizophrenia. *Arch Gen Psychiatry*, 55(12), 1093-1096.
- Yeap, S., Kelly, S. P., Sehatpour, P., Magno, E., Javitt, D. C., Garavan, H., et al. (2006). Early visual sensory deficits as endophenotypes for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives. *Arch Gen Psychiatry*, 63(11), 1180-1188.
- Zatorre, R. J., Bouffard, M., Ahad, P., & Belin, P. (2002). Where is 'where' in the human auditory cortex? *Nat Neurosci*, 5(9), 905-909.
- Zemon, V., Pinkhasov, E., & Gordon, J. (1993). Electrophysiological tests of neural models: evidence for nonlinear binocular interactions in humans. *Proc Natl Acad Sci U S A*, 90(7), 2975-2978.

CHAPTER 2

Auditory processing in schizophrenia during the middle latency period (10-50 milliseconds): High-density electrical mapping and source-analysis reveal subcortical antecedents to early cortical deficits.

Reprinted from the Journal of Psychiatry and Neuroscience, 32 (5), Leavitt, V.M., Molholm, S., Ritter, W., Shpaner, M., Foxe, J.J., Auditory processing in schizophrenia during the middle latency period (10-50 milliseconds): High-density electrical mapping and source-analysis reveal subcortical antecedents to early cortical deficits, Copyright 2007.

Abstract: Auditory sensory processing dysfunction is a core component of schizophrenia with deficits occurring at just 50ms post-stimulus firmly established in the literature. Given that initial afference of primary auditory cortex occurs at least 35ms earlier, however, an essential question remains just how early in sensory processing such deficits arise, whether they occur during initial cortical afference, or perhaps at even earlier timepoints which would implicate subcortical auditory dysfunction. To establish the onset of the earliest deficits in auditory processing, we examined the time-window demarcating the transition from subcortical to cortical processing: the period from 10-50ms during the so-called middle latency responses (MLRs), which remain to be adequately characterized in patients with schizophrenia. Auditory evoked potentials (AEPs) to simple tone-pips were recorded from 15 controls and 21 patients with schizophrenia using high-density electrical scalp recordings. Between-groups analyses assessed the integrity of the MLRs across groups. In addition, two source-localization models were created to address whether a distinction between subcortical and cortical generators of the MLRs can be made and whether evidence for differential dorsal and ventral pathway contributions to auditory processing deficits can be established. Robust auditory processing deficits were found for patients as early as 15ms. Evidence for subcortical generators of the earliest MLR component (P20) was provided by source-analysis. Topographical mapping and source localization also pointed to greater decrements in processing in the dorsal auditory pathway of patients, providing support for a theory of pervasive deficits that are organized along the lines of a dorsal-ventral distinction. Auditory sensory dysfunction in schizophrenia begins extremely early in processing, is evident during initial cortical afference, and is also seen at earlier

subcortical processing stages in the thalamus. The implication is that well-established sensory processing deficits in schizophrenia may be secondary to earlier subcortical dysfunction. Our findings do not preclude the possibility of even earlier deficits in auditory sensory processing during the auditory brainstem response.

Introduction

Examination of basic sensory processes in patients with schizophrenia has revealed surprisingly early and often quite severe processing deficits across sensory modalities with patients showing impairment in some of the most basic visual (Butler, Schechter, Zemon, Schwartz, Greenstein, Gordon, Schroeder, Javitt, 2001; Foxe, Doniger, & Javitt, 2001; Schwartz, Maron, Evans, & Winstead, 1999a, 1999b), somatosensory (Buchsbaum et al., 1986), and auditory (Javitt, Doneshka, Grochowski, & Ritter, 1995; Javitt, Strous, Grochowski, Ritter, & Cowan, 1997; Oades, Dittmann-Balcar, Zerbin, & Grzella, 1997) sensory functions. In the present study, we sought to further characterize early auditory dysfunction in this population by examining the auditory evoked potential (AEP) of patients from time points earlier than 50 ms (P1), a processing period about which there is little consensus in the literature. That is, the P1 component of the AEP appears to be the earliest point in processing at which there is reasonable agreement that clear deficits are present in schizophrenia (e.g. Boutros, Korzyukov, Jansen, Feingold, & Bell, 2004; Clementz, Blumenfeld, & Cobb, 1997; Clementz, Geyer, & Braff, 1998; Erwin, Mawhinney-Hee, Gur, & Gur, 1991; Erwin, Shtasel, & Gur, 1994; Freedman et al., 1987), and dysfunction at this stage of processing is often cited as evidence of early auditory sensory impairment. While 50 ms may well be early, when one considers the timing of the initial afferent volley in primary auditory cortex, it becomes clear that a substantial amount of cortico-cortical processing will already have occurred by this timepoint. Both intracranial recordings in humans and source analysis of scalp-recorded data have shown that primary afference in A1 occurs at least 35 ms earlier (Liegeois-Chauvel, Musolino, Badier, Marquis, & Chauvel, 1994; Rupp et al., 2000; Scherg & Von Cramon, 1986). Given what is known about the speed

of transmission across sensory regions into higher-order cortices (e.g. Bullier, 2001; Foxe & Schroeder, 2005; Foxe & Simpson, 2002; Lakatos, in press; Schroeder et al., 2001), this timing raises the possibility, if not probability, that processing during the timeframe of the auditory P1 component is already subject to feedback inputs from higher-order regions in both auditory association cortices and perhaps even from frontal cortex (see Knight, Staines, Swick, & Chao, 1999). Thus, if we are to definitively establish that early feed forward (or “bottom up”) sensory processing is impaired in this population, we will need to establish whether there are deficits during the earlier so-called middle latency responses (MLR), which can be seen from 15-50 ms. Since these potentials are typically of very small amplitude when recorded at the scalp, this has proven very difficult to establish in this population and a detailed study is warranted.

Here, we evaluated the relative integrity of the middle-latency AEP in patients compared to healthy controls on a passive auditory task in which a standard, repetitive tone was presented binaurally. Auditory evoked potentials have been broken down into early, middle, and late latency components. Typically, the responses occurring prior to 10 ms (brainstem responses I to VII) are termed early; those which peak between 10 and 35 ms (N_0 , P_0 , P_{20} , P_a , N_b) are middle; and components after and including 50 ms are considered late (P_1 , N_1 , P_2 , N_2 , etc.) (Picton, Hillyard, Krausz, & Galambos, 1974). However, in the literature, the P_1 is often identified as a middle latency component (e.g. Adler, Waldo, & Freedman, 1985; Boutros et al., 2004), and there is further overlap in the terminology, with one study that claimed to investigate middle latency components concerned solely with the P_1 and P_2 (Mukundan, 1986), and another defining middle latency components as those which onset between 10-80 ms (Grillon, Ameli, & Braff,

1991). For our purposes, when we refer to middle latency components, we will mean those up to the P1, which tends to peak at approximately 50 ms.

There is a notable paucity of literature characterizing middle latency AEPs in patients with schizophrenia. To the best of our knowledge, there have only been three studies of middle latency components in humans with schizophrenia to date (Grillon et al., 1991; Huang et al., 2003; Roemer, Shagass, Straumanis, & Amadeo, 1979). In one study, no difference was seen between the P_a (22-38 ms) and P_b (45-60 ms) of controls and patients (Grillon et al., 1991). The second study is difficult to interpret, because middle latency components were analyzed by deriving a single average from all components found within the 15-100 ms window (Roemer et al., 1979), thereby incorporating both middle and late components into a single metric. The third study also used a time window from 30-100 ms post-stimulus, and focused on the P50/M50 as the first point of divergence between patients and controls. As such, it is equivocal whether deficits in patients exist in the middle latency AEP. There is, however, emerging evidence from animal models of schizophrenia that points to auditory dysfunction in MLRs, although drawing parallels to humans can be difficult. A study employing a human patient population is clearly warranted.

A secondary goal of our investigation was exploratory in nature: we sought to determine whether a strategy could be developed to assess the relative integrity of dorsal and ventral auditory pathways in our patient population. In the auditory system, there is emerging evidence of functionally distinct dorsal and ventral pathways governing sound localization and sound object recognition, respectively (Arnott, Binns, Grady, & Alain, 2004; Clarke, Bellmann, Meuli, Assal, & Steck, 2000; Clarke et al., 2002; Poremba et al., 2003; Rauschecker & Tian, 2000; Recanzone, 2001; Romanski et al., 1999; Tian, Reser,

Durham, Kustov, & Rauschecker, 2001; Weeks et al., 1999; Zatorre, Bouffard, Ahad, & Belin, 2002). Electrophysiological studies of schizophrenia patients have found differential impairment of dorsal and ventral pathways in the visual system, namely, the dorsal pathway shows greater deficits (Doniger, Foxe, Murray, Higgins, & Javitt, 2002; Foxe et al., 2001; Foxe, Murray, & Javitt, 2005). A theoretical justification for differential impairment that has been set forth is the so-called “dual trends theory,” which forwards the thesis that pathology in the brains of patients is organized along the lines of a dorsal/ventral distinction, and furthermore that patients demonstrate deficits at all cytoarchitectonic levels of the “dorsal trend” (Christensen & Bilder, 2000). To our knowledge, an electrophysiological investigation of early sensory processing within the dorsal and ventral auditory pathways has not yet been conducted with schizophrenia patients or indeed, in healthy controls. The auditory ventral stream comprises regions anterior to the primary auditory core region whereas the dorsal auditory stream courses posteriorly into the caudolateral belt areas and on into parietal cortex. Given the anatomic separation of these two streams, we reasoned that by carefully tracking the scalp topographies of processing prior to P1, and through source-localization methods, we might be able to observe a dissociation of activation flow that corresponds to the ventral and dorsal streams respectively.

Materials and methods

Subjects

Twenty-one male patients aged 20-50 (mean = 36 ± 10) served (data from one patient were eliminated due to anomalous morphology and no discernible componentry; demographics reported are for the analyzed sample). Of these, seventeen had a diagnosis of chronic schizophrenia and four of schizoaffective disorder, as defined by DSM-IV

criteria. Control subjects were comprised of fifteen (two female) paid volunteers aged 22-52 years (mean = 35 ± 9.4). Mean age of patients and control subjects did not differ significantly ($t_{34} = 2.03$, $p = 0.72$). All reported normal hearing. Handedness was determined by the Edinburgh Handedness Inventory (Oldfield, 1971); 3 patients and 1 control were left-handed.

Patients met the following inclusion/exclusion criteria: **Inclusion:** 1) current DSM-IV-defined diagnosis of schizophrenia or schizoaffective disorder. A best estimate diagnostic approach was utilized in which information from the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) (First, Frances, Pincus, Vettorello, & Davis, 1994) was supplemented by information from family members, psychiatrists, and medical records to generate a diagnosis, 2) ages 18 to 55, 3) male or female, 4) any race, 5) competent and willing to sign informed consent. **Exclusion:** 1) organic brain disorder, mental retardation, or significant medical illness, 2) current substance-induced psychotic disorder or a psychotic disorder due to a general medical condition determined by DSM-IV criteria, 3) significant risk of suicidal or homicidal behavior, 4) participants with prior intermittent alcohol or substance use were not excluded unless they met DSM-IV criteria for current alcohol or drug dependence in the last 6 months, 5) any history of hearing loss or injury to the ears, 6) any additional Axis I diagnoses.

Normal controls met the following inclusion/exclusion criteria: **Inclusion:** 1) matched for age to patients with schizophrenia, 2) any race, 3) absent any current Axis I or Axis II disorder or mood or psychotic disorder for the last 5 years as assessed by the SCID-I/NP (i.e., Non-Patient version), 4) no current or past history of psychotropic medication usage, 5) no family history of psychotic illness, 6) age 18 to 55, and 7) willing to sign informed consent. **Exclusion:** 1) organic brain disorder, mental

retardation, or significant medical illness, 2) significant risk of suicidal or homicidal behavior, 3) participants with prior intermittent alcohol or substance use were not excluded unless they met DSM-IV criteria for current alcohol or drug dependence in the last 6 months, 4) any history of hearing loss or injury to the ears.

For all patients, demographic information was collected including age, sex, and illness duration (See **Table 1**). Symptom ratings were analyzed using the Brief Psychiatric Rating Scale (BPRS) and the Scale for the Assessment of Negative Symptoms (SANS) (Lindenmayer, Bernstein-Hyman, & Grochowski, 1994). Clinical global impression (CGI) ratings were obtained. Doses of anti-psychotic, anti-cholinergic and adjuvant medications (e.g., anti-depressants, sedative/hypnotics, anti-manics, anti-epileptics) were recorded. Anti-psychotic doses were translated into chlorpromazine equivalents using the best available literature at the time of data analysis for conversion of dose levels of newer anti-psychotics (e.g., sertindole, seroquel).

Regarding medications, several studies have indicated that the effects of medications do not account for early sensory processing deficits. For example, work done in our lab revealed visual processing deficits in both medicated and unmedicated patients, as well as in first degree relatives of patients with schizophrenia (reviewed in Butler et al, 2005). Ford et al (1994) showed that both auditory and visual ERPs, especially the early automatic components, were unaffected by antipsychotic administration. In the auditory domain, Michie (2001) reported that duration MMN reduction cannot be attributed to neuroleptic medication. Valkonen-Korhonen and colleagues (2003) reviewed findings that while antipsychotic agents may improve attention-dependent processing, they do not necessarily ameliorate pre-attentive deficits. And, in a delayed tone-matching task, Rabinowicz and colleagues (Rabinowicz, Silipo, Goldman, & Javitt, 2000) reported that

Table 1. Demographic and Clinical Characteristics of Schizophrenia Patient Group (N=21)

Diagnosis: Schizophrenia/Schizoaffective Disorder	17/4
Neuroleptics: Atypical/Typical/Both	16/1/4
Chlorpromazine (CPZ)-equivalent $\pm$ SD, daily (mg)	1440 $\pm$ 621.6
Education $\pm$ SD	11 $\pm$ 2.8
Illness Duration $\pm$ SD	16 $\pm$ 9.4
Intelligence Quotient (IQ) $\pm$ SD	94 $\pm$ 13.6
BPRS Positive Symptom $\pm$ SD	10 $\pm$ 4.5*
SANS total all items except global at baseline $\pm$ SD	33 $\pm$ 7.7*

*Data from BPRS and SANS was collected for all but one participant

patients' impaired performance could not be attributed to medication. In terms of the effects of psychoactive drugs other than antipsychotics, one investigation of diazepam failed to find an effect for this benzodiazepine on P50 gating (van Luitelaar, 2003). Another group of investigators found that neuroleptic medication acting on dopaminergic systems actually increased P50 amplitudes in patients (Moxon, Gerhardt, & Adler, 2003).

Procedure

Subjects were seated in a comfortable chair in a dimly illuminated, sound-attenuated, electrically shielded (Braden Shielding Systems) chamber and asked to keep head and eye movements to a minimum, while watching a silent, subtitled movie. Standard 1000 Hz 74 dB SPL tones of 250 ms duration, with a 10 ms rise/fall time and with interstimulus interval (ISI) of 500 ms, were delivered binaurally to subjects through

headphones. Note that 10% of the total tones presented were duration deviants (100 ms); these deviants were not analyzed here and will be investigated further in a subsequent study. Acoustical stimuli were created using the SOUND module and presented using the GENTASK module of the Neuroscan STIM system. Stimuli were transduced through Sennheiser HD600 headphones. Subjects ignored the sounds and viewed silent subtitled movies on a monitor throughout the task.

Data acquisition

Continuous EEG was acquired through the ActiveTwo Biosemi™ electrode system from 168 scalp electrodes, digitized at 512 Hz. For display purposes, data were filtered with a low-pass 0-phase shift 96 dB 40 Hz filter after acquisition. With the Biosemi system, every electrode or combination of electrodes can be assigned as the “reference” and this is done purely in software after acquisition. BioSemi replaces the “ground” electrodes that are used in conventional systems with two separate electrodes: Common Mode Sense (CMS) active electrode and Driven Right Leg (DRL) passive electrode. These 2 electrodes form a feedback loop, thus rendering them “references.” For a detailed description of the referencing and grounding conventions used by the Biosemi active electrode system, the interested reader is referred to the following website: <http://www.biosemi.com/faq/cms&drl.htm>. All data were re-referenced to the nasion after acquisition, for analysis. After each recording session, before the electrode cap was removed from the subject’s head, the 3D coordinates of the electrodes with reference to anatomic landmarks on the head (nasion, pre-auricular notches) were digitized using a Polhemus Magnetic 3D digitizer. EEG was averaged off-line. Data were epoched (-100 ms pre-stimulus to 600 ms post-stimulus) and then averaged. It is of note that upwards of 2700 trials were collected for each subject. Baseline was defined as the

mean voltage over -50 to 0 ms preceding the onset of the stimulus. Trials with blinks and large eye-movements were rejected offline on the basis of horizontal and vertical electrooculogram recordings. An artifact rejection criterion of ± 80 to 100 μ volts was used at all other electrode sites to exclude periods of high EMG and other noise-transients. From the remaining artifact-free trials, averages were computed for each subject. These averages were then visually inspected for each individual to ensure that clean recordings with sufficient numbers of trials were obtained and that no artifacts were still included. Data were ultimately averaged across all subjects (grand mean averages) within a given group (patient or control) for visual comparison at the group level and for display purposes. The reader should note that throughout this paper, we use the familiar nomenclature of the modified 10-20-electrode system to refer to the positioning of electrode sites (American Electroencephalographic Society, 1991). Since our montage contains considerably more scalp-sites than this nomenclature allows for, in some cases, we will be referring to the nearest neighboring site within the 10-20 system.

Analysis strategy

For each electrode, the data from all subjects within each group (patients and controls) were collapsed into a single average waveform. These group-averaged waveforms were then visually inspected across all scalp-sites and the familiar components of the auditory evoked potential were identified. This allowed for definition of the precise timing of a given component and delineation of the scalp-sites at which each component was of maximal amplitude. As one might expect for these simple tonal stimuli, this led to identification of the typical sequence of AEP components (P_o , P_{20} , P_a , P_1 , N_1 , etc.) albeit with more precise scalp localization than typical, due to the very high-density montage used here. The timing and scalp topographies of the components

identified here are highly consistent with those found in the literature (Picton et al., 1974). Defining the componentry in this way has the benefit that the overall waveform can be used to constrain the number of analyses undertaken. It also allows the experimenter to define the exact timeframes and scalp sites from which measures will be taken for statistical analysis, without reference to the differential responses between patients and controls. Further, although the use of broadly defined component peaks is an excellent means of limiting the number of statistical tests that will be conducted, it is important to bear in mind that these components clearly represent the activity of many simultaneously active brain generators at any given moment (e.g., Foxe and Simpson, 2002). Limiting the analysis to a set of discrete component peaks for electrodes where the componentry are maximal represents a highly conservative approach to the analysis of high-density ERP data and raises the likelihood of missed effects (so-called Type II errors) in these rich datasets. Therefore, an exploratory (*post-hoc*) analysis phase was also undertaken (described below).

For each component of interest (P_o , P_{20} , P_a , P_1), the area under the waveform for an epoch centered on the peak of the grand mean was calculated (epochs were 4, 6, or 10 ms depending upon the width of the respective component's peak). These area measures were then used as the dependent variable. In order to investigate differences between the AEPs of patients and controls, we tested each identified component with a 2 x 2 x 3 mixed ANOVA. The factors were Group (patients vs. controls), Hemisphere (right vs. left), and Electrode. Analyses were performed across three pairs of scalp electrodes for each component; three electrodes at homologous locations on each side of the scalp were chosen that best represented the maximal amplitude of the component of interest in a

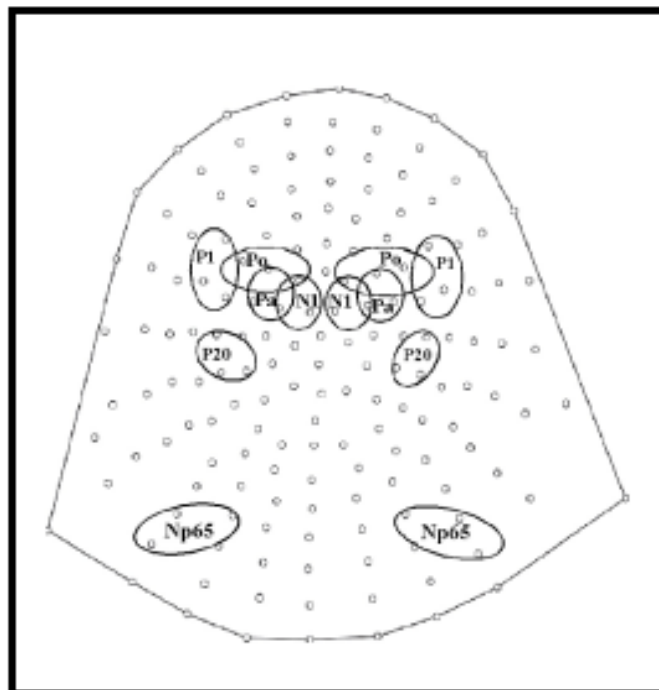
given analysis (see **Figure 1**). Statistical analyses were conducted using the SPSS™ software package (SPSS 11.5).

The ERP data were also inspected *post hoc* for further components of interest. A novel component, a negativity occurring over posterior parieto-occipital scalp at ~65 ms, was identified. The amplitude of this negativity was measured within a 10-ms window centered on its estimated peak latency of ~65 ms at 3 electrode sites in each hemisphere (PO7, PO3, O1, PO8, PO4, O2).

Power analysis

Since a central premise of the present study is that potentially small effects may have been missed or overlooked in previous studies, we sought here to fully characterize issues of power to identify effects in the low amplitude early MLR responses. Our primary question was the earliest patient differences in the AEP. In order to determine our sensitivity to any such differences, we conducted power analyses based on single

Figure 1. Selected scalp areas used for analysis of each component of interest. Maximum amplitude for each component was found in the outlined regions.



electrode comparisons (2-tailed t-test) using average amplitudes of each component of interest at a single time point, the peak latency. For this power analysis, we chose a single electrode at the maximum amplitude to represent each component rather than aggregating electrodes to avoid obfuscating small effects. In this way, we were able to determine where we had power to find significance and where we might lack power.

Topographic mapping

Voltage maps were constructed using the BESA (Version 5.0.2) software package (MEGIS Software GmbH, Munich, Germany). In addition, the scalp distributions of the AEPs were examined in scalp current density (SCD) maps. SCD maps are derived by computing the second spatial derivative of the field potential from the spherical spline interpolation of the surface voltage recordings (according to the methods of Perrin, Pernier, Bertrand, & Echallier, 1989), as implemented in BESA. BESA uses a 4th order spherical spline to interpolate the potential distribution over a spherical head model, optimally fit to the electrode cloud. The main advantages of the SCD technique are that it eliminates the contribution of the reference electrode and also mathematically eliminates effects of volume conduction on the surface potential due to tangential current flow within the scalp. Hence, SCD produces scalp topography maps that are considerably “sharper” than voltage maps, emphasizing local changes in ERP amplitude that are relatively insensitive to contributions from remote generators. Thus, the major strength of SCD analysis is the possibility for improved visualization of approximate locations of intracranial generators through the reduced spatial superposition of gradients originating from multiple intracranial sources (see e.g. Urbano, Babiloni, Onorati, & Babiloni, 1996).

Statistical cluster plots

As described above, we took a conservative approach to the analysis of the high-density ERP data in order to limit the number of statistical tests performed, with the spatio-temporal properties of the componentry delimiting the tests. Our conservative approach raises the likelihood of missed effects. We therefore performed an exploratory analysis as a means of fully exploring the richness of our data set and as a hypothesis-generating tool for future research. We have devised a simple method for testing the entire data matrix for possible effects, which we term *statistical cluster plots* (see Molholm et al., 2002; Murray et al., 2002). These cluster plots were derived by calculating point-wise, paired, two-tailed *t*-tests between the AEP of patients and controls. The results were then arrayed on a single grid, with scalp regions (electrode positions) plotted on the *y*-axis and post stimulus time plotted on the *x*-axis, thus providing a snapshot overview of significant differences between the groups across scalp regions over time. In the present data treatment, periods of significant difference were only plotted if a strict alpha criterion of 0.01 was exceeded and then only if this criterion was exceeded for at least 6 consecutive data points (see Wetherill & Levitt, 1965).

Source Analysis

We used dipole source-analysis, as implemented in the BESA (brain electric source analysis) software suite (Version 5.0.4), to estimate the intracranial generators underlying the greatest patient-control differences. BESA models the best-fit location and orientation of multiple intracranial dipole generator configurations to produce the waveform observed at the scalp, using iterative adjustments to minimize the residual variance between the solution and the observed data (see, for example, Scherg and Von Cramon, 1985; Simpson et al., 1995). For the purpose of the modeling, an idealized

three-shell spherical head model with a radius of 85 mm and scalp and skull thickness of, respectively, 6 and 7 mm was assumed. Group averaged waveforms were used to maintain the highest possible signal-to-noise ratio. No filters were applied in BESA.

We employed two *a priori* strategies for source modeling. The first was to step through each of our components of interest individually, building on the model with each addition of a dipole pair. First, in the control group, two dipoles were allowed to freely fit for both location and orientation within a 6-12 ms time window around the first peak, using the genetic algorithm module of BESA 5.0.4. Additional pairs of symmetrically constrained dipoles were fitted to the next two components such that a six-dipole solution was created. The solution for the control group was then applied to the patient group. Talairach coordinates for all dipoles were used to estimate the Brodmann areas of the closest gray matter structures. It must be pointed out that in dipole analysis, each of the modeled equivalent current dipoles represents an oversimplification of the activity in the areas, and therefore each should be considered as representative of ‘centers of gravity’ and not necessarily discrete neural locations (Murray et al., 2002; Dias, Foxe, & Javitt, 2003; Foxe, McCourt, & Javitt, 2003).

Our second strategy was employed to assess where in auditory cortex the earliest differences between patients and controls occurred. We reasoned that if the earliest differences fell anterior to the auditory core region, this would implicate the ventral auditory stream, and if these differences fell posterior and superior to the auditory core (Heschl’s gyrus), this would implicate generators in the auditory dorsal stream. The specific steps we took for this source analysis (Source Analysis II) are further explicated in the results section.

Results

Electrophysiological results (general description)

We begin with a description of the general ERP patterns observed in the data of our 15 control subjects. **Figure 2** shows data from group-averaged waveforms taken from an anterior and a posterior electrode. We were able to reliably identify componentry as early as the P_o , which peaked at ~15 ms post-stimulus over frontal, fronto-central, and central scalp-sites. The next component we saw clearly was the P_{20} , which peaked posteriorly at ~21 ms. Next, the P_a was present at ~38 ms over frontal and fronto-central sites. The P_1 , peaked at ~46 ms at fronto-central and central sites. The N_1 peaked at ~95 ms over central scalp.

We compared the electrophysiological responses of healthy controls to those of our patient group (see **Figure 3**). As in the controls, the classical AEP componentry was evident and the earliest peaks (P_o , P_{20} and P_a) all had identical latencies to those of the controls. Very slight delays in peak latency were noted for the P_1 , which peaked at ~50 ms fronto-centrally and centrally. The N_1 peaked over central scalp-sites at ~95 ms. By fully describing and characterizing middle latency components of the auditory evoked potential over the entire scalp surface of controls and schizophrenia patients, we found evidence for the earliest point of auditory sensory dysfunction in schizophrenia from timepoints as early as the first identifiable MLR component (P_o). In what follows, we will step systematically through the individual componentry of the MLR as well as the following $Np65$ and N_1 components.

Figure 2. Early components of the auditory evoked potential in a group of healthy controls (N=15). Waveforms are derived from group averages taken from an anterior site (gray waveform) and a posterior electrode (black waveform). Components are labeled on the basis of the latency of the peak amplitude, polarity, and sequential position of the major deflections. The majority of the early AEPs are clearly identified in the waveform from the anterior site.

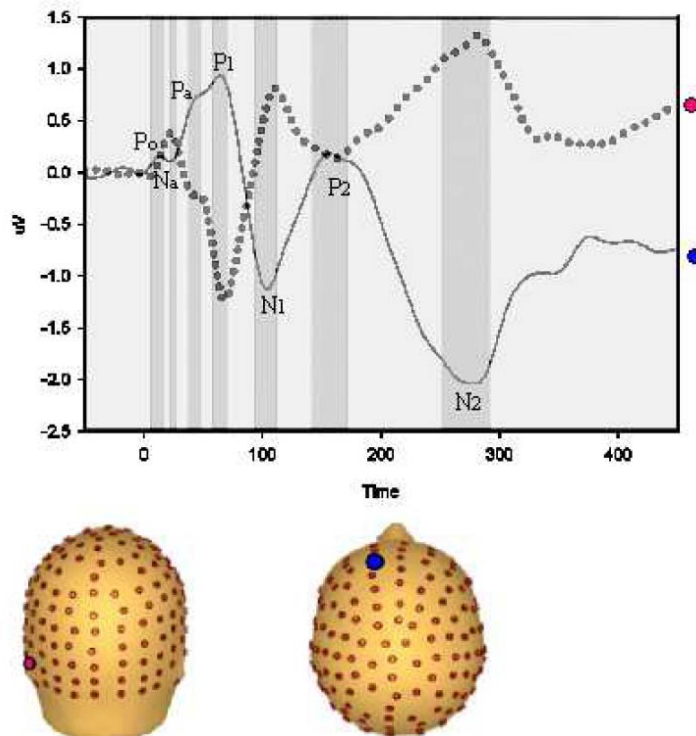
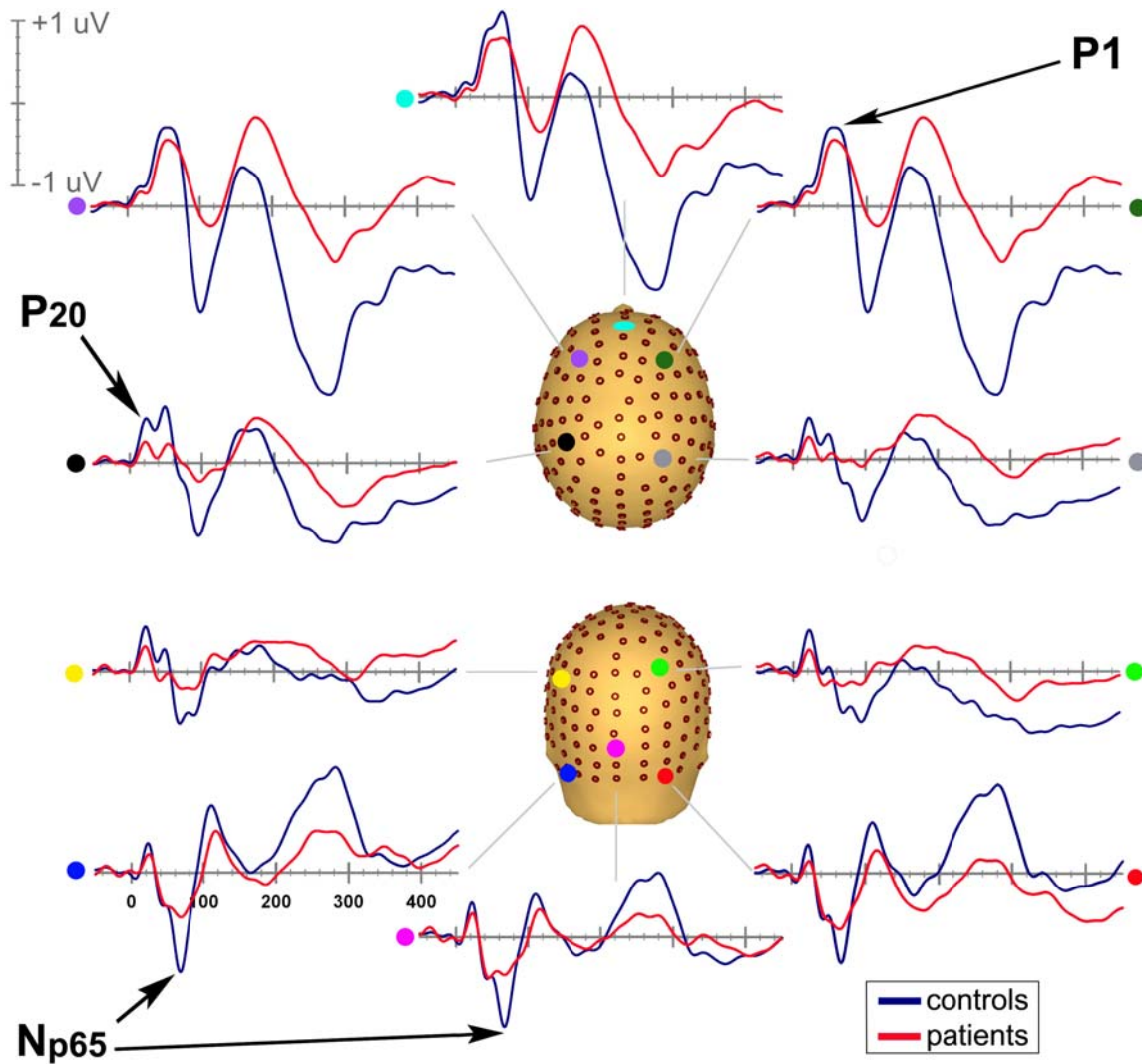


Figure 3. Auditory-evoked potentials in controls (n=15) are blue, and patients (n=21) are red (ISI=500ms). Data from 10 electrodes spanning anterior to posterior scalp sites are presented.



Individual components

The P₀

The P₀ had a peak latency of ~15 ms in both groups and was evident at both frontal and parietal scalp sites. The ANOVA revealed a significant main effect of Group ($F(1,34) = 35.65, p = 0.031$), reflecting the fact that the amplitude of P₀ was significantly attenuated for patients. No other main effect or interaction was significant (for summary of ANOVA results, see **Table 2**). Topographic mapping showed a similar parietal distribution for the P₀ in both groups (**Figure 4**, Row A). A subtraction map (rightmost panel) shows the map of the difference between controls and patients, indicating a largely similar distribution to that of the base P₀ map. The exploratory statistical cluster plots (see **Figure 5**) indicated that this difference began very early and assessment of the running t-tests showed an onset at just 8ms. We conducted a *post-hoc* ANOVA over the 8-12 ms window to better characterize this effect. A main effect of Group was significant ($F(1,34) = 8.99, p = 0.005$).

The P₂₀

In our data, the P₂₀ was represented by a positivity that peaked at ~21 ms posteriorly and centrally in both groups. The ANOVA revealed a significant main effect of group ($F(1,34) = 7.47, p=0.01$). It also revealed a significant effect of hemisphere ($F(1,34) = 6.43, p=0.016$), attributable to greater amplitudes at this latency over the left hemisphere for both controls and patients. As with the P₀, topographic maps (see **Figure 4**, Row B) show a strong parietal positivity with a concomitant fronto-polar negativity for controls. The P₂₀ distribution for patients was very similar, with a parietal positivity. The fronto-polar negativity was substantially weaker. This was particularly evident in the subtraction map, where the largest difference between groups was concentrated over

Table 2. Earliest differences found between patients and controls in AEPs: Auditory brainstem responses (ABRs) and mid latency components.

Early latency components: ABRs (0-10 msec)	n	Patient status	Results
Pfefferbaum et al, 1980	15 P, 15 C	Med=8 Unmed=7	NS
Szelenberger et al, 1983	20 P, 50 C	All med	NS
Brecher & Begleiter, 1985	9 P, 9 C	All med	NS
Harell et al, 1986	20 P, 10 C	Med=10 Unmed=10	Later latency of wave III in unmed patients
Hayashida et al, 1986	88 P, 88 C	All med	18/ 88 P had signif. decreased mean amplitudes of wave I, II, III, IV/ V; 40/ 88 P had signif. later latencies of wave I, IV/ V
Kimhi et al, 1987	14 P, 10 C	All unmed	Later latency of III, IV in P; increased interpeak latency III-V and I-V in P
Lindstrom et al, 1987	20 P	Med=9 Unmed=11	10/ 20 abnormal
Lindstrom et al, 1990	39 P, 47 C	All unmed	15/ 39 abnormal
Grillon et al, 1990	14 P, 16 C	All med	Wave I-III delay in patients
McKay et al, 2000	44 P, 22 C	Not reported	NS
Mid latency components (10-35 msec)			
Grillon et al, 1991	18 P, 18 C	All med	NS

P=patients, **C**=controls, **NS**=no significant differences seen

Figure 4. Voltage scalp topographies from the control and patient group-averaged waveforms, for the P_o, P₂₀, P_a, and P₁, and the corresponding control minus patient difference.

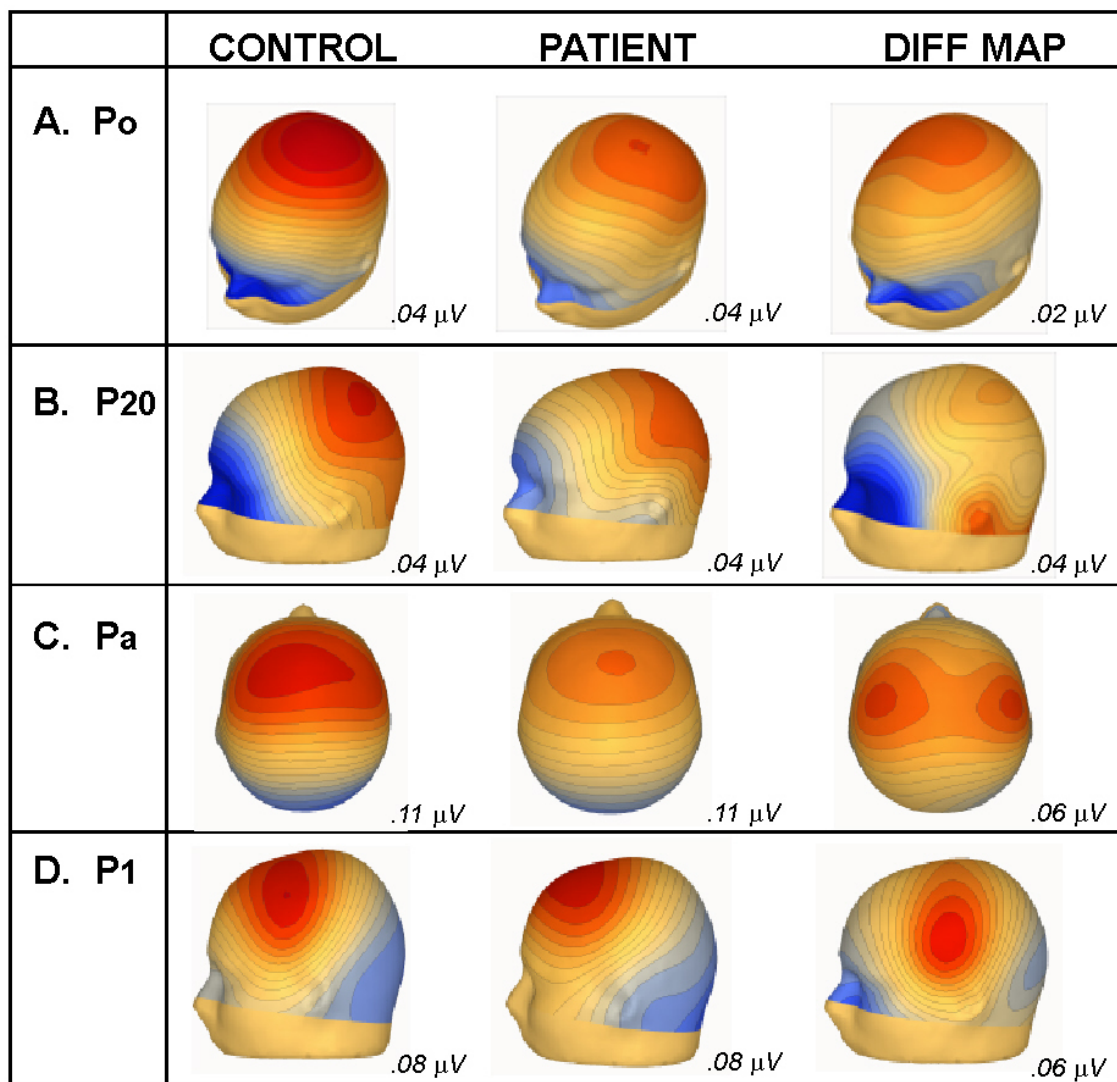
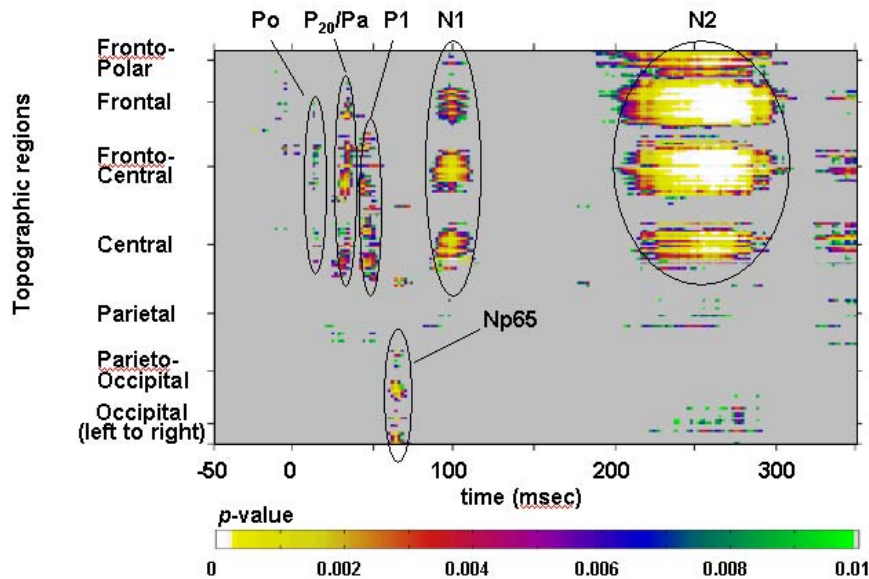


Figure 5. Statistical cluster plot of the results of the point-wise running t -tests comparing the amplitudes of the patient and control AEPs. Time with respect to stimulus onset is presented on the x axis and topographic regions of 168 electrode positions on the y axis. Color corresponds to significance level. Note that there is overlap between the P_{20} and P_a .



fronto-polar/inferior-frontal scalp. The subtraction map also suggested that a lateral infero-temporal source might be implicated during this timeframe.

The P_a

The P_a had a peak latency of ~ 38 ms over anterior scalp-sites for both patients and controls. An ANOVA for this component revealed a significant main effect of Group ($F(1,34)=12.16$, $p=0.001$), again reflecting substantial attenuation of P_a amplitude in patients. Topographic mapping showed a fronto-central positivity for both groups, broadly distributed across both hemispheres, with a concomitant occipital negativity (see **Figure 4**, Row C). The subtraction map had a clearly dissociable distribution from that of the base P_a maps. It revealed a pair of bilateral positive foci that were more lateralized and concentrated somewhat more posteriorly over central scalp. The fact that this

difference map is clearly dissociable from the base P_a map indicates the multiple generator configurations that must necessarily underlie the activity pattern during this processing period. The maps suggest that the P_a reflects both lateral activity as well as contributions from more fronto-central generators. This pattern also suggests that the fronto-central aspect of the response is more preserved in patients, whereas the bulk of the deficit for this group is in the more lateral responses.

The P1

As with the P_a , the P1 component likely reflects the activity of multiple simultaneously active generators. Over fronto-central regions, the P1 had a peak latency of ~46 ms for controls and patients. A robust main effect of group was found ($F(1,33) = 6.68, p=0.014$). The topographies of the P1 for controls showed a central positivity with a concomitant occipital negativity, while the patients' positivity was distinctly more frontal and had a similar occipital negativity (see **Figure 4**, Row D). Here, the subtraction map was distinctly different from either base P1 map, again suggesting contributions from more posterior generators.

The N_{p65}

A previously uncharacterized negative-going component was discovered in the course of this investigation. Appearing posteriorly at ~65 ms, it was very pronounced in our controls. Here, we refer to this component as the N_{p65} . This component was highly attenuated in patients. The amplitude of the N_{p65} was measured within a 6-ms window centered on its peak latency of 62 ms at 3 electrode sites on the left and 3 on the right. An ANOVA revealed a robust effect of Group ($F(1, 34) = 11.25, p=0.002$) (See **Figure 6**). The component is clearly dissociable from the known AEPs.

Issues of Power

In our investigation of the earliest components that reveal differences between patients and controls, we used the data to make estimates of power (see **Table 3**). Our hypothesis was that there would be significant attenuation of AEPs in patients compared to controls from time points as early as the first recognizable component, the P_0 . However, we anticipated the effect size for this difference to be quite small. Indeed the power analysis revealed the lowest level of power for the P_0 ; nevertheless, this low was a healthy 75%. While this is slightly below 80%, we are confident in this medium sized effect, with highly significant differences in the amplitude of the P_0 of patients and controls.

Statistical Cluster Plots

In order to better detect effects between patients and controls in this large dataset, we computed a statistical cluster plot (see Methods). This served as a hypothesis-generating tool, in that it provided us with a snapshot of where and when significant

Figure 6. The Np65: A pronounced negative going deflection over posterior scalp, peaking at 65 ms. This is shown for patients (red) and controls (blue), from right and left occipital sites where the response was maximal.

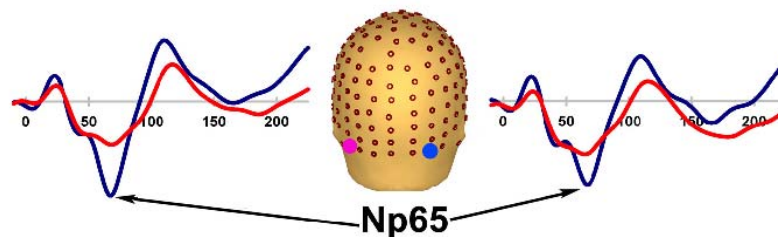


Table 3. Power analysis results for auditory components of interest between patients and controls*.

Component	P ₀	P ₂₀	P _a	P ₅₀	N _{p65}	N1
Peak latency	15 msec	21 msec	38 msec	46 msec	62 msec	93 msec
Electrode site	FC2	C3	FC1	FC3	PO7	FCz
Average amplitude**	P 0.150 C 0.399	P 0.191 C 0.502	P 0.474 C 0.962	P 0.511 C 1.238	P 0.611 C 1.321	P 0.219 C 1.501
SD	P 0.247 C 0.301	P 0.302 C 0.302	P 0.280 C 0.560	P 0.444 C 0.852	P 0.479 C 0.637	P 0.876 C 0.993
Statistical power reached	75%	92%	93%	92%	98%	99%
p value [±]	p=.008	p=.005	p=.006	p=.007	p=.001	p=.000
Minimum n needed to reach power of 80%	19 P, 19 C	12 P, 12 C	11 P, 11 C	11 P, 11 C	8 P, 8 C	7 P, 7 C

*Single electrodes were used to generate estimates of power for each component.

** Values are taken from group averages (patient n=21, control n=15) referenced to the nasion before baseline correcting. [±] 2-tailed t-test, 2 sample unequal variance

differences were occurring between groups. We thus observed the clear and distinct clusters corresponding in latency to known auditory components (P₀, P₂₀, P_a, P₁, N_{p65}, N1, and N2) (see **Figure 5**). This reveals differences at the earliest discernible component, which appear to propagate up the auditory processing stream. By and large, the statistical cluster plots correspond to the effects uncovered by our ANOVAs, for which we had *a priori* hypotheses. In addition the plot revealed an unpredicted difference at about 65 ms which we have termed the N_{p65}. Further, substantial amplitude differences were observed at the latency of the N2 as we would expect, given that patient deficits at later latencies follow upon the earlier deficits that are the focus of the present study.

Results of Dipole Source Analysis I: Subcortical-cortical distinction

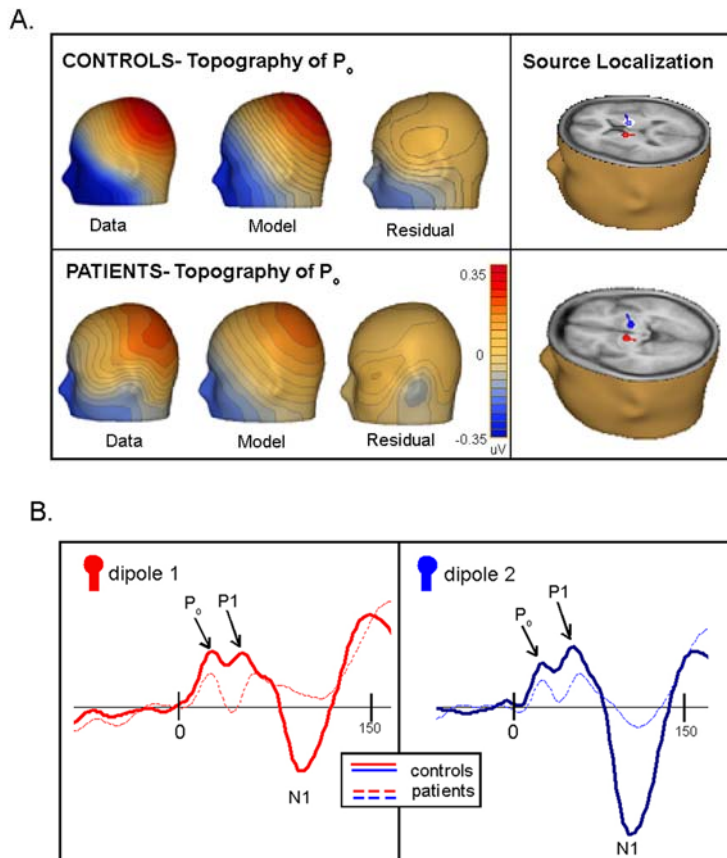
To determine the location of the generators of the middle latency components, the BESA genetic algorithm dipole analysis module was used. A symmetrically constrained pair of dipoles was allowed to freely fit for a 6-ms time window around the first peak, the P_0 (12-18 ms). The resulting model, explaining 95.8% of the variance, placed sources bilaterally in the thalamus (Talairach coordinates: $x=13$, $y=-7$, $z=7$). Given previous findings of major contributions from primary auditory cortex to the middle latency potentials (see Discussion), we constrained a pair of dipoles to the primary auditory cortices bilaterally (46, -24, 12) to test whether such a model could also satisfactorily explain P_0 activity. This model explained only 70.3% of the variance. Furthermore, when the dipoles were now allowed to freely fit from this starting point in primary auditory cortex, they return to the thalamus (see **Figure 7, Panel A**).

In the next step, we fixed the first dipole pair in their original thalamic locations and then a symmetrically constrained second dipole pair was fit to a 6-ms time window around the next discernible peak, the P_{20} (18-24 ms). Bilateral sources were modeled in the insula (45, 10, 15), with 98.2% of the variance explained. These sources fell approximately 10 mm anterior to the primary auditory cortex. As a test, dipoles were fixed in the core of primary auditory cortices bilaterally (46, -24, 12); this model explained 96.8% of the variance.

A third symmetrically constrained dipole pair was allowed to fit to a 12-ms time window around the next discernible peak, the P_a (32-44 ms). This model placed bilateral sources in the region of the inferior parietal lobule (IPL; 43, -28, 25). This model explained 99.2% of the variance across the 32-44 ms epoch. Given that this model was

only explaining 1.0% more of the variance than the previous, 4-dipole model, they likely reflect subtle contributions from posterior regions. Previous electrophysiological

Figure 7. Dipole source analysis I. **Panel A:** Source analysis of the P_o in controls and patients reliably models the generators bilaterally in the thalamus; this 2-dipole model explains fully 95.8% of the variance for controls and 87.6% for patients during a 12-18 ms time window. **Panel B:** Overlay of the fit of dipoles 1 (red) and 2 (blue) in patients and controls.



investigations (e.g. Yoshiura, Ueno, Iramina, & Masuda, 1995; Yvert, Crouzeix, Bertrand, Seither-Preisler, & Pantev, 2001) have shown Heschl's gyrus to be the generator of the P_a . Once more, we fixed this dipole pair in primary auditory cortex (46, -24, 12), and found that they still explained fully 94.3% of the variance for this epoch.

When the epoch around the P1 was selected (50-72 ms), the 6-dipole solution above already explained 98.7% of the variance, rendering further dipoles uninformative. For the entire epoch of interest, encompassing the P_o, P₂₀, P_a, and P1, (0-72 ms), the model explained 98.6% of the variance. For the epoch 0-50 ms, which leaves out the very prominent contribution of the P1, fully 98.3% of the variance continued to be explained.

Next, we applied this model to our patient data. For the 0-72 ms epoch, the model explained 97.8% of the variance. Excluding the P1, the model explains 98% of the variance for the epoch 0-50 ms.

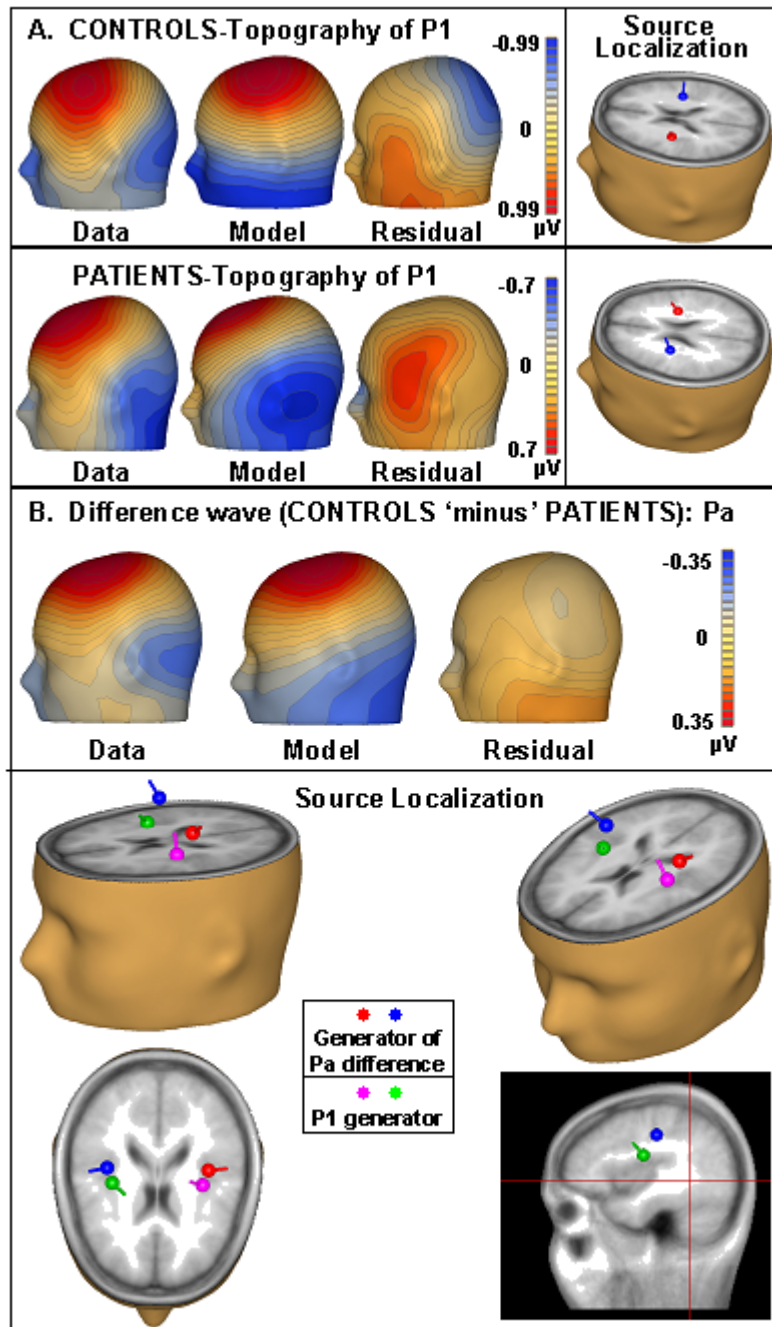
Results of Dipole Source Analysis II: Exploration of dorsal-ventral dissociation

In order to explore where the differences between patients and controls are localized, we employed the following strategy. We first separately source-localized the P1 for controls and patients to provide us with a metric of one well-known auditory component, the major generators of which are well known to be in and around the core region of auditory cortices (Farrell, Tripp, Norgren, & Teyler, 1980; Godey, Schwartz, de Graaf, Chauvel, & Liegeois-Chauvel, 2001; Liegeois-Chauvel et al., 1994; Reite, Teale, Zimmerman, Davis, & Whalen, 1988; Reite, Teale, Zimmerman, Davis, Whalen et al., 1988) (see **Figure 8, Panel A**). A pair of symmetric dipoles was placed in primary auditory cortex, (42, -28, 12); the model explained 92.2% of the variance. For the patients, this model explained 94.0% of the variance.

Next, we sought to localize the generator of one early significant difference between the auditory evoked potential of patients and controls, the P_a (see **Figure 8, Panel B**). Utilizing a difference wave (controls minus patients) for this model, we freely fit a pair of symmetric dipoles to the 25-45 ms time frame to determine where the generators for the early difference were localized, relative to those of the P1. With 88.6%

of the variance explained, we found bilateral stable generators that were superior and posterior to those of the P1 for controls and patients (47, -18, 24). Our first dipole source model (Dipole Source Analysis I) corroborates this finding; in that model, bilateral sources for the P_a were localized 13 mm posterior and superior to primary auditory cortex, in the inferior parietal lobule.

Figure 8. Source analysis II. **Panel A:** Source analysis of the P1 for both patients and controls reveals remarkably similar localizations of the generators for both groups. **Panel B:** The green and purple dipoles demarcate the modelled source of the P1 in controls. The red and blue dipoles, which show the modeled difference (controls minus patients) for the P_a , are both posterior and superior to the first pair.



Discussion

The present data show robust decreases in amplitude during the middle latency AEP in patients with schizophrenia. In fact, significant differences were uncovered as early as just 15 ms post stimulation. Regarding the mid-latency components, we see significant attenuation in patients as early as the P_o (15 ms), the first auditory component following the ABR. The next of the classically defined mid-latency components, the P₂₀, is also substantially attenuated in our patient group, as is the following P_a (39 ms). As such, these data strongly support the notion that auditory sensory processing is impaired in schizophrenia from the moment of initial cortical afference in primary auditory cortex, and also appear to strongly imply that impairment begins even earlier, during subcortical processing. The implications of these results are discussed in more detail in what follows.

Early auditory processing deficits in schizophrenia

There is a substantial literature describing effects on later-latency AEP components (>50 ms) of patients with schizophrenia, and deficits in these components (e.g. P1, N1, MMN) have been consistently documented (Javitt, Jayachandra, Lindsley, Specht, & Schroeder, 2000; Michie, 2001; Valkonen-Korhonen et al., 2003). Likewise, investigations of very early subcortical responses, so-called auditory brainstem responses (ABRs) are abundant, although findings from these studies have been somewhat equivocal (see **Table 4**). For example, Lindstrom and colleagues published two studies (Lindstrom, Klockhoff, Svedberg, & Bergstrom, 1987; Lindstrom, Wieselgren, Klockhoff, & Svedberg, 1990), with the first reporting abnormal ABRs in just 10 of 20 patients, and the second reporting less than half of the patients (15 of 39) showing abnormal ABRs. Four studies by other groups also found significant latency delays in ABRs of patients (Grillon, Ameli, & Glazer, 1990; Harell, Englender, Demer, Kimhi, &

Table 4. Summary of the results of the ANOVAs comparing the amplitude of the early AEP components of patients and controls (with factors of group, hemisphere, and electrode (2 X 2 X 3)).

Component	Time Window	Scalp region	EFFECTS (p values)		
			Hemisphere	Group	Group X Hemisphere
P ₀	13-17 ms	Fronto-central	.310	.031*	.457
P ₂₀	18-24 ms	Central	.016*	.010*	.980
P _a	36-42 ms	Fronto-central	.072	.001**	.433
P1	46-52 ms	Fronto-central	.256	.014*	.535
N _{p65}	59-65 ms	Parieto-occipital	.499	.002**	.460
N1	88-98 ms	Fronto-central	.326	.001**	.677

Zohar, 1986; Hayashida et al., 1986; Kimhi, Englender, Zohar, & Harell, 1987), while rather frustratingly, four other studies found no differences at all between the ABRs of patients and controls (Brecher & Begleiter, 1985; McKay, Headlam, & Copolov, 2000; Pfefferbaum, Horvath, Roth, Tinklenberg, & Kopell, 1980; Szelenberger, 1983). While our understanding of ABRs in schizophrenia clearly remains somewhat incomplete, these studies do appear to suggest that auditory processing deficits may well occur before initial afference of primary auditory cortex (i.e. subcortically). Unfortunately, the next time period of auditory processing that has been the focus of significant research efforts begins with the auditory P1 component, some 45 ms after the end of the ABR. As outlined in the Introduction, the intervening MLR potentials have been largely skipped over, despite the fact that they demarcate a key period in sensory processing in that they bracket the point of initial afference of primary auditory cortex.

With regard to the P1, unlike the ABR responses, there is widespread agreement in the literature pointing to patient deficits. (e.g. Boutros et al., 2004; Clementz et al., 1997; Clementz et al., 1998; Erwin et al., 1991; Erwin et al., 1994; Freedman et al.,

1987). This component is most often studied in the context of a gating paradigm that involves presentation of a tone (S1) followed by a short inter-stimulus-interval (200-500 ms) before presentation of a second tone (S2) (e.g. Adler et al., 1985; Braff, 1993; Clementz et al., 1997; Freedman et al., 1987; Nagamoto, Adler, Waldo, & Freedman, 1989). What is typically done is that the amplitude of the P1 evoked by the second of these tones (S2) is measured as a function of the amplitude of the P1 evoked by the first tone (S1). Control subjects show a clearly attenuated P1 to S2, presumably due to sensory gating. This attenuation is frequently found to be decreased in patients (Braff, 1993; Clementz et al., 1997; Clementz et al., 1998; Freedman et al., 1987; Nagamoto et al., 1989). More importantly for the present study, it has been shown that this effect is in large part a consequence of an attenuated P1 to the first S1 stimulus (Clementz & Blumenfeld, 2001). But our data suggest that the point of divergence between the auditory evoked response of patients and healthy individuals comes at a much earlier point, the significance of which lies in the bridging of our knowledge about subcortical versus cortical deficits in schizophrenia.

Source localization of mid-latency auditory evoked responses

Thus far, what we know about the sources of the mid-latency potentials has been largely determined through magneto-encephalographic (MEG) recordings, and there tends to be consensus in the MEG literature that these components are mainly generated in primary auditory cortex. Using 37-channel MEG recordings, Kuriki and colleagues (Kuriki, Nogai, & Hirata, 1995) source-localized the M10, M18 and M30 to the medial part of Heschl's gyrus on the supratemporal plane. However, they modeled data from only four subjects (just two for the M10), and these researchers acknowledged that the existence of additional subcortical sources could not be excluded. Also using 37-channel

MEG and recording from six subjects, Yvert and colleagues (2001) localized the P_a , N_b and P_b (28, 40, and 52 ms respectively) to medial and antero-lateral portions of Heschl's gyri. Yoshiura and colleagues (1995) used 7-channel MEG recordings taken from seven subjects; the sources of N_a , P_a , N_b , and P_b were all estimated to be in the supratemporal auditory cortex. Makela and colleagues (1994) recorded from 9 control subjects with a 122-channel array, also pointing to cortical generators for the P30. It is clear from these studies that at least the later MLR components are generated mainly in auditory cortices on the superior temporal plane, quite consistent with the source localizations reported here, but these recordings do not rule out subcortical sources for the earliest MLR components. It is important to emphasize that a major limitation of MEG is in its insensitivity to activity from deep sources (Hillebrand & Barnes, 2002) and it is thought that subcortical sources cannot be effectively detected (Okada, 1993). Indeed, Hillebrand and Barnes found that source depth was the single most important factor in determining the sensitivity of MEG to brain activity (Hillebrand & Barnes, 2002). They show that the probability of finding a source decreases as the distance from the skull surface increases. Furthermore, they specifically determined that MEG has a relatively low detection probability for areas in the temporal lobe, an issue that will simply be further compounded for deeper sources in the thalamus.

Another human study of the mid-latency AEPs used intracranial recordings in auditory cortices of 37 humans to localize the generators of auditory components at 30, 50, 60 and 75 ms (Liegeois-Chauvel et al., 1994); all were found to be distributed medio-laterally along Heschl's gyrus. However, intracranial recordings taken from primary auditory cortex are by definition insensitive to subcortical generators, as they will only detect highly local activity. These researchers acknowledged that their data could not

exclude a subcortical generator for the earliest of the MLRs, the N_a , which was a negative inversion of the P_{20} found in their dataset at 19 ms.

Until now, there has been limited discussion of subcortical versus cortical sources of the MLRs. One exception was a study done by Kaseda and colleagues (Kaseda, Tobimatsu, Morioka, & Kato, 1991). This electrophysiological investigation of the mid-latency responses found the N_a to be abnormal in patients with localized lesions of the thalamus and subcortical white matter. Consistent with their findings, our data suggest that there are thalamic generators of the earliest of the middle latency components (P_o), and cortical generators of the P_{20} , P_a and P_1 . While our model is unable to identify the specific thalamic nucleus of the source, as resolution of this spatial order is clearly beyond the capacity of dipole analysis, it seems highly likely that the medial geniculate body (MGB) is the major generator. Our topographic map of the P_o corroborates the existence of a subcortical generator, as it reflects widely distributed activity over frontal and posterior regions, with a distribution that is not consistent with generators on the supratemporal plane or primary auditory cortex (see **Figure 4**).

The implication is clear that the earliest afferent inputs to primary auditory cortex arrive from subcortical regions that already show evidence of dysfunction in patients with schizophrenia, arguing for a bottom-up model of auditory processing deficits. A recent study from our group by Butler and colleagues (Butler, Martinez, Foxe, Kim, Silipo, Mahoney, Shpaner, Jalbrikowski, Javitt, in press) reflects analogous findings in the visual system of patients; these researchers found cortical processing deficits preceded by subcortical dysfunction. These findings may represent an organizing principle for neurocognitive dysfunction in schizophrenia.

Dorsal/Ventral Auditory Pathways

There is growing evidence for functionally distinct auditory pathways in humans (Anourova et al., 2001; Arnott et al., 2004; Brunetti et al., 2005; Clarke et al., 2000; Clarke et al., 2002; Poremba et al., 2003; Scott, 2005; Weeks et al., 1999; Zatorre et al., 2002) pointing to a what/where distinction analogous to that seen in the visual system (Mishkin, Lewis, & Ungerleider, 1982). These have been identified as a spatial stream which subserves sound localization and courses dorsally, and a pattern or object stream which subserves sound object recognition and courses ventrally (Rauschecker & Tian, 2000; Romanski et al., 1999; Tian et al., 2001). Dorsal and ventral streams have been studied in the visual system to a much greater extent than in the auditory system, and it is well established in the visual system that two functionally distinct pathways exist (Mishkin et al., 1982). In work done in our laboratory, we have seen consistent deficits of dorsal stream processing in the visual system of schizophrenia patients, relative to ventral stream processing: visual P1 amplitudes were significantly reduced to a much greater degree over dorsal scalp than ventral in a patient group in a study by Foxe and colleagues (2001), a finding that has since been replicated twice by our group in studies of dorsal/ventral visual stream interaction in schizophrenia (Doniger et al., 2002; Foxe et al., 2005). While the present study was not designed to expressly test the functional integrity of the dorsal and ventral auditory pathways in patients, automatic sensory activation of these pathways is an inherent result of performing virtually any auditory task. Therefore, we analyzed these data with an eye toward the relative functioning of these separable streams. Topographic analysis of the early sensory processing effects suggested more posterior generators were involved in the observed deficits and exploratory source-analysis suggested that these deficits were localized within regions of the inferior parietal

lobes. As such, these data are consistent with relatively greater impairment of dorsal auditory pathway functioning in patients.

If it is determined that patients have a dorsal auditory deficit, one obvious prediction is that they should show deficits in auditory sound localization tasks. To date, a handful of studies have assessed sound localization in schizophrenia, with mixed results (Balogh, 1979; Balogh & Leventhal, 1982; de Gelder, Vroomen, Annen, Masthof, & Hodiament, 2003; Guterma & Klein, 1991; Hatashita-Wong & Silverstein, 2003; McGhie, 1961; Michie, Fox, Ward, Catts, & McConaghy, 1990; Mickey & Dalack, 2005; Olsson & Nielzen, 1999). In 1961, McGhie and Chapman (1961) collected subjective reports from patients suggesting they experienced difficulty identifying the source of a sound. Balogh and Leventhal (1982) examined the ability of patients to make judgments about the direction of auditory stimuli; results were mixed. De Gelder and colleagues (2003) reported that a patient group performed as well as controls in sound localization, but these findings were derived from an audiovisual integration task. Another study found the “precedence effect,” a phenomenon by which inhibitory processes in the auditory system aid in sound localization, to be intact in patients (Mickey & Dalack, 2005). None of these studies has investigated the underlying neurophysiology of sound localization in schizophrenia. While the exploratory results presented here do suggest deficits specific to the dorsal pathway, studies that employ tasks that are specifically designed to tap the functional integrity of both dorsal and ventral pathways are clearly warranted.

Implications of Early Sensory Deficits for Higher-Order Function

The hallmark of schizophrenia is dysfunction of higher-order cognitive functioning; this, however, raises the question of how early sensory deficits play into

the clinical manifestations of the disorder. Good evidence is now forthcoming that these early deficits may well be the antecedents of what on the face of it appear to be higher-order deficits. When Kraepelin described dementia praecox in 1893, he identified the dysfunction of attention as a cardinal feature of the disease. However, we now know that disrupted attentional processes may actually be due to basic auditory processing deficits. Evidence to support this assertion comes from studies of the auditory mismatch negativity (MMN); numerous studies have found the MMN to both duration and frequency deviants to be highly attenuated in schizophrenia patients (Javitt et al., 1995; Javitt et al., 1997; Oades et al., 1997) and this attenuation has been correlated with behavioral outcomes such as subsequent deficits in attention-dependent processing (Javitt, 2000). One patient study found that lack of left hemisphere lateralization of the MMN was associated with positive symptoms (as reviewed by Ford & Roth, 2004). Baldeweg and colleagues (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004) found MMN amplitude in patients to be significantly correlated with cognitive impairment. Further evidence that higher order processing is impaired subsequent to deficits in basic sensory processing comes from auditory and visual experiments done in our laboratory. Leitman and colleagues (Leitman, 2005) have shown that impairments in interpreting affective prosody, on the face of it a higher-level social-cognitive function, are secondary to basic auditory deficits. In the visual system, deficits in the magnocellular system are associated with reading difficulties (Revheim et al, in press), while early visual processing deficits are associated with deficits in independent living skills in patients (Butler et al., 2005).

Conclusions

The present study establishes that auditory sensory processing deficits are ubiquitous in patients with schizophrenia from time points as early as 15 ms. A source localization model of the first major component of the MLR (P20) in healthy controls and patients indicates that it is generated subcortically, while subsequent mid-latency components are mainly generated cortically. This argues for a bottom-up model of impairment in auditory sensory processing. Furthermore, the present findings warrant further investigation of a possible dorsal-ventral distinction in auditory processing of patients. Such an investigation could lead us to a better understanding of possible organizing principles of dysfunction in schizophrenia. Elucidating such over-arching principles will ultimately allow for the development of more specific diagnostic and therapeutic interventions. Measures developed in the course of investigations such as this may serve as endophenotypes for etiological investigations of schizophrenia (e.g. Yeap et al., 2006).

Acknowledgments

This work was supported by grants from the National Institute of Mental Health (RO1- MH65350 to JJF; RO1- MH49334 to DCJ) and by a Ruth L. Kirschstein pre-doctoral fellowship to VL (NRSA – MH074284). SM received support from a Kirschstein post-doctoral fellowship (NRSA – MH068174). We are indebted to Manuel Gomez-Ramirez and Galia Koonyevsky for their ongoing support and to the team at the Cognitive Neurophysiology laboratory for their dedication and hard work. We would like to thank Ms. Gail Silipo for her assistance in recruiting subjects and her enduring dedication to the patients. The principle investigator, Dr. Foxe, takes responsibility for

the integrity of the data and the accuracy of the data analysis, and attests that all authors had full access to all the data in the study.

References

- Adler, L. E., Waldo, M. C., & Freedman, R. (1985). Neurophysiologic studies of sensory gating in schizophrenia: comparison of auditory and visual responses. *Biol Psychiatry*, 20(12), 1284-1296.
- Anourova, I., Nikouline, V. V., Ilmoniemi, R. J., Hotta, J., Aronen, H. J., & Carlson, S. (2001). Evidence for dissociation of spatial and nonspatial auditory information processing. *Neuroimage*, 14(6), 1268-1277.
- Arnott, S. R., Binns, M. A., Grady, C. L., & Alain, C. (2004). Assessing the auditory dual-pathway model in humans. *Neuroimage*, 22(1), 401-408.
- Baldeweg, T., Klugman, A., Gruzelier, J., & Hirsch, S. R. (2004). Mismatch negativity potentials and cognitive impairment in schizophrenia. *Schizophr Res*, 69(2-3), 203-217.
- Balogh, D. W. (1979). A study of schizophrenics' ability to localize the source of a sound. *J Nerv Ment Dis*, 169, 484-487.
- Balogh, D. W., & Leventhal, D. B. (1982). The use of temporal and amplitude cues by schizophrenics, psychiatric controls, and aged normals in auditory lateralization. *J Nerv Ment Dis*, 170(9), 553-560.
- Boutros, N. N., Korzyukov, O., Jansen, B., Feingold, A., & Bell, M. (2004). Sensory gating deficits during the mid-latency phase of information processing in medicated schizophrenia patients. *Psychiatry Res*, 126(3), 203-215.
- Braff, D. L. (1993). Information processing and attention dysfunctions in schizophrenia. *Schizophr Bull*, 19(2), 233-259.
- Brecher, M., & Begleiter, H. (1985). Brain stem auditory evoked potentials in unmedicated schizophrenic patients. *Biol Psychiatry*, 20(2), 199-202.
- Brunetti, M., Belardinelli, P., Caulo, M., Del Gratta, C., Della Penna, S., Ferretti, A., et al. (2005). Human brain activation during passive listening to sounds from different locations: an fMRI and MEG study. *Hum Brain Mapp*, 26(4), 251-261.
- Buchsbaum, M. S., Awsare, S. V., Holcomb, H. H., DeLisi, L. E., Hazlett, E., Carpenter, W. T., et al. (1986). Topographic differences between normals and schizophrenics: the N120 evoked potential component. *Neuropsychobiology*, 15(1), 1-6.
- Bullier, J. (2001). Feedback connections and conscious vision. *Trends Cogn Sci*, 5(9), 369-370.

- Butler, P. D., Martinez, A., Foxe, J.J., Kim, D., Silipo, G., Mahoney, J., Shpaner, M., Jalbrikowski, M., Javitt, D.C. (in press). Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. *Brain*.
- Butler, P. D., Schechter, I., Zemon, V., Schwartz, S.G., Greenstein, V.C., Gordon, J., Schroeder, C.E., Javitt, D.C. (2001). Dysfunction of early-stage visual processing in schizophrenia. *Am J Psychiatry*, 158(7), 1126-1133.
- Butler, P. D., Zemon, V., Schechter, I., Saperstein, A. M., Hoptman, M. J., Lim, K. O., et al. (2005). Early-stage visual processing and cortical amplification deficits in schizophrenia. *Arch Gen Psychiatry*, 62(5), 495-504.
- Christensen, B. K., & Bilder, R. M. (2000). Dual cytoarchitectonic trends: an evolutionary model of frontal lobe functioning and its application to psychopathology. *Can J Psychiatry*, 45(3), 247-256.
- Clarke, S., Bellmann, A., Meuli, R. A., Assal, G., & Steck, A. J. (2000). Auditory agnosia and auditory spatial deficits following left hemispheric lesions: evidence for distinct processing pathways. *Neuropsychologia*, 38(6), 797-807.
- Clarke, S., Bellmann Thiran, A., Maeder, P., Adriani, M., Vernet, O., Regli, L., et al. (2002). What and where in human audition: selective deficits following focal hemispheric lesions. *Exp Brain Res*, 147(1), 8-15.
- Clementz, B. A., & Blumenfeld, L. D. (2001). Multichannel electroencephalographic assessment of auditory evoked response suppression in schizophrenia. *Exp Brain Res*, 139(4), 377-390.
- Clementz, B. A., Blumenfeld, L. D., & Cobb, S. (1997). The gamma band response may account for poor P50 suppression in schizophrenia. *Neuroreport*, 8(18), 3889-3893.
- Clementz, B. A., Geyer, M. A., & Braff, D. L. (1998). Poor P50 suppression among schizophrenia patients and their first-degree biological relatives. *Am J Psychiatry*, 155(12), 1691-1694.
- de Gelder, B., Vroomen, J., Annen, L., Masthof, E., & Hodiament, P. (2003). Audio-visual integration in schizophrenia. *Schizophr Res*, 59(2-3), 211-218.
- Dias, E. C., Foxe, J. J., & Javitt, D. C. (2003). Changing plans: a high density electrical mapping study of cortical control. *Cereb Cortex*, 13(7), 701-715.
- Doniger, G. M., Foxe, J. J., Murray, M. M., Higgins, B. A., & Javitt, D. C. (2002). Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. *Arch Gen Psychiatry*, 59(11), 1011-1020.

- Erwin, R. J., Mawhinney-Hee, M., Gur, R. C., & Gur, R. E. (1991). Midlatency auditory evoked responses in schizophrenia. *Biol Psychiatry*, 30(5), 430-442.
- Erwin, R. J., Shtasel, D., & Gur, R. E. (1994). Effects of medication history on midlatency auditory evoked responses in schizophrenia. *Schizophr Res*, 11(3), 251-258.
- Farrell, D. E., Tripp, J. H., Norgren, R., & Teyler, T. J. (1980). A study of the auditory evoked magnetic field of the human brain. *Electroencephalogr Clin Neurophysiol*, 49(1-2), 31-37.
- First, M. B., Frances, A. J., Pincus, H. A., Vettorello, N., & Davis, W. W. (1994). DSM-IV in progress. Changes in substance-related, schizophrenic, and other primarily adult disorders. *Hosp Community Psychiatry*, 45(1), 18-20.
- Ford, J. M., Roth, W.T. (2004). Deficient response modulation of event-related brain potentials in schizophrenia. *Current Opinion in Psychiatry*, 17, 91-96.
- Ford, J. M., White, P. M., Csernansky, J. G., Faustman, W. O., Roth, W. T., & Pfefferbaum, A. (1994). ERPs in schizophrenia: effects of antipsychotic medication. *Biol Psychiatry*, 36(3), 153-170.
- Foxe, J. J., Doniger, G. M., & Javitt, D. C. (2001). Early visual processing deficits in schizophrenia: impaired P1 generation revealed by high-density electrical mapping. *Neuroreport*, 12(17), 3815-3820.
- Foxe, J. J., McCourt, M. E., & Javitt, D. C. (2003). Right hemisphere control of visuospatial attention: line-bisection judgments evaluated with high-density electrical mapping and source analysis. *Neuroimage*, 19(3), 710-726.
- Foxe, J. J., Murray, M. M., & Javitt, D. C. (2005). Filling-in in Schizophrenia: a High-density Electrical Mapping and Source-analysis Investigation of Illusory Contour Processing. *Cereb Cortex*.
- Foxe, J. J., & Schroeder, C. E. (2005). The case for feedforward multisensory convergence during early cortical processing. *Neuroreport*, 16(5), 419-423.
- Foxe, J. J., & Simpson, G. V. (2002). Flow of activation from V1 to frontal cortex in humans. A framework for defining "early" visual processing. *Exp Brain Res*, 142(1), 139-150.
- Freedman, R., Adler, L. E., Gerhardt, G. A., Waldo, M., Baker, N., Rose, G. M., et al. (1987). Neurobiological studies of sensory gating in schizophrenia. *Schizophr Bull*, 13(4), 669-678.
- Godey, B., Schwartz, D., de Graaf, J. B., Chauvel, P., & Liegeois-Chauvel, C. (2001). Neuromagnetic source localization of auditory evoked fields and intracerebral

- evoked potentials: a comparison of data in the same patients. *Clin Neurophysiol*, 112(10), 1850-1859.
- Grillon, C., Ameli, R., & Braff, D. L. (1991). Middle latency auditory evoked potentials (MAEPs) in chronic schizophrenics. *Schizophr Res*, 5(1), 61-66.
- Grillon, C., Ameli, R., & Glazer, W. M. (1990). Brainstem auditory-evoked potentials to different rates and intensities of stimulation in schizophrenics. *Biol Psychiatry*, 28(9), 819-823.
- Guterman, Y., & Klein, E. (1991). The role of head movement and pinnae in auditory localization in schizophrenia and psychosis. *Schizophr Res*, 6(1), 67-73.
- Harell, M., Englender, M., Demer, M., Kimhi, R., & Zohar, M. (1986). Auditory brain stem responses in schizophrenic patients. *Laryngoscope*, 96(8), 908-910.
- Hatashita-Wong, M., & Silverstein, S. M. (2003). Coping with voices: selective attention training for persistent auditory hallucinations in treatment refractory schizophrenia. *Psychiatry*, 66(3), 255-261.
- Hayashida, Y., Mitani, Y., Hosomi, H., Amemiya, M., Mifune, K., & Tomita, S. (1986). Auditory brain stem responses in relation to the clinical symptoms of schizophrenia. *Biol Psychiatry*, 21(2), 177-188.
- Hillebrand, A., & Barnes, G. R. (2002). A quantitative assessment of the sensitivity of whole-head MEG to activity in the adult human cortex. *Neuroimage*, 16(3 Pt 1), 638-650.
- Huang, M. X., Edgar, J. C., Thoma, R. J., Hanlon, F. M., Moses, S. N., Lee, R. R., et al. (2003). Predicting EEG responses using MEG sources in superior temporal gyrus reveals source asynchrony in patients with schizophrenia. *Clin Neurophysiol*, 114(5), 835-850.
- Javitt, D. C. (2000). Intracortical mechanisms of mismatch negativity dysfunction in schizophrenia. *Audiol Neurotol*, 5(3-4), 207-215.
- Javitt, D. C., Doneshka, P., Grochowski, S., & Ritter, W. (1995). Impaired mismatch negativity generation reflects widespread dysfunction of working memory in schizophrenia. *Arch Gen Psychiatry*, 52(7), 550-558.
- Javitt, D. C., Jayachandra, M., Lindsley, R. W., Specht, C. M., & Schroeder, C. E. (2000). Schizophrenia-like deficits in auditory P1 and N1 refractoriness induced by the psychomimetic agent phencyclidine (PCP). *Clin Neurophysiol*, 111(5), 833-836.

- Javitt, D. C., Strous, R. D., Grochowski, S., Ritter, W., & Cowan, N. (1997). Impaired precision, but normal retention, of auditory sensory ("echoic") memory information in schizophrenia. *J Abnorm Psychol*, 106(2), 315-324.
- Kaseda, Y., Tobimatsu, S., Morioka, T., & Kato, M. (1991). Auditory middle-latency responses in patients with localized and non-localized lesions of the central nervous system. *J Neurol*, 238(8), 427-432.
- Kimhi, R., Engender, M., Zohar, M., & Harell, M. (1987). Brainstem auditory evoked responses in hospitalized unmedicated schizophrenic patients. *Isr J Psychiatry Relat Sci*, 24(4), 289-294.
- Knight, R. T., Staines, W. R., Swick, D., & Chao, L. L. (1999). Prefrontal cortex regulates inhibition and excitation in distributed neural networks. *Acta Psychol (Amst)*, 101(2-3), 159-178.
- Kuriki, S., Nogai, T., & Hirata, Y. (1995). Cortical sources of middle latency responses of auditory evoked magnetic field. *Hear Res*, 92(1-2), 47-51.
- Lakatos, P., Pincze, Z., Fu, K.G., Karmos, G., Schroeder, C.E. (in press). Timing of pure tone and noise-evoked responses in macaque auditory cortex. *Neuroreport*.
- Leitman, D. I., Foxe, J.J., Butler, P.D., Saperstein, A., Javitt, D.C. (2005). Do affective speech recognition deficits in schizophrenia have early cortical antecedents? *Biol Psychiatry*.
- Liegeois-Chauvel, C., Musolino, A., Badier, J. M., Marquis, P., & Chauvel, P. (1994). Evoked potentials recorded from the auditory cortex in man: evaluation and topography of the middle latency components. *Electroencephalogr Clin Neurophysiol*, 92(3), 204-214.
- Lindenmayer, J. P., Bernstein-Hyman, R., & Grochowski, S. (1994). Five-factor model of schizophrenia. Initial validation. *J Nerv Ment Dis*, 182(11), 631-638.
- Lindstrom, L., Klockhoff, I., Svedberg, A., & Bergstrom, K. (1987). Abnormal auditory brain-stem responses in hallucinating schizophrenic patients. *Br J Psychiatry*, 151, 9-14.
- Lindstrom, L. H., Wieselgren, I. M., Klockhoff, I., & Svedberg, A. (1990). Relationship between abnormal brainstem auditory-evoked potentials and subnormal CSF levels of HVA and 5-HIAA in first-episode schizophrenic patients. *Biol Psychiatry*, 28(5), 435-442.
- Makela, J. P., Hamalainen, M., Hari, R., & McEvoy, L. (1994). Whole-head mapping of middle-latency auditory evoked magnetic fields. *Electroencephalogr Clin Neurophysiol*, 92(5), 414-421.

- McGhie, A. a. C., J. (1961). Disorders of attention and perception in early schizophrenia. *Br J Med Psychol*, 34, 103-116.
- McKay, C. M., Headlam, D. M., & Copolov, D. L. (2000). Central auditory processing in patients with auditory hallucinations. *Am J Psychiatry*, 157(5), 759-766.
- Michie, P. T. (2001). What has MMN revealed about the auditory system in schizophrenia? *Int J Psychophysiol*, 42(2), 177-194.
- Michie, P. T., Fox, A. M., Ward, P. B., Catts, S. V., & McConaghy, N. (1990). Event-related potential indices of selective attention and cortical lateralization in schizophrenia. *Psychophysiology*, 27(2), 209-227.
- Mickey, B. J., & Dalack, G. W. (2005). Auditory gating in schizophrenia: a pilot study of the precedence effect. *Schizophr Res*, 73(2-3), 327-331.
- Mishkin, M., Lewis, M. E., & Ungerleider, L. G. (1982). Equivalence of parieto-preoccipital subareas for visuospatial ability in monkeys. *Behav Brain Res*, 6(1), 41-55.
- Molholm, S., Ritter, W., Murray, M. M., Javitt, D. C., Schroeder, C. E., & Foxe, J. J. (2002). Multisensory auditory-visual interactions during early sensory processing in humans: a high-density electrical mapping study. *Brain Res Cogn Brain Res*, 14(1), 115-128.
- Moxon, K. A., Gerhardt, G. A., & Adler, L. E. (2003). Dopaminergic modulation of the P50 auditory-evoked potential in a computer model of the CA3 region of the hippocampus: its relationship to sensory gating in schizophrenia. *Biol Cybern*, 88(4), 265-275.
- Mukundan, C. R. (1986). Middle latency components of evoked potential responses in schizophrenics. *Biol Psychiatry*, 21(11), 1097-1100.
- Murray, M. M., Wylie, G. R., Higgins, B. A., Javitt, D. C., Schroeder, C. E., & Foxe, J. J. (2002). The spatiotemporal dynamics of illusory contour processing: combined high-density electrical mapping, source analysis, and functional magnetic resonance imaging. *J Neurosci*, 22(12), 5055-5073.
- Nagamoto, H. T., Adler, L. E., Waldo, M. C., & Freedman, R. (1989). Sensory gating in schizophrenics and normal controls: effects of changing stimulation interval. *Biol Psychiatry*, 25(5), 549-561.
- Oades, R. D., Dittmann-Balcar, A., Zerbin, D., & Grzella, I. (1997). Impaired attention-dependent augmentation of MMN in nonparanoid vs paranoid schizophrenic patients: a comparison with obsessive-compulsive disorder and healthy subjects. *Biol Psychiatry*, 41(12), 1196-1210.

- Okada, Y. (1993). Neurogenesis of evoked magnetic fields. In R. G. Williamson SH, Kaufman L, Modena I (Ed.), *Biomagnetism: an Interdisciplinary Approach* (pp. 399-408). New York: Plenum Press.
- Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, 9(1), 97-113.
- Olsson, O., & Nielzen, S. (1999). Contralateral induction by frequency spectrum in hallucinating schizophrenics. *Psychiatry Res*, 87(1), 65-75.
- Perrin, F., Pernier, J., Bertrand, O., & Echallier, J. F. (1989). Spherical splines for scalp potential and current density mapping. *Electroencephalogr Clin Neurophysiol*, 72(2), 184-187.
- Pfefferbaum, A., Horvath, T. B., Roth, W. T., Tinklenberg, J. R., & Kopell, B. S. (1980). Auditory brain stem and cortical evoked potentials in schizophrenia. *Biol Psychiatry*, 15(2), 209-223.
- Picton, T. W., Hillyard, S. A., Krausz, H. I., & Galambos, R. (1974). Human auditory evoked potentials. I. Evaluation of components. *Electroencephalogr Clin Neurophysiol*, 36(2), 179-190.
- Poremba, A., Saunders, R. C., Crane, A. M., Cook, M., Sokoloff, L., & Mishkin, M. (2003). Functional mapping of the primate auditory system. *Science*, 299(5606), 568-572.
- Rabinowicz, E. F., Silipo, G., Goldman, R., & Javitt, D. C. (2000). Auditory sensory dysfunction in schizophrenia: imprecision or distractibility? *Arch Gen Psychiatry*, 57(12), 1149-1155.
- Rauschecker, J. P., & Tian, B. (2000). Mechanisms and streams for processing of "what" and "where" in auditory cortex. *Proc Natl Acad Sci U S A*, 97(22), 11800-11806.
- Recanzone, G. H. (2001). Spatial processing in the primate auditory cortex. *Audiol Neurotol*, 6(4), 178-181.
- Reite, M., Teale, P., Zimmerman, J., Davis, K., & Whalen, J. (1988). Source location of a 50 msec latency auditory evoked field component. *Electroencephalogr Clin Neurophysiol*, 70(6), 490-498.
- Reite, M., Teale, P., Zimmerman, J., Davis, K., Whalen, J., & Edrich, J. (1988). Source origin of a 50-msec latency auditory evoked field component in young schizophrenic men. *Biol Psychiatry*, 24(5), 495-506.
- Roemer, R. A., Shagass, C., Straumanis, J. J., & Amadeo, M. (1979). Somatosensory and auditory evoked potential studies of functional differences between the cerebral hemispheres in psychosis. *Biol Psychiatry*, 14(2), 357-373.

- Romanski, L. M., Tian, B., Fritz, J., Mishkin, M., Goldman-Rakic, P. S., & Rauschecker, J. P. (1999). Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. *Nat Neurosci*, 2(12), 1131-1136.
- Rupp, A., Hack, S., Gutschalk, A., Schneider, P., Picton, T. W., Stippich, C., et al. (2000). Fast temporal interactions in human auditory cortex. *Neuroreport*, 11(17), 3731-3736.
- Scherg, M., & Von Cramon, D. (1985). Two bilateral sources of the late AEP as identified by a spatio-temporal dipole model. *Electroencephalogr Clin Neurophysiol*, 62(1), 32-44.
- Scherg, M., & Von Cramon, D. (1986). Evoked dipole source potentials of the human auditory cortex. *Electroencephalogr Clin Neurophysiol*, 65(5), 344-360.
- Schroeder, C. E., Lindsley, R. W., Specht, C., Marcovici, A., Smiley, J. F., & Javitt, D. C. (2001). Somatosensory input to auditory association cortex in the macaque monkey. *J Neurophysiol*, 85(3), 1322-1327.
- Schwartz, B. D., Maron, B. A., Evans, W. J., & Winstead, D. K. (1999a). High velocity transient visual processing deficits diminish ability of patients with schizophrenia to recognize objects. *Neuropsychiatry Neuropsychol Behav Neurol*, 12(3), 170-177.
- Schwartz, B. D., Maron, B. A., Evans, W. J., & Winstead, D. K. (1999b). Smooth pursuit tracking deficits of patients with schizophrenia at specific within-sine wave bins. *Neuropsychiatry Neuropsychol Behav Neurol*, 12(4), 221-229.
- Scott, S. K. (2005). Auditory processing--speech, space and auditory objects. *Curr Opin Neurobiol*, 15(2), 197-201.
- Simpson, G. V., Pflieger, M. E., Foxe, J. J., Ahlfors, S. P., Vaughan, H. G., Jr., Hrabe, J., et al. (1995). Dynamic neuroimaging of brain function. *J Clin Neurophysiol*, 12(5), 432-449.
- Szelenberger, W. (1983). Brain stem auditory evoked potentials and personality. *Biol Psychiatry*, 18(2), 157-174.
- Tian, B., Reser, D., Durham, A., Kustov, A., & Rauschecker, J. P. (2001). Functional specialization in rhesus monkey auditory cortex. *Science*, 292(5515), 290-293.
- Urbano, A., Babiloni, C., Onorati, P., & Babiloni, F. (1996). Human cortical activity related to unilateral movements. A high resolution EEG study. *Neuroreport*, 8(1), 203-206.

- Valkonen-Korhonen, M., Purhonen, M., Tarkka, I. M., Sipila, P., Partanen, J., Karhu, J., et al. (2003). Altered auditory processing in acutely psychotic never-medicated first-episode patients. *Brain Res Cogn Brain Res*, 17(3), 747-758.
- van Luijtelaar, G. (2003). The effects of diazepam on sensory gating in healthy volunteers. *Neurosci Lett*, 341(1), 65-68.
- Weeks, R. A., Aziz-Sultan, A., Bushara, K. O., Tian, B., Wessinger, C. M., Dang, N., et al. (1999). A PET study of human auditory spatial processing. *Neurosci Lett*, 262(3), 155-158.
- Wetherill, G. B., & Levitt, H. (1965). Sequential Estimation of Points on a Psychometric Function. *Br J Math Stat Psychol*, 18, 1-10.
- Yeap, S., Kelly, SP, Sehatpour, P, et al. (2006). Are Early Visual Processing Deficits Endophenotypic for Schizophrenia? A High-Density Electrical Mapping Study in Clinically Unaffected First-Degree Relatives. *Arch Gen Psychiatry*, in press.
- Yoshiura, T., Ueno, S., Iramina, K., & Masuda, K. (1995). Source localization of middle latency auditory evoked magnetic fields. *Brain Res*, 703(1-2), 139-144.
- Yvert, B., Crouzeix, A., Bertrand, O., Seither-Preisler, A., & Pantev, C. (2001). Multiple supratemporal sources of magnetic and electric auditory evoked middle latency components in humans. *Cereb Cortex*, 11(5), 411-423.
- Zatorre, R. J., Bouffard, M., Ahad, P., & Belin, P. (2002). Where is 'where' in the human auditory cortex? *Nat Neurosci*, 5(9), 905-909.

CHAPTER 3

“What” and “Where” in auditory sensory processing I: A high-density electrophysiological investigation of distinct neural processes underlying sound object recognition and sound localization

Abstract:

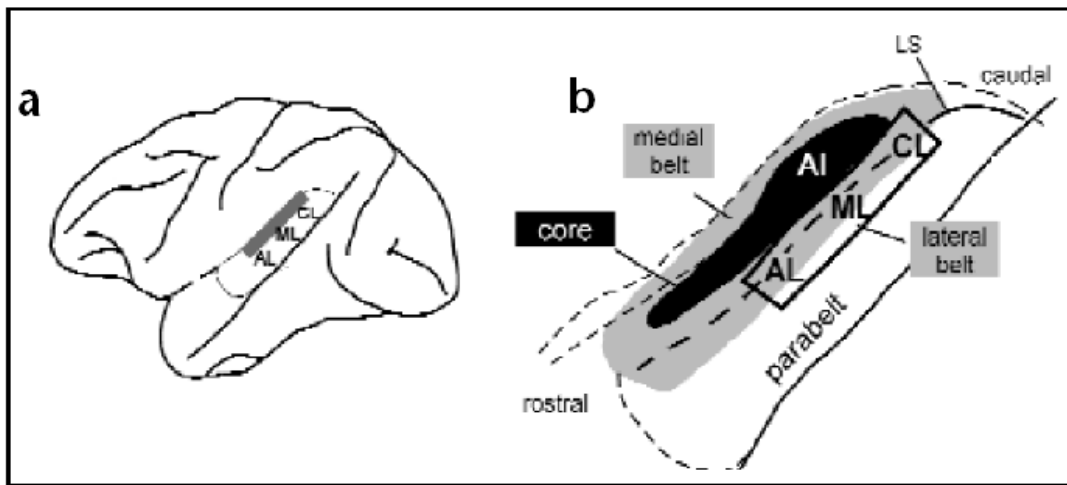
This investigation was conducted to determine whether separate physiological networks underlying functionally distinct tasks of sound localization and sound object recognition- the so-called *what* and *where* auditory pathways- can be identified. High-density (168-channel) electrophysiological recordings were collected from participants as they completed tasks that explicitly distinguished dorsal (*where*) from ventral (*what*) auditory pathway functions. The ***where*** task was to identify the location (1 of 7 speakers arranged on a 180-degree arc in the free field) from which an auditory stimulus (an animal call) was delivered. In an identical stimulus setup, the ***what*** task was to identify a pre-specified target animal from seven randomly delivered animal calls. The auditory stimuli for both conditions were delivered in the free field: participants sat in a darkened room facing an azimuth of speakers. Participants were required to make a response immediately after each stimulus was delivered. Topographic analysis suggested distinct dorsal and ventral auditory processing networks underlying the *what* and *where* functions in auditory sensory processing. Waveform analysis revealed substantial differences between the two conditions in the auditory evoked potentials (AEPs) during the 114-134 timeframe. Interestingly and somewhat surprisingly, our analyses of electrophysiological responses and topographic data suggested that the aforementioned timeframe was the only point of significant divergence between the two conditions.

Introduction

There is growing evidence for functionally and anatomically distinct auditory pathways. Findings in non-human primates (Rauschecker & Tian, 2000; Romanski et al., 1999; Tian, Reser, Durham, Kustov, & Rauschecker, 2001) and humans (Anourova et al., 2001; Clarke, Bellmann, Meuli, Assal, & Steck, 2000; Clarke et al., 2002; Poremba et al., 2003; Weeks et al., 1999; Zatorre, Bouffard, Ahad, & Belin, 2002) point to a *what/where* distinction analogous to that seen in the visual system (Mishkin, Lewis, & Ungerleider, 1982). These data suggest a system whereby auditory inputs are communicated dorsally from primary auditory cortex for the extraction of information regarding spatial localization in parietal cortical regions (the *where* pathway), and ventrally from primary auditory cortex along medial and inferior temporal cortex for the processing of the specific features of the signal such as spectral content and temporal integration (the ventral *what* pathway).

Much of what we know about *what* and *where* auditory pathways comes from studies in nonhuman primates, and suggests that the earliest evidence for separable and functionally distinct pathways can be seen in the medial geniculate nucleus (MGN) of the thalamus (Kaas & Hackett, 1999; Rauschecker & Tian, 2000; Romanski et al., 1999). Rauschecker and Tian (Rauschecker & Tian, 2000) summarized work utilizing histochemical techniques and anatomical tracer dyes to track the trajectory of neuronal subpopulations from the MGN to primary auditory cortex (A1). Adjacent to A1 are a rostral area (R) and a caudomedial area (CM) (**Figure 1**). While A1 and R have been shown to receive input from the ventral portion of the MGN, CM is the target of dorsal and medial divisions of MGN. The lateral belt areas receiving input from A1 and R may represent the beginning of an auditory pattern or object stream, as the neurons here

Figure 1. Anatomical regions of nonhuman primate (monkey) brain involved in processing of spatial and nonspatial stimuli. AI=primary auditory cortex; CL=caudolateral belt region; AL=anterolateral belt region; ML=medial lateral belt region. (Adapted from Romanski et al., 1999, with permission).



Adapted from Romanski et al., 1999, with permission

respond to species-specific vocalizations and other complex sounds (Rauschecker & Tian, 2000; Romanski et al., 1999). Conversely, neurons in caudal regions CM and CL (caudolateral area) have been shown to be highly specific for spatial position (as described by Tian et al., 2001). Romanski and colleagues (Romanski et al., 1999) traced the streams further in rhesus monkeys, finding distinct targets for the ventral and dorsal pathways in non-spatial and spatial domains of prefrontal cortex, respectively.

In humans, there is also mounting evidence for *what* and *where* auditory streams. Arnott and colleagues compiled a meta-analysis of neuroimaging studies of ventral and dorsal auditory processing in humans (Arnott, Binns, Grady, & Alain, 2004). By reviewing 11 spatial studies and 27 nonspatial studies, these authors concluded that physiologically distinct areas for processing spatial and nonspatial features of sounds could be identified. For the so-called spatial studies, centers of activation clustered around the inferior parietal lobule, the temporal lobe posterior to primary auditory cortex, and the superior frontal sulcus. For the so-called nonspatial studies, centers of activation

were seen clustered around inferior frontal cortex. While there was substantial overlap in areas of activation, the clusters of activation corresponded well with the notion that *where* processing occurs in a dorsally positioned processing stream and *what* processing in a ventrally positioned processing stream. The studies included utilized positron emission tomography (PET) and/or functional magnetic resonance imaging (fMRI). Thus far, there have been relatively few electroencephalographic (EEG)/ magnetoencephalographic (MEG) investigations of these pathways within the human auditory system. Therefore, while we have some idea of the anatomical localization of the processing of these distinct types of information from both the animal literature and human neuroimaging, our understanding of the temporal dynamics needs augmenting. Furthermore, the paradigms that have been employed to tap into functional capacities of auditory processing have varied greatly. For instance, a large portion of the nonspatial studies examined in the Arnott meta-analysis used human speech, which could potentially introduce a confound in that speech may represent a special case for humans, who have developed highly specialized areas for speech processing. It has been proposed that the dorsal pathway in humans may not only process auditory space, but may also be a very important region for speech perception (Belin & Zatorre, 2000), revealing a possible overlap of presumptive dorsal and ventral pathway functions. Furthermore, a study by Gilkey and Anderson (1995) demonstrated that subjects performing a localization task with speech sounds versus clicks were less accurate when making front/back and up/down (vertical plane) discriminations for speech sounds than for clicks. Participants were equally accurate when making left/right (horizontal plane) determinations regardless of stimulus type. Employing speech as stimuli in a localization task may not be the most effective means of parsing *what* and *where* auditory processing pathways.

Much of what we know about the dorsal and ventral auditory pathways in humans comes from lesion studies (Clarke et al., 2000; Clarke et al., 2002; Clarke & Thiran, 2004). In a series of case studies, Clarke and colleagues investigated auditory recognition and localization in four patients with circumscribed left hemisphere lesions (2000). Two of four patients showed impaired recognition of environmental sounds but intact ability to localize sounds. In one, the lesion included postero-inferior portions of the frontal convexity and the anterior third of the temporal lobe. In the other, the lesion included left superior, middle and inferior temporal gyri and lateral auditory areas, but spared Heschl's gyrus, the acoustic radiation and the thalamus. The third patient was impaired in auditory motion perception and localization, but normal in environmental sound recognition; here, the lesion included the parieto-frontal convexity and the supratemporal region. The fourth patient was impaired in both tasks, with a lesion comprising large portions of the supratemporal region, temporal, postero-inferior frontal and antero-inferior parietal convexities. A subsequent investigation by the same group examined 15 patients with right focal hemispheric lesions (Clarke et al., 2002). Again, sound recognition and sound localization were shown to be disrupted independently. In this study, patients with selective sound localization deficits tended to have lesions involving inferior parietal and frontal cortices, as well as superior temporal gyrus, whereas patients with selective recognition deficits had lesions of the temporal pole, the anterior part of fusiform, and the inferior and middle temporal gyrus. This double dissociation clearly supports somewhat independent processing streams for sound recognition and sound localization in humans. These studies do not, however, speak to the time course of the underlying processes of interest.

Human EEG and MEG studies have shed light on this, although findings are equivocal in terms of how early in the processing hierarchy information is preferentially processed by a specific pathway; that is, how quickly stimuli are parsed in terms of a *what/where* distinction. In the context of a match-to-sample task for location (*where*) that varied by memory load, Anurova et al.(2003) found very late effects of task differences on the amplitude of the auditory N2 component at approximately 400 ms. These researchers employed simple tones of three different frequencies (220, 440, and 880 Hz), delivered to one of two locations (left and right). In an fMRI/EEG study using a match-to-sample task, Alain and colleagues (2001) also found relatively late task-related effects from 300 ms onwards in the context of a match-to-sample task utilizing noise bursts delivered via headphones; stimuli were five pitch-varied noise bursts delivered via headphones to five simulated spatial locations. In another study, Anourova and colleagues (2001) simultaneously collected EEG and MEG, and found N1 peak latency differences, but no amplitude differences between *what* and *where* tasks: identical blocks of tone stimuli were presented to subjects who were instructed to attend either to sound location or frequency. Stimuli were simple tones of two frequencies (1000 and 1500 Hz) delivered via headphones to two simulated locations (an interaural intensity difference was applied; perceived location was either left or right). Utilizing MEG and fMRI and a match-to-sample task, Ahveninen et al.(2006) found amplitude and latency effects at ~70-150 ms (the auditory N1); however, the stimuli used here were speech sounds delivered to two simulated locations, which may introduce a special set of confounds as discussed above. De Santis and colleagues (2007) found “*what/where*” related effects on the amplitude of the auditory N1, but it is important to point out that their paradigm involved a passive listening task and subjects did not explicitly perform spatial or object

judgments. Stimuli used were bandpass filtered noise bursts (250 Hz or 500 Hz) delivered to two perceived locations (an interaural time difference was used; locations were left and right). Although these investigators were aiming for a setup where the stimuli used in their *what* and *where* conditions were “identical,” this was not in fact the case, and the design resulted in unique stimulus configurations for each condition. In the *what* task, 80% of the stimuli were of one frequency and 20% of a second frequency in the first block. A second block was run in which the 80/20 ratio was reversed, and for analysis, they collapsed over both blocks. While the *what* stimuli were in this 80/20 ratio, stimuli for the *where* condition were equally distributed (50/50). An analogous 80/20 design was used for the *where* task. As such, this design takes the form of a standard oddball paradigm, and would have produced the well-known mismatch negativity (MMN) to the low-probability stimuli. The researchers attempt to circumvent this possible confound by analyzing only the frequent tones. Unfortunately, it is also known that the first frequent “standard” tone following an infrequent “deviant” tone also receives differential processing under such designs, and a robust MMN is often seen to this presumed “standard” tone (see e.g. Nousak, Deacon, Ritter, & Vaughan, 1996, Roeber, Widmann, & Schroger, 2003). Upon careful reading, responses to these first standards appear to have been included in the De Santis analysis (2007). Indeed, in the Nousak investigation, an MMN was elicited by the standard after the deviant despite the researchers’ efforts to prevent it. Moverover, in all five of the aforementioned studies, stimuli were tones, noise bursts, or vowel sounds, and all utilized simulated three-dimensional (3D) environments delivered via headphones. None utilized ecologically valid environmental sounds delivered in the free field and one could certainly question the “objectness” of these stimuli.

A prior investigation of mid-latency auditory evoked responses (MLRs) from our group suggested that there is a constitutive divergence of activation into separable pathways in the context of a passive listening task, a divergence that begins very early in processing during the auditory Pa component, which peaks at just 35 ms (Leavitt, Molholm, Ritter, Shpaner, & Foxe, 2007). While that study was not designed to expressly test the functionality of the dorsal and ventral auditory pathways per se, automatic sensory activation of these pathways is an inherent result of receiving any auditory stimulation or performing any auditory task. By analogy, visual stimuli constitutively activate both the dorsal and ventral visual streams even when no object or spatial processing tasks are required (see, e.g., Schroeder, Mehta, & Givre, 1998)[†]. Indeed, in non-human primate studies, the animals are often anaesthetized during recordings and yet both the dorsal and ventral pathways are activated (e.g. Schmolesky et al., 1998). Our aim here was to determine just how early in auditory processing we could find evidence for dissociable pathways under specific *what* and *where* task conditions. Our premise was that functionally distinct and ecologically valid tasks would allow us to amplify separate activations that we have observed within dorsal and ventral pathways. Furthermore, there may very well be clinical usefulness for dissociating these pathways. Prior investigations conducted by our group in patients with schizophrenia have suggested that their dorsal pathway may be relatively more impaired than their ventral pathway (Leavitt et al., 2007; Ross, Saint-Amour, Leavitt, Javitt, & Foxe, 2007; Ross, Saint-Amour, Leavitt, Molholm et al., 2007). In other work done in our laboratory, we have seen consistent deficits of dorsal stream processing in the visual system of schizophrenia patients, relative to ventral

[†] That is, both pathways are activated by typical visual inputs, but it is possible to activate them in relative isolation by manipulating stimulus properties (e.g. the use of isoluminant chromatic contrast). See Lalor, Yeap, Reilly, Pearlmutter, & Foxe, 2008.

stream processing: visual P1 amplitudes were significantly reduced to a much greater degree over dorsal scalp than ventral in a patient group in a study by Foxe and colleagues (2001), a finding that has since been replicated twice by our group in studies of dorsal/ventral visual stream interaction in schizophrenia (Doniger, Foxe, Murray, Higgins, & Javitt, 2002; Foxe, Murray, & Javitt, 2005). Further, Foxe and colleagues (2005) used inverse source-localization to confirm that the major sources of this deficit were in the dorsal stream. While deficits in auditory processing are clearly evident in schizophrenia, the dorsal/ventral distinction has not yet been explicitly explored in the auditory system of patients.

Here, we hypothesized that distinct tasks of sound localization and sound object identification would differentially activate the dorsal and ventral auditory pathways. We further hypothesized that the divergence of activation in these respective pathways would be evident in the early auditory evoked responses of participants. Motivated by our finding in a prior study that suggested dorsal stream impairment in patients with schizophrenia as early as 35 ms (Leavitt et al., 2007), we set out to determine whether divergence of the auditory streams could be characterized in control subjects from this early time point. By using dedicated tasks of sound localization and sound object recognition, our goal was to amplify the auditory evoked potentials (AEPs) and thus identify the respective streams. Furthermore, given that focused auditory attention in humans has been shown to selectively modulate sensory processing in auditory cortex from as early as 20 ms post-stimulus (Woldorff et al., 1993), we postulated that an effortful, attended task would enable us to identify the separate auditory streams from a time point earlier than previously identified in the literature (e.g., Ahveninen et al., 2006; Alain et al., 2001; Anourova et al., 2001; Anurova et al., 2003; De Santis, Clarke et al.,

2007). Ahveninen and colleagues (2006) utilized a selective attention task to tap the separate pathways, however, these researchers used phonemes as their stimuli. By employing animal calls as stimuli, we avoided any interference of language-specific areas that may be activated in response to human speech sounds. We also wanted to avoid using simple tones since work in monkeys has shown considerably better responses in prefrontal neurons to natural sounds or monkey vocalizations than to pure tones (as described in Rama et al., 2004). In using a larger set of complex animal calls and thereby attaching semantic meaning to our stimuli, our intention was to maximize object-processing while avoiding possible confounds induced by the use of speech stimuli. Similarly, by using free-field spatial stimuli delivered from seven possible locations, we intended to get away from simple left-right judgments over headphones that may have been less effective at invoking spatial mechanisms. Identical stimuli were maintained for both tasks, and only the task itself was varied.

An ancillary goal of our design was to examine differences in evoked responses for each of the speaker locations in each condition. Collecting hundreds of sweeps for each of seven speaker locations in both conditions enabled us to analyze individual speaker locations within-condition. Collapsing over all speakers may obfuscate these spatial effects. Our hypothesis is that there will be an interaction of condition and spatial location of stimuli; that is, we will see space-specific effects for the *where* condition that are absent in the *what* condition. This will implicate underlying neural processes for localizing sound that are optimized in the context of a localization task while not engaged in the context of a non-spatial object identification task.

Methods

The procedures for this study were approved by the Institutional Review Board of The Nathan S. Kline Institute for Psychiatric Research/Rockland Psychiatric Center and the Institutional Review Board of The Graduate Center of the City University of New York.

Subjects

Informed consent was obtained from twelve (ten male) healthy control subjects aged 23-56 years (mean = 33 ± 11.4). All reported normal hearing. One subject was left-handed, as determined by the Edinburgh Test for Handedness (Oldfield, 1971). None of the participants had current or prior neurological or psychiatric illnesses, nor were any currently taking psychotropic medications. All subjects were paid a modest fee for their participation.

Stimuli

Precisely the same stimuli were used for both the *what* and *where* conditions: seven animal sounds (cow, dog, duck, elephant, frog, pig, and sheep), adapted from Fabiani et al. (1996). These sounds were of uniquely identifiable vocalizations. They were modified using Cool Edit Pro Version 2 such that each had a duration of 250 ms, and were presented over seven Blaupunkt PCx352 90 watt 3.5" 2-way coaxial speakers at a comfortable listening level of approximately 80 dB sound pressure level. Interstimulus interval (ISI) was variable to avoid anticipatory effects; stimuli in both conditions were delivered every 2500-3500 ms.

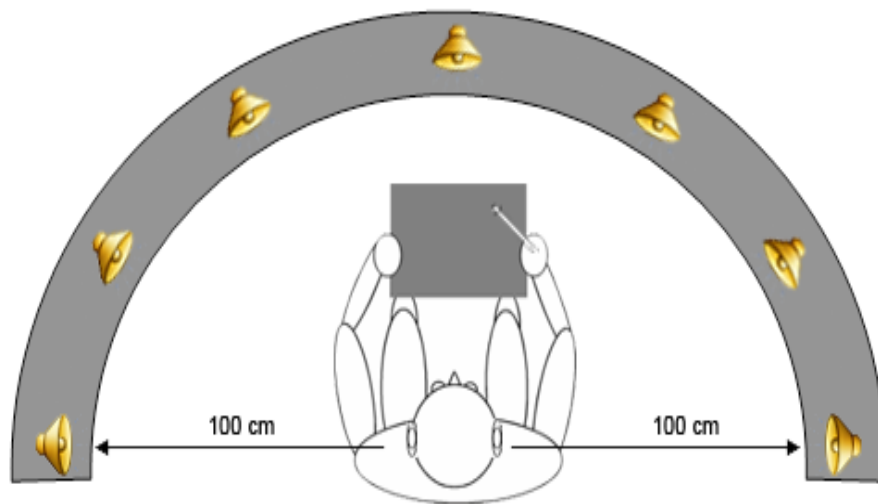
Procedure

Participants were seated in a comfortable chair in a dimly illuminated, sound-attenuated, electrically shielded (Braden Shielding Systems) chamber and asked to keep head and eye movements to a minimum. Auditory stimuli were presented from seven spatial locations via speakers arranged in the participant's median plane along a frontal arc of $\pm 90^\circ$

(-90° , -60° , -30° , 0 , $+30^\circ$, $+60^\circ$, $+90^\circ$) and centered on the participant's head (1.0 m distance) (see **Figure 2**). This arc was adjustable on a pulley system such that it could be positioned

Figure 2. Graphic representation of speaker locations. Seven speakers were arranged in the participant's median plane along a frontal arc of $\pm 90^\circ$ (-90° , -60° , -30° , 0 , $+30^\circ$, $+60^\circ$, $+90^\circ$) and centered on the participant's head (1.0 m distance).

Experimental Apparatus



level with the horizontal plane of each individual subject at head height. Speakers were concealed behind a black curtain to prevent participants from forming a visual representation of speaker positions. A 12"x 12" digitized Wacom graphics tablet was mounted in front of and aligned with the participant's median sagittal plane of the trunk. It consisted of a stylus that the participant used to draw a freehand line towards the source of the sound as it was perceived (during the localization task). The tablet was obscured from view by a partition. There were two blocked conditions, which were counterbalanced for order across subjects: 1) **WHERE task:** The *where* task was to indicate the location that a sound came from; subjects

completed a minimum of 13 and not more than 15 blocks. Each block contained 168 stimulus presentations (24 per speaker). Spatial presentation of the stimuli followed a random order. Subjects responded by drawing a line on the graphic tablet out to the radius in the direction of each animal call after it was delivered. The angle and trajectory of the line was recorded by the computer in Presentation 4.0. Then, the participant returned the stylus to the midpoint of the tablet; the resting position. This position was indicated by a depression in the tablet. 2)

WHAT task: The *what* task was to identify a target animal from seven randomly delivered animal calls. There were 14 blocks; target animals were randomized across blocks. On each block, the subject was given an auditory cue: “This is your target...” followed by one of the seven randomly selected target animal calls. After that, the seven animal calls were randomly delivered throughout the block, precisely as in the *where* task. In this task subjects were to respond to a designated target with one response, and to all non-targets with another response. There were two response types, drawing either a line or a circle on the tablet. The pairing of response type to stimulus type (target or non-target) was counter-balanced across subjects. The target stimuli occurred on 15.6% of trials. Each animal served as target in two of 14 runs, in randomized order both within and between subjects. An alternate *what* task, **WHAT II**, was run on six of the twelve subjects. In this alternate paradigm, our goal was to eliminate the target vs. non-target aspect of the task. Here, as in the *where* task, each stimulus would effectively be a target requiring a response. In *What II*, subjects identified each stimulus verbally immediately after stimulus delivery. As before, the seven animal calls were randomly delivered throughout the block. A rater was present in the room recording each response on a laptop.

Data acquisition

Continuous EEG was acquired through the ActiveTwo Biosemi™ electrode system from 168 scalp electrodes, digitized at 512 Hz. For display purposes, data were filtered with a low-pass 0-phase shift 96 dB 40 Hz filter after acquisition. The reference electrode was assigned in software after acquisition. BioSemi replaces the "ground" electrodes that are used in conventional systems with two separate electrodes: Common Mode Sense (CMS) active electrode and Driven Right Leg (DRL) passive electrode. These 2 electrodes form a feedback loop, thus rendering them “references.” For a detailed description of the referencing and grounding conventions used by the Biosemi active electrode system, the interested reader is referred to the following website: <http://www.biosemi.com/faq/cms&drl.htm>. All data were re-referenced to the nasion after acquisition, for analysis (in one subject, the supranasion was used for re-referencing, as the nasion was contaminated by artifact). After each recording session, before the electrode cap was removed from the subject’s head, the 3D coordinates of all 168 electrodes with reference to anatomic landmarks on the head (nasion, pre-auricular notches) were digitized using a Polhemus Magnetic 3D digitizer. EEG was averaged off-line. Data were epoched (-100 ms pre-stimulus to 500 ms post-stimulus) and then averaged. Baseline was defined as the mean voltage over -100 to 0 ms preceding the onset of the stimulus. Trials with blinks and large eye-movements were rejected offline on the basis of horizontal and vertical electrooculogram recordings. An artifact rejection criterion of ± 100 μ volts was used at all other electrode sites to exclude periods of high EMG and other noise-transients. From the remaining artifact-free trials, averages were computed for each subject. These averages were then visually inspected for each individual to ensure that clean recordings with sufficient numbers of trials were obtained and that no artifacts were still included. In both the *what* and *where* conditions, the average number of accepted sweeps was

upwards of 3000 trials. Prior to group averaging, data at electrodes contaminated by artifacts were interpolated for each subject. Data were re-baselined over the interval –50 to 20 ms after interpolating. Data were ultimately averaged across all subjects (grand mean averages) for visual comparison at the group level and for display purposes. The reader should note that throughout this paper, we use the familiar nomenclature of the modified 10-20-electrode system to refer to the positioning of electrode sites ("American Electroencephalographic Society guidelines for standard electrode position nomenclature," 1991). Since our montage contains considerably more scalp-sites than this nomenclature allows for, in some cases, we will be referring to the nearest neighboring site within the 10-20 system.

Analysis strategy

For each electrode, the data from all subjects were collapsed into a single average waveform for each of the speakers and averaged over all seven locations. These group-averaged waveforms were then visually inspected across all scalp-sites. To constrain our analyses, we first identified the well-characterized auditory components prior to and including the N1: P20, Pa, P1, and N1 (see, for example, Leavitt et al., 2007; Picton, Hillyard, Krausz, & Galambos, 1974). Analyses were performed across three pairs of scalp electrodes for each component; we chose three electrodes at homologous locations on each side of the scalp (for a total of six electrodes) that best represented the maximal amplitude of the component of interest in a given analysis and averaged across the three electrodes. Statistical analyses were conducted with the SPSS software package (SPSS version 11.5). Limiting our analyses to those electrodes where the components are maximal represents a highly conservative approach to the analysis of high-density ERP data and raises the likelihood of missed effects (so-called Type II errors) in these rich datasets. Therefore, an

exploratory (*post-hoc*) analysis phase was also undertaken (described below under “Statistical cluster plots”).

For each component of interest (P20, Pa, P1, N1), we calculated the area under the waveform for an epoch centered on the peak of the grand mean (the time window used for each epoch was either 10 or 20 ms depending on the width of the respective component’s peak). We then averaged these measures across the three representative electrode sites for each hemisphere. These area measures were then used as the dependent variable. To investigate differences between the AEPs of subjects in the *what* and *where* conditions, we tested each identified component with a 2x2 analysis of variance (ANOVA). The factors were condition (*what* vs. *where*) and hemi-scalp (right vs. left).

To verify that our object identification task was effective, we compared the average waveform for responses to targets only to the same for the standard (i.e., nontarget) stimuli. The Nd component (also referred to as the response negativity) has been shown to be elicited when subjects attend to relevant auditory stimuli, when relevance is defined along a physical dimension (see, for example, Molholm, Ritter, Javitt, & Foxe, 2004). The presence of a robust Nd component would provide confirmation that our subjects were in fact actively engaged in the object detection task.

It is important to note that our first level of analysis was performed using an average of all seven speakers, collapsed into a single waveform for each condition. However, the experiment was designed such that every subject was exposed to hundreds of trials from each individual speaker, therefore enabling us to analyze the ERPs generated in response to each spatial location separately. As a second level of analysis, we inspected seven separate waveforms within each condition. We compared these seven averages for our subjects both within and across condition.

Source reconstruction

Cortical source reconstructions were generated by applying the minimum-norm least squares method as implemented in the BESA software suite (version 5.1; Gräefelfing, Germany). The minimum-norm approach is a commonly used method to estimate a distributed electrical current image in cortex as a function of time (see e.g. Hamalainen & Ilmoniemi, 1994). The source activities of 1426 regional sources are computed. Since the number of sources is much larger than the number of sensors, the inverse problem is highly underspecified and must be stabilized by a mathematical constraint (i.e. the minimum norm). Out of the many current distributions that can account for the recorded sensor data, the solution with the minimum L2 norm, i.e. the minimum total power of the current distribution, is displayed in BESA. To compute the minimum norm here, we utilized an idealized three-shell spherical head model with a radius of 85 mm and assumed scalp and skull thickness of 6 and 7 mm, respectively. The minimum norm was applied to the data across the latency interval 90-130 ms, spanning the N1 timeframe. Baseline period was used to compute mean noise levels, resulting in a signal-to-noise ratio for the selected epoch of 8.67. Weighting was at the individual channel level with a noise scale factor of 1.00. Depth-weighting was applied such that the lead field of each regional source was scaled with the largest singular value of the singular value decomposition of the source's lead field. Spatio-temporal weighting was also applied using the signal subspace correlation method of Mosher and Leahy (1998) (dimension setting = 6).

Statistical cluster plots

As described above, we took a conservative approach to the analysis of the high-density ERP data in order to limit the number of statistical tests performed, with the

spatio-temporal properties of the componentry delimiting the tests. Our conservative approach raises the likelihood of missed effects. We therefore performed an exploratory analysis as a means of fully exploring the richness of our data set and as a hypothesis-generating tool for future research. We have devised a simple method for testing the entire data matrix for possible effects, which we term *statistical cluster plots* (see Molholm et al., 2002; Murray et al., 2002). These cluster plots were derived by calculating point-wise, paired, two-tailed *t*-tests between the *what* and *where* conditions. The results were then arrayed on a single grid, with scalp regions (electrode positions) plotted on the *y*-axis and post stimulus time plotted on the *x*-axis, thus providing a snapshot overview of significant differences between conditions across scalp regions over time. In the present data treatment, periods of significant difference were only plotted if an alpha criterion of 0.05 was exceeded and then only if this criterion was exceeded for at least 5 consecutive data points (~10 ms) (see Wetherill & Levitt, 1965).

Topographic Modulations

To statistically identify periods of topographic modulation, we calculate the global dissimilarity (Lehmann & Skrandies, 1980) between *what* and *where* responses for each time point of each subject's data. Global dissimilarity is an index of configuration differences between two electric fields, independent of their strength. This parameter equals the square root of the mean of the squared differences between the potentials measured at each electrode (vs. the average reference), each of which is first scaled to unitary strength by dividing by the instantaneous global field power. Dissimilarity can range from 0 to 2, where 0 indicates topographic homogeneity and 2 indicates topographic inversion. We applied a Monte Carlo MANOVA (Manly, 1991) to test for statistical differences in the dissimilarity between *what* and *where* conditions. This is a nonparametric bootstrapping procedure, wherein each

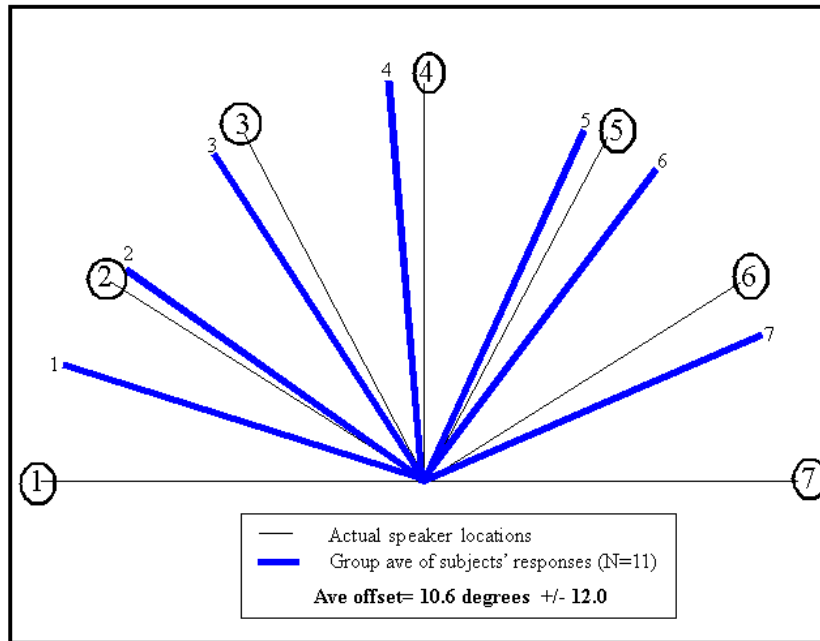
subject's data from each time point was permuted such that they could “belong” to either stimulus condition. The dissimilarity was then calculated for each of the 5000 such permutations for each time point and was used to generate a distribution of values against which the observed data could be compared. From such, we determined the probability of obtaining a dissimilarity value from the permutations that exceeded the actual measured value. Since electric field changes are indicative of different underlying generator configurations (e.g., Fender, 1987; Lehmann, 1987), this test provides a statistical means of determining if and when the brain networks activated by the *what* and *where* conditions differ.

Results

Behavioral results

Mean accuracy was 85.4% for the sound identification task. For the sound localization task, all responses across participants (responses for 11 participants were analyzed; one had to be excluded from the behavioral analysis due to a technical problem capturing responses) were averaged for each of the seven speaker locations (**Figure 3**). The average error of responses for all seven locations collapsed was 10.6 ± 12.0 degrees. The average error to speaker 4, the midline speaker, (where we might well expect a very high degree of accuracy) was 4.5 degrees; moreover, all 11 subjects erred to the left of center.

Figure 3. Behavioral results for the ‘where’ condition. Blue lines identify the average of responses across 11 participants (one had to be excluded due to a technical problem capturing responses) for each of the seven speaker locations. Average offset of responses for all seven locations collapsed was 10.6 ± 12 degrees.



Greater accuracy was seen for responses to speakers located in participants' left hemifield (Speakers 1, 2, 3), as compared to right hemifield (Speakers 5, 6, 7). The average error for responses to left speakers was 3.6 ± 11.0 degrees, to those on the right, 11.7 ± 9.3 degrees. This between hemifield difference was significant ($p = 0.006$).

Electrophysiological results I: General description

In both tasks, stimuli elicited clear ERPs, which contained P20, Pa, P1, and N1 components (**Figure 4a**). To ensure against order effects playing a role in our results, we compared componentry of subjects who took part in each condition respectively on Day 1 (e.g., the Day 1 *what* group vs. the Day 1 *where* group). Group averaged waveforms are displayed in **Figure 4b**. At the N1 period, the relative relationship of the two conditions (that is, greater deflection for the *what* condition) is consistent with that seen in the full subject group.

Figure 4a. Auditory evoked potentials in participants (N=12) generated during the *what* task (red) and the *where* task (black). Data from eight electrodes spanning frontal, central, and centroparietal regions are presented.

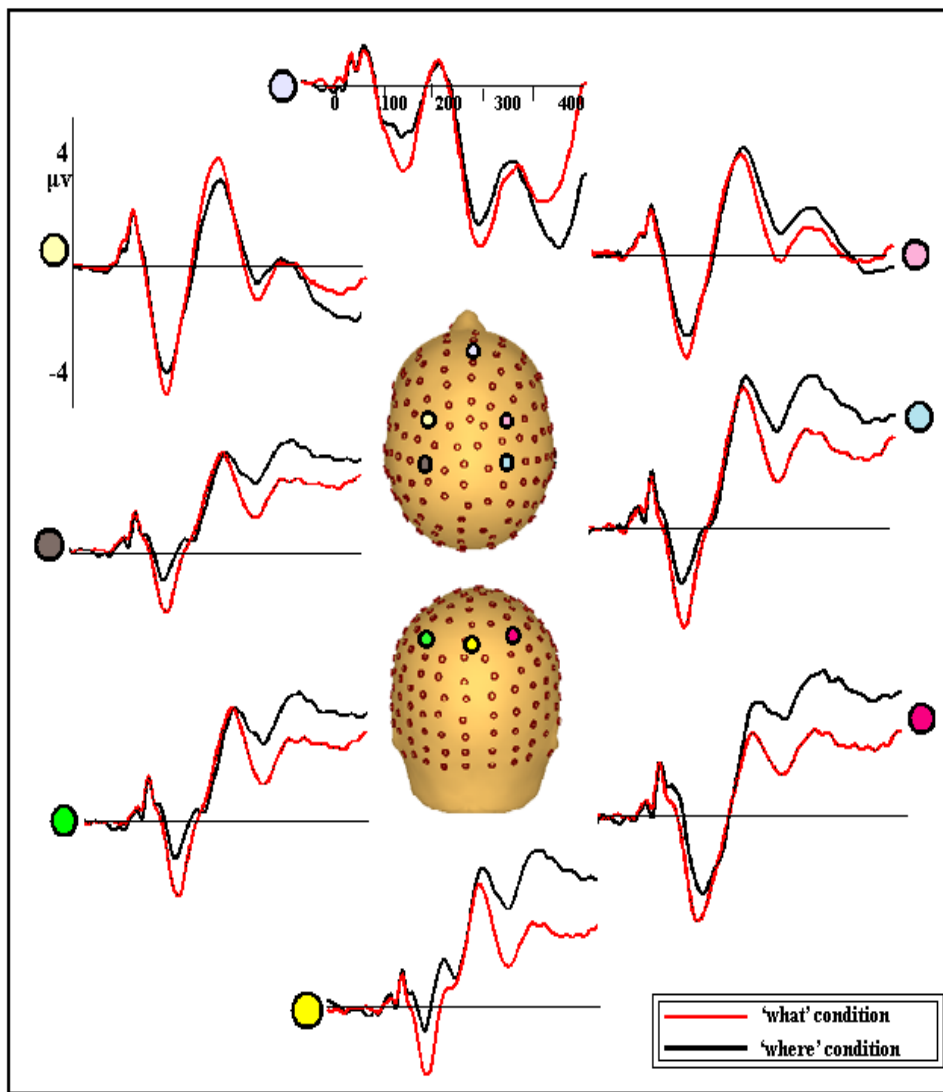
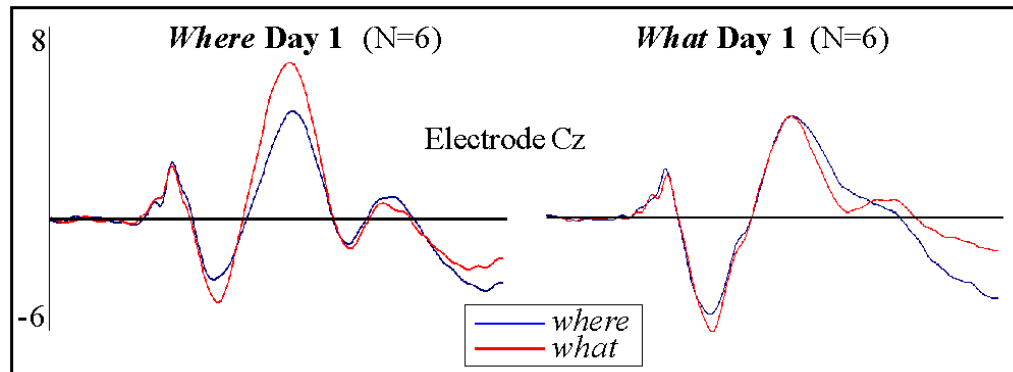


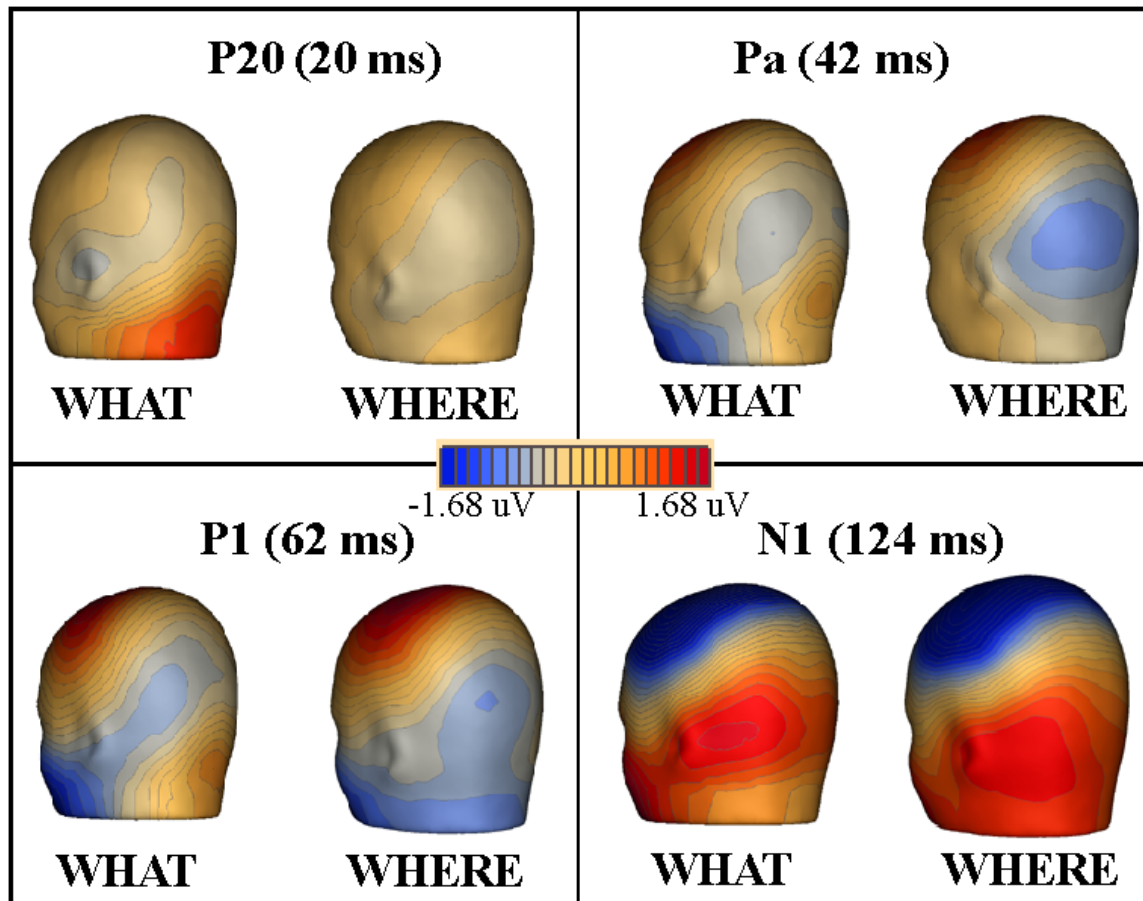
Figure 4b. Representative electrode from subgroups who participated in the *what* condition first (N=6) and in the *where* condition first (N=6).



Typical scalp distributions for the whole group are displayed in **Figure 5**. The time period 15-25 ms was selected around the P20 peak in our dataset. An ANOVA revealed no significant main effect of task, *what* versus *where*, ($F_{1,11} = .006$, $p = 0.938$), nor was there a significant interaction effect for condition by hemisphere ($F_{1,11} = 2.509$, $p = 0.141$). The Pa peak in our data was at approximately 42 ms; analysis of 10-ms time window around the peak of the Pa found neither a main effect of condition ($F_{1,11} = 1.061$, $p = 0.325$), nor for condition by hemisphere ($F_{1,11} = .079$, $p = 0.783$). The P1 peak was found at approximately 62 ms. Analysis of a 10-ms time window around the peak of the P1 yielded neither a main effect of condition ($F_{1,11} = .966$, $p = 0.347$), nor a condition by hemisphere interaction ($F_{1,11} = .298$, $p = 0.596$). In our data, the N1 was evident as a negativity that peaked fronto-centrally at approximately 124 ms in both conditions. To account for the broader deflection of this component, a 20-ms time window was selected around the peak of the N1 (114-134 ms). Here, we found a significant main effect of condition ($F_{1,11} = 5.811$, $p = 0.035$), reflecting substantially greater amplitude of the N1 in

the *what* condition. The effect size of this difference was 0.64 (using the criteria of Cohen's *d*).

Figure 5. Topographic maps of ERPs recorded during *what* and *where* tasks. Group averaged data are displayed for peak of each auditory component: P20, Pa, P1, and N1.

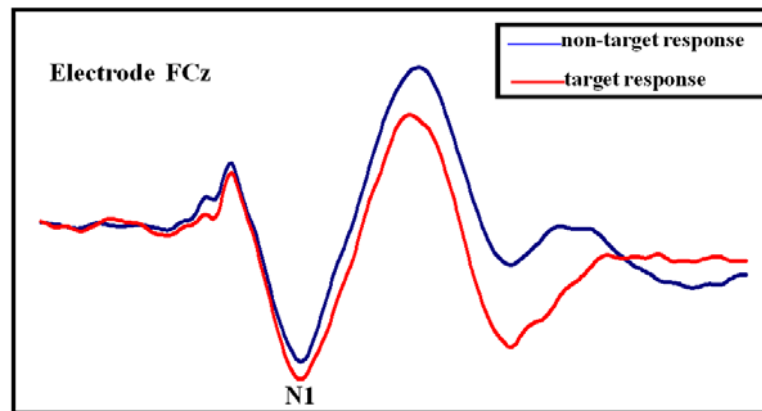


As shown in **Figure 6**, the response elicited by stimuli that included a target auditory element became more negative-going than the responses elicited by the stimuli without a target auditory element over central/fronto-central scalp. This difference extended to about 350 ms. This response pattern is consistent with elicitation of the auditory selective attention component, the Nd (see, for example, Molholm et al., 2004),

thereby providing us with compelling evidence that our subjects were truly engaged in a task of sound object recognition.

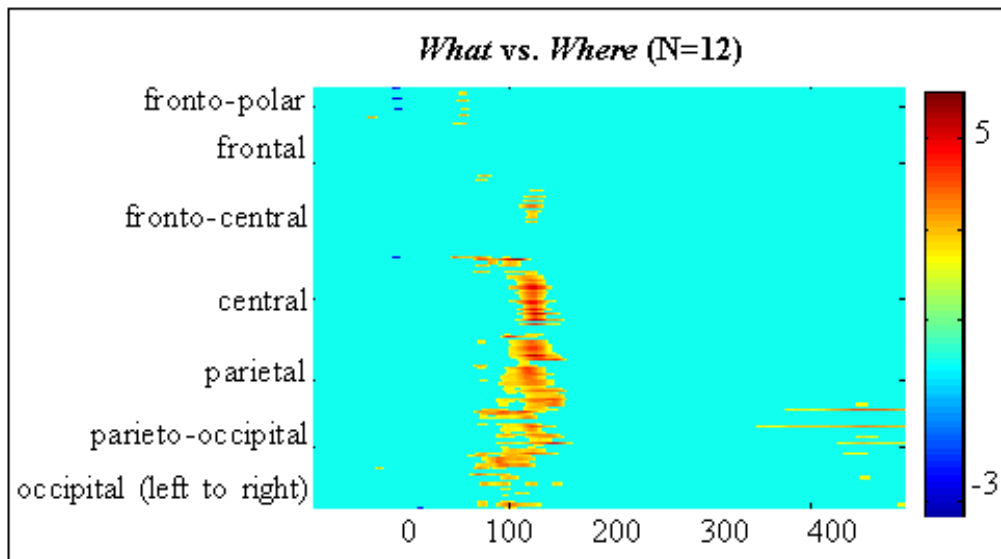
To better detect missed effects between conditions, we computed a statistical cluster plot for all seven speakers collapsed into one waveform for each condition (see Methods). This served as a hypothesis-generating tool; it provided us with a snapshot of where and

Figure 6. Group averaged waveforms for responses to the sound object recognition (*what*) task for target stimuli (red) vs. nontarget stimuli (blue). Representative electrode shown is FCz.



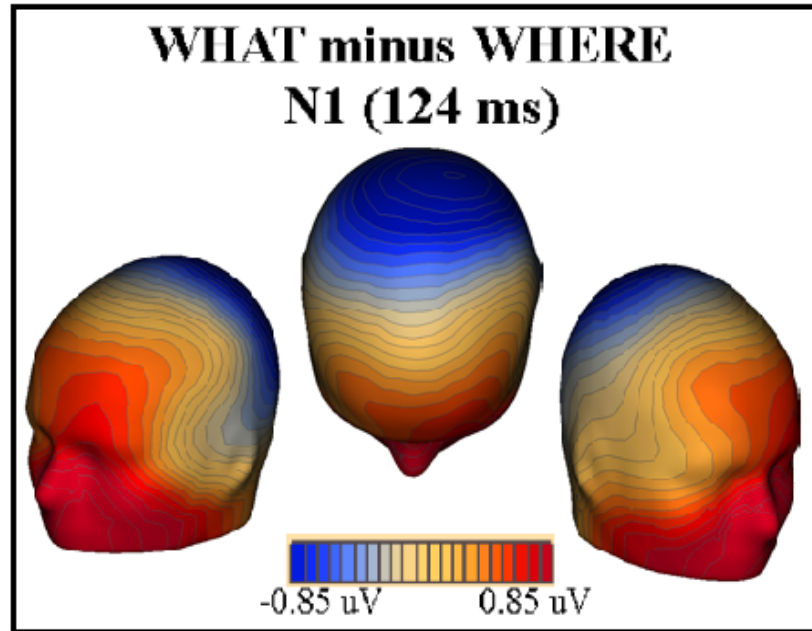
when significant differences occurred between conditions that may have been missed in our planned analyses. Consistent with our previous analysis, we observed a distinct cluster that coincided with the N1 (**Figure 7**). What proved to be rather striking was the almost complete absence of any other differences, particularly at later time points where higher-order cognitive effects generally tend to become evident in ERPs.

Figure 7. Statistical cluster plot of the results of the point-wise running two-tailed t tests comparing the amplitudes of participants' auditory evoked potentials in the *what* versus *where* conditions. Time with respect to stimulus onset is presented on the x axis and topographic regions of 168 electrode positions on the y axis. Color corresponds to t values. Periods of significant difference are only plotted if a strict alpha criterion of <0.05 was exceeded for at least five consecutive data points.



A topographic map of the differences between conditions for the N1 timeframe (**Figure 8**) reveals a topography that is not consistent with auditory components generated in primary auditory cortex. Indeed, it is suggestive of substantial contributions from frontal generators, thereby reflecting processes that more likely involve ventral auditory pathway.

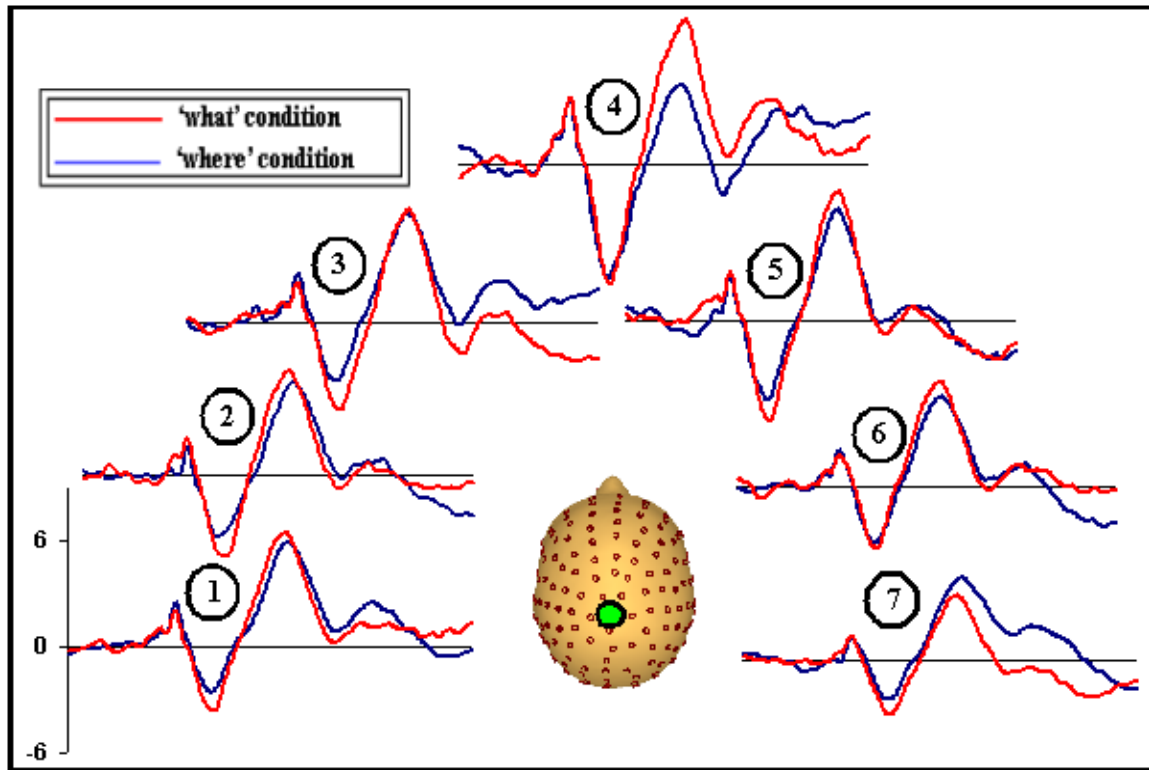
Figure 8. Topographic map of the differences between conditions (*what* minus *where*) during the N1 timeframe.



Electrophysiological results II: Location Specific Averages

We examined each of the seven separate speaker averages within each condition to determine whether evidence of an interaction between speaker location and task could be seen. When we compared between tasks, the N1 difference was consistent; that is, the N1 amplitude in the *what* task was consistently greater than in the *where* task (**Figure 9a**). To determine the significance of this and to probe for any further effects, individual statistical cluster plots for each speaker location were generated. A significant difference between conditions emerged around the time window for the N1 at each speaker location with the exception of Speaker 4 (the midline speaker). It is important to note that the latency of the

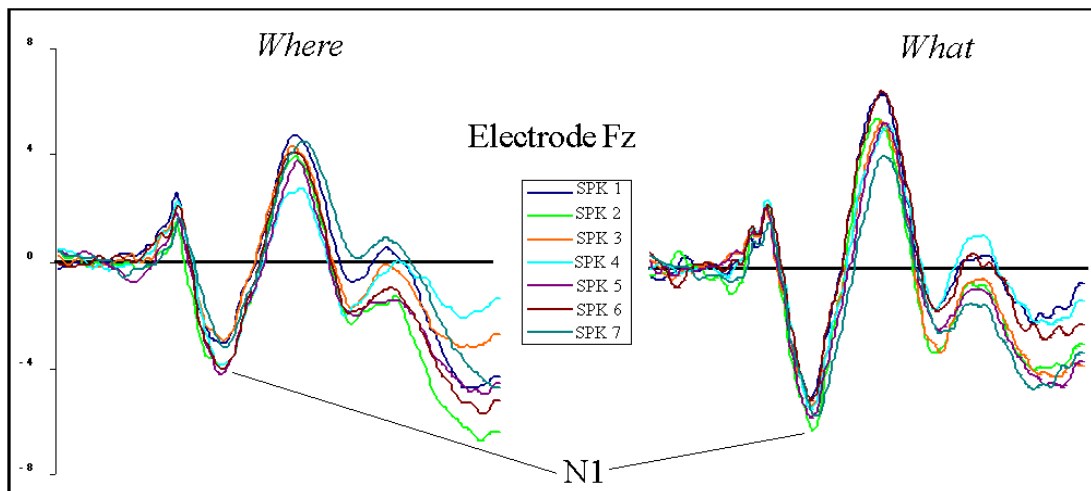
Figure 9a. *What* (red) and *where* (blue) group averaged waveforms taken from electrode Cz are shown for seven individual speaker averages. In the figure, each waveform pair is shown at a location consistent with the speaker from which it was derived.



difference was shifted, depending on the spatial orientation of the speaker. That is, for Speaker 1, the between-condition difference emerged the earliest, prior to 100 ms (~80 ms), while the difference at Speaker 7 became significant after 100 ms (~120 ms). A closer inspection of the individual speaker waveforms revealed that the N1 peak was actually later for responses to Speaker 7 than Speaker 1 in both conditions, by approximately 10 ms. This determination was made by a visual inspection of midline electrodes where the N1 was maximal; therefore, the effect cannot be due to laterality effects. For both the *what* and *where* tasks, the N1 responses to each individual speaker location from one representative electrode where the N1 component is maximal (Fz) were overlaid and these are presented in **Figure**

9b. Whereas, in the object task, the N1 response elicited to each speaker was highly stable in that the amplitude was very similar across speakers, the spatial task evoked responses to each speaker location that showed greater variability. To test this statistically, a 2x2x7 analysis of variance was conducted with factors of condition (*what* vs. *where*), speaker (1 to 7), and speaker hemifield (left vs. right) to determine whether there was a significant interaction between speaker location and task. We took the average N1 amplitude from three frontocentral electrodes (around FCz) using a 40 ms time window around the N1 peak (importantly, this window was shifted such that it centered on the peak of the N1 for each speaker, as these latencies varied). No significant interaction was found for speaker by condition ($F(2,10) = 1.057$, $p > 0.1$), nor was there a three-way interaction between hemifield, speaker, and condition ($F(2,10) = 0.410$, $p > 0.1$).

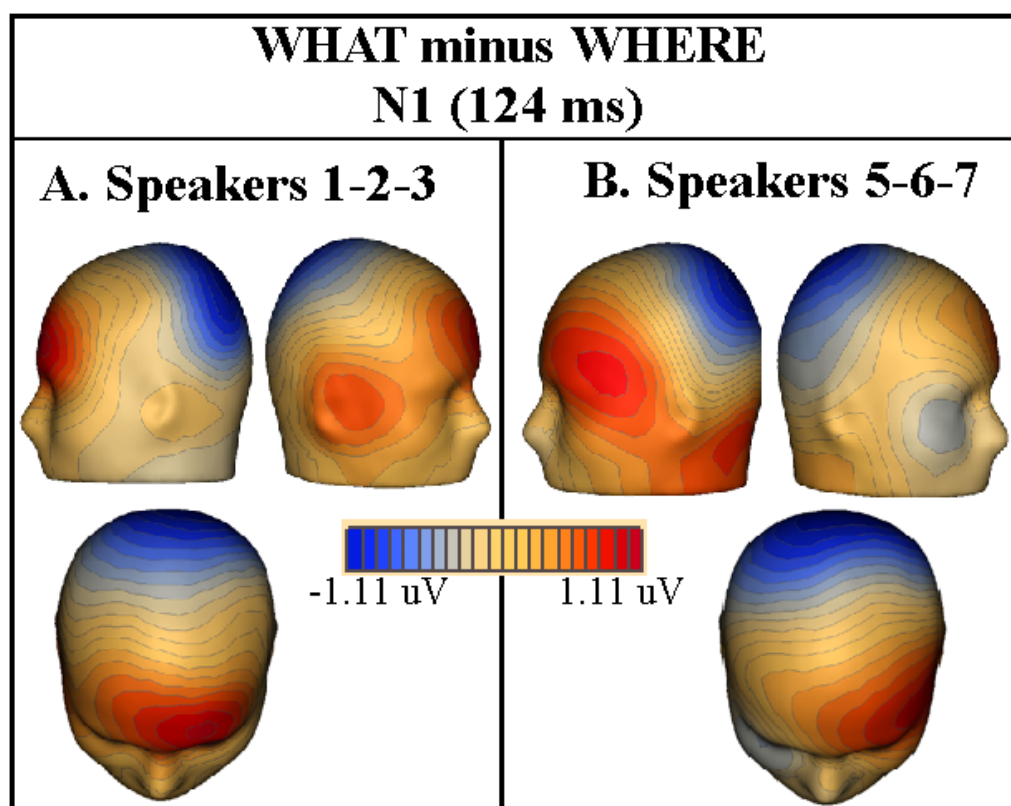
Figure 9b. Separate waveforms for each of the speakers are overlaid from each condition at one representative electrode (Fz).



Topographic maps of the difference between conditions (*what* minus *where*) were created for an average of the left hemifield speakers (1-2-3) and the right hemifield speakers (5-6-7). Subtle but distinct differences can be seen for these, suggesting

contributions from unique underlying generator configurations to stimuli that come from the left hemifield compared to those from the right (Figure 9c).

Figure 9c. Topographic maps of the N1 difference between conditions (*what* minus *where*) showing distinct topographies for speakers on the left (Speakers 1-2-3) compared to the right (Speakers 5-6-7).

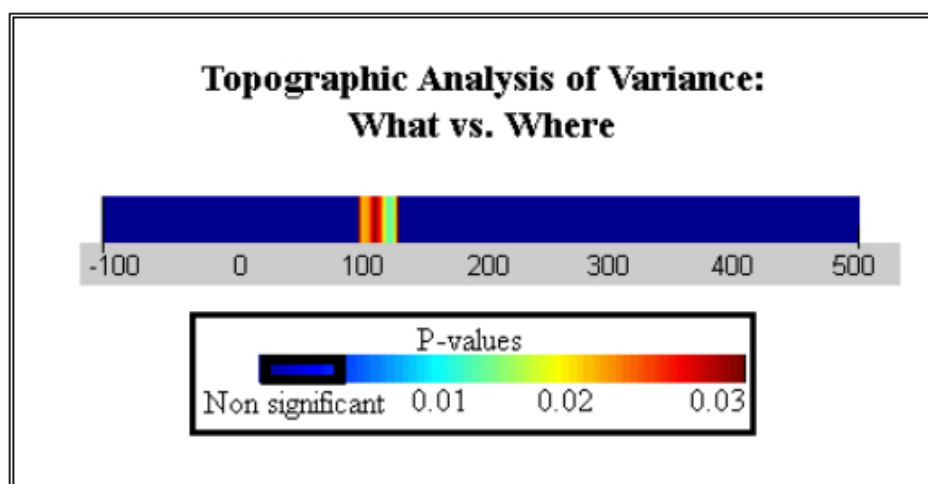


Topographic Modulation Analysis

Averaging across all seven spatial locations, the global dissimilarity metric allowed us to identify a distinct period of statistically significant differences in topographic modulations between the *what* and *where* conditions over the N1 period, indicative of the activation of distinct configurations of intracranial brain generators for each experimental condition (**Figure 10**). That is, the observed effect at N1 was not only due to a change in the amplitude of activation within a given generator configuration, but

crucially, to actual differences in the configurations of neural generators underlying the two tasks.

Figure 10. Statistical plot of topographic modulations. Areas of non-significance appear in blue; areas where significance exceeds $p < .03$ are displayed in a graduated color scheme according to the legend shown. Note that this significance cluster falls in a time frame coincident with the N1 component.

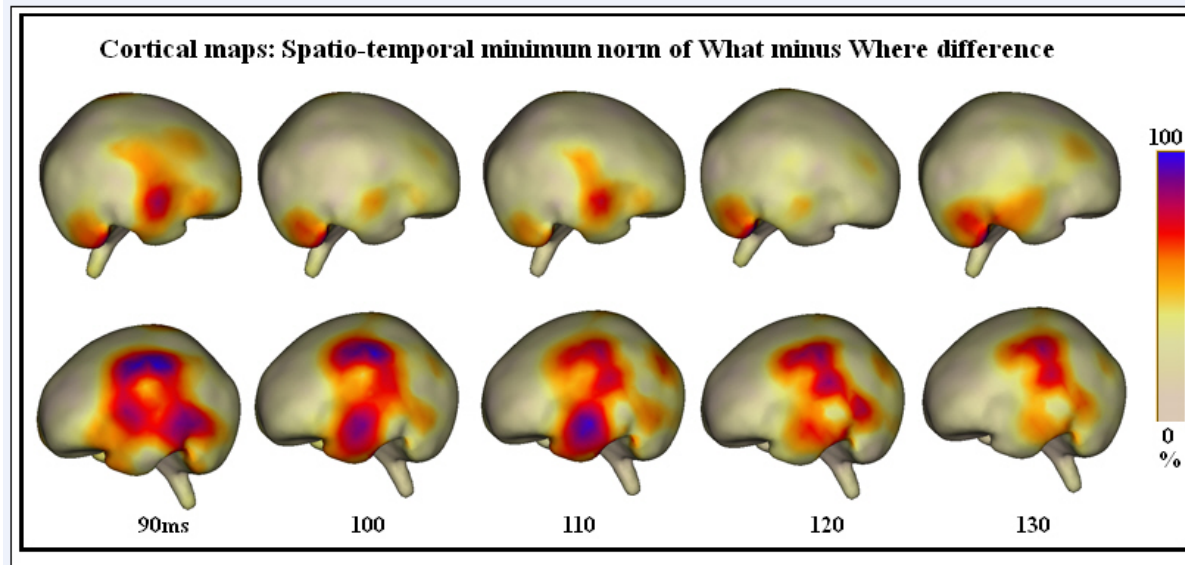


Cortical Activation: Minimum Norm Maps

Intracortical source reconstructions at 10 ms intervals, starting from 90 ms, suggested a strong left hemisphere bias for differential processing between conditions. Two stable clusters of activation, suggestive of separable processing streams, can be seen. At 90 ms, the strongest activation is seen in a cluster over left inferior and superior parietal areas, and this activation continues to be apparent throughout the sampled epoch, although it weakens as time progresses. The second stable cluster, emerges at approximately 100 ms over anterior temporal regions and peaks at 110 ms, after which point it dissipates substantially (See **Figure 11**). As such, these two activation clusters

appear to have somewhat different timecourses. Activation in the right hemisphere suggests much less involvement of underlying generators.

Figure 11. Cortical maps displaying the spatiotemporal minimum norm topographies for *what* minus *where* difference waveforms.

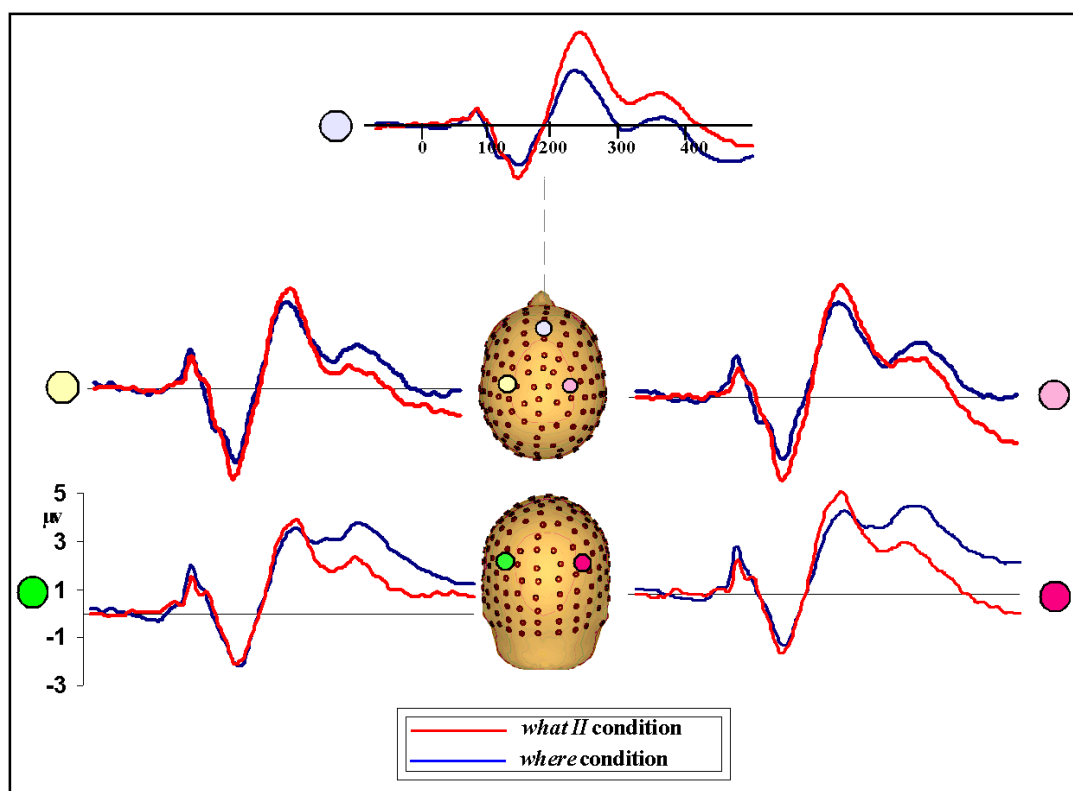


Results for Alternate *What* Paradigm: *What II*

A statistical cluster plot analysis comparing the two *what* paradigms across the entire epoch (-100 to 500) failed to find any areas of significance, suggesting that the differences between *what I* and *what II* were negligible (plots not shown). This supported the notion that one paradigm was just as effective as the other in characterizing neural processes underlying sound identification. Next, we conducted an analysis comparing *what II* and *where*. We reasoned that if differences between these tasks were found, it would support the view that both *what I* and *what II* are tapping processes of sound object identification, distinct from processes of sound localization. We used a one-tailed t-test, guided by our hypothesis that the difference between these conditions would replicate the direction seen for *what I* versus *where*. The N1 difference was apparent between

conditions. Comparing the waveforms, we saw that the direction of the effect was the same: *what II* resulted in a greater deflection of the N1 relative to *where*, as seen in *what I* (Figure 12).

Figure 12. Waveforms from participants (N=6) comparing performance in *what II* and *where* conditions. The direction of the N1 amplitude difference between conditions mirrors that seen in *what I* versus *where*; that is, the N1 amplitude for *what II* is greater than *where*.



Discussion

The present data showed a robust difference in processing over a surprisingly delimited time frame for subjects performing a task of sound object recognition and sound localization using exactly the same stimulus setup. This difference was characterized by greater negative-going amplitude during the N1 processing timeframe for the *what* condition compared to the *where* condition. This effect was seen consistently at electrode sites over frontal, central, centro-parietal and parietal scalp regions. While this difference occurred during the N1 timeframe, it was clearly not a simple modulation of N1 amplitude as it had a completely different topographic distribution to that of the N1. Global dissimilarity measures using topographic modulation analysis confirmed that the difference between tasks during this timeframe was driven by a shift in the underlying generator configuration. Additionally, applying a minimum norm source reconstruction algorithm to the difference wave revealed distinct activations that corresponded well with activity within putative dorsal and ventral auditory structures.

The goal of the present investigation was to find the earliest discernible point of differential processing in the context of spatial and nonspatial auditory tasks. However, a crucial distinction must be made here, and that is that feature processing pathways in cortex are not laid out as one-way highways. Namely, when auditory information is received, it comprises both spatial and nonspatial object features. While the organism may be biased to preferentially process one or the other of these aspects at any given time, this is not to say that the stimulus is stripped of its unattended features. Findings from studies of mismatch negativity (MMN) make clear that both location and object-based properties of auditory stimuli are automatically processed even when attention is directed away from the auditory modality (e.g., Paavilainen, Karlsson, Reinikainen, &

Naatanen, 1989; Ritter, De Sanctis, Molholm, Javitt, & Foxe, 2006; Tata & Ward, 2005); indeed, MMNs to these features are automatically elicited in people when they are asleep (e.g. Ruby, Caclin, Boulet, Delpuech, & Morlet, 2008) or even in a coma (e.g. Fischer, Morlet, & Giard, 2000; Wijnen, van Boxtel, Eilander, & de Gelder, 2007). Moreover, there is a clear suggestion from our prior investigation of mid-latency auditory evoked responses that there may well be a constitutive divergence of activation into separable pathways in the context of a passive listening task (Leavitt et al, 2007). While that study was not designed to expressly test the functionality of the dorsal and ventral auditory pathways per se, automatic sensory activation of these pathways is an inherent result of receiving any auditory stimulation or performing any auditory task. Here, we asked subjects to actively attend to one stimulus feature, location or identity, in a given condition. Clearly, however, neural processing of the “unattended” feature occurred to some degree as well. Indeed, there is a growing body of functional imaging literature showing that irrelevant features of objects seem to be processed by the brain, despite having no current task relevance (e.g. Wylie, Javitt, & Foxe, 2004). This capacity to attend to non-primary stimulus features has even been shown cross-modally, as in an audio-visual task (Molholm et al, 2004). This so-called “spread” of attention is further evidenced by findings in the visual modality that directing spatial attention to one part of an object results in the facilitation of sensory processing of the entire object (e.g. Martinez, Ramanathan, Foxe, Javitt, & Hillyard, 2007). Therefore, while in the present investigation we have identified a point of task-specific divergence at approximately 120 ms, it is clear that this does not represent the first point at which processing for these qualities truly begins. As shown in Leavitt et al (2007), there is evidence for dissociable pathways as early as 35 ms and this is also likely an overestimate.

Two previous studies have also shown modulation during the auditory N1 timeframe, but in both of these, the direction of the effect was actually opposite to that seen here, with responses in the *where* condition showing larger amplitude (Ahveninen et al., 2006; Anourova et al., 2001; De Santis, Clarke et al., 2007). A third MEG study found no amplitude differences for N1 (Anourova et al., 2001). We contend that these differences are likely explained by paradigmatic differences. The stimuli used by these investigators were simple tones (Anourova et al., 2001; De Santis, Clarke et al., 2007) and vowel pairs (Ahveninen et al., 2006) and it could be argued that these stimuli might be relatively ineffective at activating object-processing regions. Here, by employing complex, and considerably more ecological sounds, it is likely that a greater activation of *what* processing regions was invoked. Whereas sound localization may be more automatic, and engaged more quickly (as suggested by Anourova et al., 2001), object recognition and identification relies more heavily on accessing a memory trace and it is a reasonable assumption that invoking a memory trace of a complex sound employs a greater neural network than that of a simple tone. This may very well explain why our finding stands in contrast to those of prior studies. Similarly, in all of these prior investigations, only a limited number of spatial locations were used during the spatial condition. In most, only two positions were used and only in one case (Anurova 2003) were three used. Here, seven discrete locations were used. It stands to reason that performing the current task required a great deal more effort, and consequently, greater involvement of underlying neural networks for spatial discrimination. Moreover, our subjects were not explicitly aware that there were seven discrete speakers, and so the number of sound sources was unknown to them and likely created higher demands on them.

It could be considered surprising that while we found significant task-related differences during the N1 processing timeframe, there were no subsequent time points where significant differences were seen. With such different tasks as localizing sound and making a sound object identification, one might well predict that distinct higher-order cognitive processes might be engaged at later latencies, such as the P300 component, which has been shown to index attention-related information processing (e.g. Linden, 2005; Polich, 1986). On the other hand, the lack of differences during later timeframes here provides confirmation that attentional processes were not differentially engaged between the two tasks, suggesting that the location and object tasks were well-matched for difficulty.

Also notable here is that we utilized seven distinct spatial locations in the auditory free field and collected hundreds of sweeps from each, enabling us to individually examine the brain responses of our participants to seven different points in space within the context of a spatial and a non-spatial task. Our hypothesis was that we would see an interaction of task and spatial location. Topographic maps of the difference between EPs generated in response to left hemifield speakers and right hemifield speakers suggest differences in the underlying generator configurations for each condition.

The behavioral findings for the *where* task are interesting, in that they appear to represent an auditory analogue to the pattern of pseudoneglect that has been consistently observed in the visual system of healthy controls. Specifically, pseudoneglect refers to a leftward attentional bias that occurs in normally functioning individuals and causes them to bisect visually presented lines slightly to the left of their true center (e.g. McCourt, 2001; Foxe, McCourt, & Javitt, 2003; McCourt, Shpaner, Javitt, & Foxe, 2008). Here, subjects consistently mislocated the centrally presented sound approximately 4.5 degrees

leftward of veridical center. This leftward bias can also be seen for the pair of closest flanking speakers (speakers 3 and 5). Another interesting aspect of these data was the observation of significantly more accurate responses to the three speakers in the left hemisphere (Speakers 1, 2, 3) than to the three speakers in the right hemisphere (Speakers 5, 6, 7). This is consistent with what is known about hemispheric differences in sound localization in humans; namely, that auditory spatial processing is more accurate for sounds in the left hemifield (Burke, Letsos, & Butler, 1994). These investigators interpreted their findings to suggest the pivotal role played by the right hemisphere in auditory spatial acuity. Consistently, a number of studies have implicated greater involvement of the right hemisphere in sound localization. For example, one study utilizing magnetoencephalography (MEG) demonstrated that the overall amplitude and variation of the N1m component was larger in the right hemisphere than left (Tiitinen et al., 2006). Right hemisphere dominance in processing auditory spatial information was also supported by a sound localization study utilizing individuals with callosotomies, hemispherectomies, or callosal agenesis (Hausmann, Corballis, Fabri, Paggi, & Lewald, 2005).

Clinical usefulness: Implications for patients with schizophrenia

Employing effortful tasks of sound object recognition and sound localization allowed us to further delineate the underlying neural processes of the dorsal and ventral auditory pathways. However, the present study was also motivated by an interest in the potential clinical usefulness of a method for evaluating the functional integrity of these auditory pathways in psychiatric populations. There is evidence in the literature to suggest that pathology in the brains of patients is organized along the lines of a dorsal/ventral distinction. For example, Christensen and Bilder (2000) provide

justification for a dorsal/ventral framework of cortical dysfunction which they termed the “dual cytoarchitectonic trends theory.” They claim that evidence supports the notion that all cortical regions evolved from two primitive sources, the hippocampus (archicortex) and olfactory areas (paleocortex), and projections from these two cortical areas subsequently occupy dorsal and ventral regions of the brain. In their view, these dorsal and ventral distinctions exist across multiple cortical systems. Furthermore, they assert that the brains of patients with schizophrenia demonstrate deficits at all cytoarchitectonic levels of the “dorsal trend.” A prior study from our group has supported just such a distinction, with patients performing as well as controls on a task requiring them to discern words embedded in noise, arguably a task that tapped their ventral pathway function (Ross, Saint-Amour, Leavitt, Molholm et al., 2007). In another study, patient auditory ERPs elicited in an unattended auditory task were significantly more impaired relative to those of healthy controls from time points as early as 11 ms (Leavitt et al., 2007). Furthermore, the auditory componentry recorded by electrodes corresponding to dorsal pathways- that is, more posterior parietal regions- showed much greater deficits compared to those corresponding to ventral pathways. A recent review examined auditory hallucinations in schizophrenia patients within the context of abnormal processing within the dorsal and ventral auditory pathways (Badcock, 2008). It will be important to test the present paradigm on a sample of patients with schizophrenia to determine whether they demonstrate differential impairment on dedicated tasks involving sound object recognition and sound localization.

Conclusions

This study provides electrophysiological evidence for separable neural networks underlying sound object identification and sound localization. In the context of attended, dedicated behavioral tasks that tapped each of these processes in a very specific, ecologically valid manner, we saw differences in the event-related potentials of human subjects from as early as ~120 ms. Furthermore, by employing the free field and utilizing complex animal calls as our stimuli, we believe that our study represents the first of its kind, thereby providing the most accurate portrayal yet of the complex and likely overlapping neural systems that underlie sound localization and sound object identification.

An ancillary purpose of this study was to develop these dependant measures for assessing the relative integrity of dorsal and ventral auditory pathway function in patients with schizophrenia. The results of this pilot study are presented in Chapter 4.

References

- Ahveninen, J., Jaaskelainen, I. P., Raij, T., Bonmassar, G., Devore, S., Hamalainen, M., et al. (2006). Task-modulated "what" and "where" pathways in human auditory cortex. *Proc Natl Acad Sci U S A*, 103(39), 14608-14613.
- Alain, C., Arnott, S. R., Hevenor, S., Graham, S., & Grady, C. L. (2001). "What" and "where" in the human auditory system. *Proc Natl Acad Sci U S A*, 98(21), 12301-12306.
- American Electroencephalographic Society guidelines for standard electrode position nomenclature. (1991). *J Clin Neurophysiol*, 8(2), 200-202.
- Anourova, I., Nikouline, V. V., Ilmoniemi, R. J., Hotta, J., Aronen, H. J., & Carlson, S. (2001). Evidence for dissociation of spatial and nonspatial auditory information processing. *Neuroimage*, 14(6), 1268-1277.
- Anurova, I., Artchakov, D., Korvenoja, A., Ilmoniemi, R. J., Aronen, H. J., & Carlson, S. (2003). Differences between auditory evoked responses recorded during spatial and nonspatial working memory tasks. *Neuroimage*, 20(2), 1181-1192.
- Arnott, S. R., Binns, M. A., Grady, C. L., & Alain, C. (2004). Assessing the auditory dual-pathway model in humans. *Neuroimage*, 22(1), 401-408.
- Badcock, J. (2008). The cognitive neuropsychology of auditory hallucinations: A parallel auditory pathways framework. *Schizophrenia Bulletin*, Oct 2:1-9.
- Belin, P., & Zatorre, R. J. (2000). 'What', 'where' and 'how' in auditory cortex. *Nat Neurosci*, 3(10), 965-966.
- Burke, K. A., Letsos, A., & Butler, R. A. (1994). Asymmetric performances in binaural localization of sound in space. *Neuropsychologia*, 32(11), 1409-1417.
- Christensen, B. K., & Bilder, R. M. (2000). Dual cytoarchitectonic trends: an evolutionary model of frontal lobe functioning and its application to psychopathology. *Can J Psychiatry*, 45(3), 247-256.
- Clarke, S., Bellmann, A., Meuli, R. A., Assal, G., & Steck, A. J. (2000). Auditory agnosia and auditory spatial deficits following left hemispheric lesions: evidence for distinct processing pathways. *Neuropsychologia*, 38(6), 797-807.
- Clarke, S., Bellmann Thiran, A., Maeder, P., Adriani, M., Vernet, O., Regli, L., et al. (2002). What and where in human audition: selective deficits following focal hemispheric lesions. *Exp Brain Res*, 147(1), 8-15.
- Clarke, S., & Thiran, A. B. (2004). Auditory neglect: what and where in auditory space. *Cortex*, 40(2), 291-300.

- De Santis, L., Clarke, S., & Murray, M. M. (2007). Automatic and intrinsic auditory "what" and "where" processing in humans revealed by electrical neuroimaging. *Cereb Cortex*, 17(1), 9-17.
- De Santis, L., Spierer, L., Clarke, S., & Murray, M. M. (2007). Getting in touch: segregated somatosensory what and where pathways in humans revealed by electrical neuroimaging. *Neuroimage*, 37(3), 890-903.
- Doniger, G. M., Foxe, J. J., Murray, M. M., Higgins, B. A., & Javitt, D. C. (2002). Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. *Arch Gen Psychiatry*, 59(11), 1011-1020.
- Fabiani, M., Kazmerski, V. A., Cycowicz, Y. M., & Friedman, D. (1996). Naming norms for brief environmental sounds: effects of age and dementia. *Psychophysiology*, 33(4), 462-475.
- Fender, D. H. (1987). Source localisation of brain electrical activity. In A. S. a. R. Gevins, A. (Ed.), *Handbook of Electroencephalography and Clinical Neurophysiology Methods of Analysis of Brain Electrical and Magnetic Signals* (Vol. 1, pp. pp. 355-399). Amsterdam: Elsevier.
- Fischer, C., Morlet, D., & Giard, M. (2000). Mismatch negativity and N100 in comatose patients. *Audiol Neurotol*, 5(3-4), 192-197.
- Foxe, J. J., Doniger, G. M., & Javitt, D. C. (2001). Early visual processing deficits in schizophrenia: impaired P1 generation revealed by high-density electrical mapping. *Neuroreport*, 12(17), 3815-3820.
- Foxe, J. J., McCourt, M. E., & Javitt, D. C. (2003). Right hemisphere control of visuospatial attention: line-bisection judgments evaluated with high-density electrical mapping and source analysis. *Neuroimage*, 19(3), 710-726.
- Foxe, J. J., Murray, M. M., & Javitt, D. C. (2005). Filling-in in Schizophrenia: a High-density Electrical Mapping and Source-analysis Investigation of Illusory Contour Processing. *Cereb Cortex*.
- Gilkey, R. H., & Anderson, T. R. (1995). The accuracy of absolute localization judgments for speech stimuli. *J Vestib Res*, 5(6), 487-497.
- Hausmann, M., Corballis, M. C., Fabri, M., Paggi, A., & Lewald, J. (2005). Sound lateralization in subjects with callosotomy, callosal agenesis, or hemispherectomy. *Brain Res Cogn Brain Res*, 25(2), 537-546.
- Kaas, J. H., & Hackett, T. A. (1999). 'What' and 'where' processing in auditory cortex. *Nat Neurosci*, 2(12), 1045-1047.
- Lalor, E. C., Yeap, S., Reilly, R. B., Pearlmutter, B. A., & Foxe, J. J. (2008). Dissecting the cellular contributions to early visual sensory processing deficits in

- schizophrenia using the VESPA evoked response. *Schizophr Res*, 98(1-3), 256-264.
- Leavitt, V. M., Molholm, S., Ritter, W., Shpaner, M., & Foxe, J. J. (2007). Auditory processing in schizophrenia during the middle latency period (10-50 ms): high-density electrical mapping and source analysis reveal subcortical antecedents to early cortical deficits. *J Psychiatry Neurosci*, 32(5), 339-353.
- Lehmann, D. (1987). Principles of spatial analysis. In A. S. a. R. Gevins, A. (Ed.), *Handbook of electroencephalography and Clinical Neurophysiology Methods of Analysis of Brain Electrical and Magnetic Signals* (Vol. 1, pp. pp. 309-354). Amsterdam: Elsevier.
- Lehmann, D., & Skrandies, W. (1980). Reference-free identification of components of checkerboard-evoked multichannel potential fields. *Electroencephalogr. Clin. Neurophysiol.*, 48, 609-621.
- Linden, D. E. (2005). The p300: where in the brain is it produced and what does it tell us? *Neuroscientist*, 11(6), 563-576.
- Manly, B. F. (1991). *Randomization and Monte Carlo Methods in Biology*. London: Chapman & Hall.
- Martinez, A., Ramanathan, D. S., Foxe, J. J., Javitt, D. C., & Hillyard, S. A. (2007). The role of spatial attention in the selection of real and illusory objects. *J Neurosci*, 27(30), 7963-7973.
- McCourt, M. E. (2001). Performance consistency of normal observers in forced-choice tachistoscopic visual line bisection. *Neuropsychologia*, 39(10), 1065-1076.
- McCourt, M. E., Shpaner, M., Javitt, D. C., & Foxe, J. J. (2008). Hemispheric asymmetry and callosal integration of visuospatial attention in schizophrenia: A tachistoscopic line bisection study. *Schizophr Res*, 102(1-3), 189-196.
- Mishkin, M., Lewis, M. E., & Ungerleider, L. G. (1982). Equivalence of parieto-preoccipital subareas for visuospatial ability in monkeys. *Behav Brain Res*, 6(1), 41-55.
- Molholm, S., Ritter, W., Javitt, D. C., & Foxe, J. J. (2004). Multisensory visual-auditory object recognition in humans: a high-density electrical mapping study. *Cereb Cortex*, 14(4), 452-465.
- Molholm, S., Ritter, W., Murray, M. M., Javitt, D. C., Schroeder, C. E., & Foxe, J. J. (2002). Multisensory auditory-visual interactions during early sensory processing in humans: a high-density electrical mapping study. *Brain Res Cogn Brain Res*, 14(1), 115-128.
- Murray, M. M., Wylie, G. R., Higgins, B. A., Javitt, D. C., Schroeder, C. E., & Foxe, J. J. (2002). The spatiotemporal dynamics of illusory contour processing: combined

- high-density electrical mapping, source analysis, and functional magnetic resonance imaging. *J Neurosci*, 22(12), 5055-5073.
- Nousak, J. M., Deacon, D., Ritter, W., & Vaughan, H. G., Jr. (1996). Storage of information in transient auditory memory. *Brain Res Cogn Brain Res*, 4(4), 305-317.
- Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, 9(1), 97-113.
- Paavilainen, P., Karlsson, M. L., Reinikainen, K., & Naatanen, R. (1989). Mismatch negativity to change in spatial location of an auditory stimulus. *Electroencephalogr Clin Neurophysiol*, 73(2), 129-141.
- Picton, T. W., Hillyard, S. A., Krausz, H. I., & Galambos, R. (1974). Human auditory evoked potentials. I. Evaluation of components. *Electroencephalogr Clin Neurophysiol*, 36(2), 179-190.
- Polich, J. (1986). Attention, probability, and task demands as determinants of P300 latency from auditory stimuli. *Electroencephalogr Clin Neurophysiol*, 63(3), 251-259.
- Poremba, A., Saunders, R. C., Crane, A. M., Cook, M., Sokoloff, L., & Mishkin, M. (2003). Functional mapping of the primate auditory system. *Science*, 299(5606), 568-572.
- Rama, P., Poremba, A., Sala, J. B., Yee, L., Malloy, M., Mishkin, M., et al. (2004). Dissociable functional cortical topographies for working memory maintenance of voice identity and location. *Cereb Cortex*, 14(7), 768-780.
- Rauschecker, J. P., & Tian, B. (2000). Mechanisms and streams for processing of "what" and "where" in auditory cortex. *Proc Natl Acad Sci U S A*, 97(22), 11800-11806.
- Ritter, W., De Sanctis, P., Molholm, S., Javitt, D. C., & Foxe, J. J. (2006). Preattentively grouped tones do not elicit MMN with respect to each other. *Psychophysiology*, 43(5), 423-430.
- Roeber, U., Widmann, A., & Schroger, E. (2003). Auditory distraction by duration and location deviants: a behavioral and event-related potential study. *Brain Res Cogn Brain Res*, 17(2), 347-357.
- Romanski, L. M., Tian, B., Fritz, J., Mishkin, M., Goldman-Rakic, P. S., & Rauschecker, J. P. (1999). Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. *Nat Neurosci*, 2(12), 1131-1136.
- Ross, L. A., Saint-Amour, D., Leavitt, V. M., Javitt, D. C., & Foxe, J. J. (2007). Do you see what I am saying? Exploring visual enhancement of speech comprehension in noisy environments. *Cereb Cortex*, 17(5), 1147-1153.

- Ross, L. A., Saint-Amour, D., Leavitt, V. M., Molholm, S., Javitt, D. C., & Foxe, J. J. (2007). Impaired multisensory processing in schizophrenia: deficits in the visual enhancement of speech comprehension under noisy environmental conditions. *Schizophr Res*, 97(1-3), 173-183.
- Ruby, P., Caclin, A., Boulet, S., Delpuech, C., & Morlet, D. (2008). Odd sound processing in the sleeping brain. *J Cogn Neurosci*, 20(2), 296-311.
- Schmolesky, M. T., Wang, Y., Hanes, D. P., Thompson, K. G., Leutgeb, S., Schall, J. D., et al. (1998). Signal timing across the macaque visual system. *J Neurophysiol*, 79(6), 3272-3278.
- Schroeder, C. E., Mehta, A. D., & Givre, S. J. (1998). A spatiotemporal profile of visual system activation revealed by current source density analysis in the awake macaque. *Cereb Cortex*, 8(7), 575-592.
- Tata, M. S., & Ward, L. M. (2005). Early phase of spatial mismatch negativity is localized to a posterior "where" auditory pathway. *Exp Brain Res*, 167(3), 481-486.
- Tian, B., Reser, D., Durham, A., Kustov, A., & Rauschecker, J. P. (2001). Functional specialization in rhesus monkey auditory cortex. *Science*, 292(5515), 290-293.
- Tiitinen, H., Salminen, N. H., Palomaki, K. J., Makinen, V. T., Alku, P., & May, P. J. (2006). Neuromagnetic recordings reveal the temporal dynamics of auditory spatial processing in the human cortex. *Neurosci Lett*, 396(1), 17-22.
- Weeks, R. A., Aziz-Sultan, A., Bushara, K. O., Tian, B., Wessinger, C. M., Dang, N., et al. (1999). A PET study of human auditory spatial processing. *Neurosci Lett*, 262(3), 155-158.
- Wetherill, G. B., & Levitt, H. (1965). Sequential Estimation of Points on a Psychometric Function. *Br J Math Stat Psychol*, 18, 1-10.
- Wijnen, V. J., van Boxtel, G. J., Eilander, H. J., & de Gelder, B. (2007). Mismatch negativity predicts recovery from the vegetative state. *Clin Neurophysiol*, 118(3), 597-605.
- Woldorff, M. G., Gallen, C. C., Hampson, S. A., Hillyard, S. A., Pantev, C., Sobel, D., et al. (1993). Modulation of early sensory processing in human auditory cortex during auditory selective attention. *Proc Natl Acad Sci U S A*, 90(18), 8722-8726.
- Wylie, G. R., Javitt, D. C., & Foxe, J. J. (2004). Don't think of a white bear: an fMRI investigation of the effects of sequential instructional sets on cortical activity in a task-switching paradigm. *Hum Brain Mapp*, 21(4), 279-297.
- Zatorre, R. J., Bouffard, M., Ahad, P., & Belin, P. (2002). Where is 'where' in the human auditory cortex? *Nat Neurosci*, 5(9), 905-909.

CHAPTER 4

“What” and “Where” in auditory sensory processing II: A high-density electrophysiological investigation of distinct neural processes underlying sound object recognition and sound localization in patients with schizophrenia

Abstract:

The integrity of dorsal and ventral auditory pathways in patients with schizophrenia was examined using the *what* and *where* paradigms described in Chapter 3. Sensory processing deficits in this population are well documented in the literature. Work in the visual system has shown that patients with schizophrenia demonstrate impaired processing of dorsal stream but not ventral stream stimuli. Evidence suggests that a similar pattern of impairment may exist in the auditory system of patients; that is, processing in the *where* (dorsal) pathway may be relatively less intact than the *what* (ventral) pathway. Here, we piloted the paradigm that was developed and run on a normative sample (as described in Chapter 3) in six patients with schizophrenia. Our hypothesis was that we would see electrophysiological and behavioral evidence of differential impairment of patients' dorsal and ventral auditory pathway function; specifically, we posited that their dorsal (*where*) pathway function would be more impaired than their ventral (*what*) pathway function. Behaviorally, patients performed poorly on the *where* task, although there was a great deal of inter-individual variability. Imaging results suggested a similar electrophysiological pattern of findings to those of controls: at the N1, the deflection in the *what* condition was greater than in the *where* condition. While the amplitude difference was not found to be significant, a topographic analysis of variance revealed between-condition significance for the time period of the

N1 (100 ms), suggesting contributions from distinct underlying neural generators within each condition. This was consistent with our findings for healthy controls. No differential effect between dorsal and ventral pathway integrity in patients was observed.

Introduction

If dorsal stream auditory function is impaired in schizophrenia as the results of the previously described middle latency auditory evoked potential (AEP) investigation (**Chapter 2**) suggested, the prediction is clear that function reliant on dorsal processing will be impaired. Therefore, we proposed to assess the integrity of sound localization in patients. To date, only a handful of studies have assessed sound localization in schizophrenia, with mixed results (Balogh, 1979; Balogh & Leventhal, 1982; de Gelder, Vroomen, Annen, Masthof, & Hodiament, 2003; Guterman & Klein, 1991; Hatashita-Wong & Silverstein, 2003; McGhie, 1961; Michie, Fox, Ward, Catts, & McConaghy, 1990; Olsson & Nielzen, 1999). In 1961, McGhie and Chapman (1961) collected subjective reports from schizophrenia patients suggesting they experienced difficulty identifying the source of a sound. Balogh and Leventhal (1982) examined the ability of schizophrenia patients to make judgments about the direction of auditory stimuli. Results were mixed, with paranoid and nonparanoid schizophrenia subgroups performing differently. Although this finding is interesting, it does nothing to elucidate the relationship between dorsal and ventral pathways, since the task was only concerned with a sub function of dorsal stream processing, direction of sound movement. de Gelder and colleagues (2003) reported that a patient group performed as well as controls in sound localization, but these findings were derived from an audiovisual integration task. As such, none of these studies has investigated the underlying neurophysiology of sound localization in schizophrenia. Physiological evidence we have collected suggests that we will see impaired sound localization in schizophrenia patients. Dorsal stream componentry of schizophrenia

patients in our data from the middle latency response (MLR) study shows consistent and significant attenuation at very early time points in sensory processing, starting as early as 20 ms (Leavitt, Molholm, Ritter, Shpaner, & Foxe, 2007).

This project will assess auditory spatial localization ability in schizophrenia, and will test the hypothesis that schizophrenia patients have spatial localization deficits similar in form to well-documented tone matching deficits/pitch MMN reductions (Salisbury, Shenton, Griggs, Bonner-Jackson, & McCarley, 2002; Todd, Michie, & Jablensky, 2003). If deficits are observed, this will support the concept that deficits in information processing exist at the level of auditory sensory cortices in schizophrenia, and that such deficits may be used as a model for impairments of more complex types of memory-dependent processing in other brain regions.

Our present aim is to correlate physiological evidence of dorsal stream impairment with behavioral performance. By doing this, we will begin to have a solid understanding of how neurophysiological substrates underlie functional impairment in the auditory system of schizophrenia patients.

Here, we sought to investigate the relative contributions of the dorsal and ventral auditory pathways through the use of the behavioral tasks that were developed and tested on a normative sample (**Chapter 3**). The premise of this study is based in part on our knowledge that impairment in the visual system is organized along the lines of a dorsal-ventral distinction; that is, patients with schizophrenia demonstrate impaired processing of magnocellular-biased (dorsal) but not parvocellular-biased (ventral) stimuli (Butler et al., 2005). Evidence suggests that in the auditory system, processing in the *where* (dorsal) pathway is more impaired than the *what* (ventral) pathway (e.g., Leavitt et al., 2007; Ross

et al., 2007). The integrity of dorsal and ventral auditory pathways in patients with schizophrenia was examined using tasks that specifically tapped processes of sound localization and sound object recognition. Our hypothesis is that we will see electrophysiological and behavioral evidence of a structurally more intact ventral than dorsal pathway.

Materials and Methods

The procedures of this study were approved by the Nathan S. Kline Institute for Psychiatric Research/Rockland Psychiatric Center Institutional Review Board and the Institutional Review Board of The Graduate Center of the City University of New York. Written informed consent was obtained from each subject.

Subjects

Six patients with schizophrenia participated (mean age 44.5 +/- 5.1; 2 female; all right-handed). Patients met the following inclusion/exclusion criteria: **Inclusion:** 1) current DSM-IV-defined diagnosis of schizophrenia or schizoaffective disorder. A best estimate diagnostic approach was utilized in which information from the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) (First, Frances, Pincus, Vettorello, & Davis, 1994) was supplemented by information from family members, psychiatrists, and medical records to generate a diagnosis, 2) ages 18 to 55, 3) male or female, 4) any race, 5) competent and willing to sign informed consent, 6) normal hearing and normal or corrected-to-normal vision. **Exclusion:** 1) organic brain disorder, mental retardation, or significant medical illness, 2) current substance-induced psychotic disorder or a psychotic disorder due to a general medical condition determined by DSM-

IV criteria, 3) significant risk of suicidal or homicidal behavior, 4) participants with prior intermittent alcohol or substance use were not excluded unless they met DSM-IV criteria for current alcohol or drug dependence in the last 6 months, 5) any history of hearing loss or injury to the ears, 6) any additional Axis I diagnoses.

For all patients, demographic information was collected including age, sex, education, and illness duration. Doses of anti-psychotic, anti-cholinergic and adjuvant medications (e.g., anti-depressants, sedative/hypnotics, anti-manics, anti-epileptics) were recorded. Anti-psychotic doses were translated into chlorpromazine equivalents using the best available literature at the time of data analysis for conversion of dose levels of newer anti-psychotics (e.g., sertindole, seroquel). Average length of illness was 19.5 ± 10.6 years. Average daily dose of anti-psychotic medication, expressed as chlorpromazine (CPZ) equivalents, was 1825.5 ± 778.7 -mg. Average education was 12.3 ± 2.1 years.

Stimuli and procedures, data acquisition and analysis, and statistical analyses were identical to those described in the normative study as outlined in Chapter 3. One exception to this is that while controls were run in the two conditions on two separate days (counterbalanced for order), patients were run on one day in a shortened paradigm (seven runs of each condition, as opposed to fourteen). The shortened paradigm still allowed us to collect hundreds of sweeps, providing a sufficient signal-to-noise ratio. The two conditions were run separately, with a one-hour lunch break in the middle. Again, they were counterbalanced for order. The shortened paradigm was employed to accommodate for the following key considerations in working with patients: 1) It is difficult for patients to maintain their energy and attention for the several hours required by the original paradigm used with our normative sample; and 2) Due to the transience of

patients on our unit, it was more practical to run them on one day rather than risk subject attrition.

Results

Behavioral results

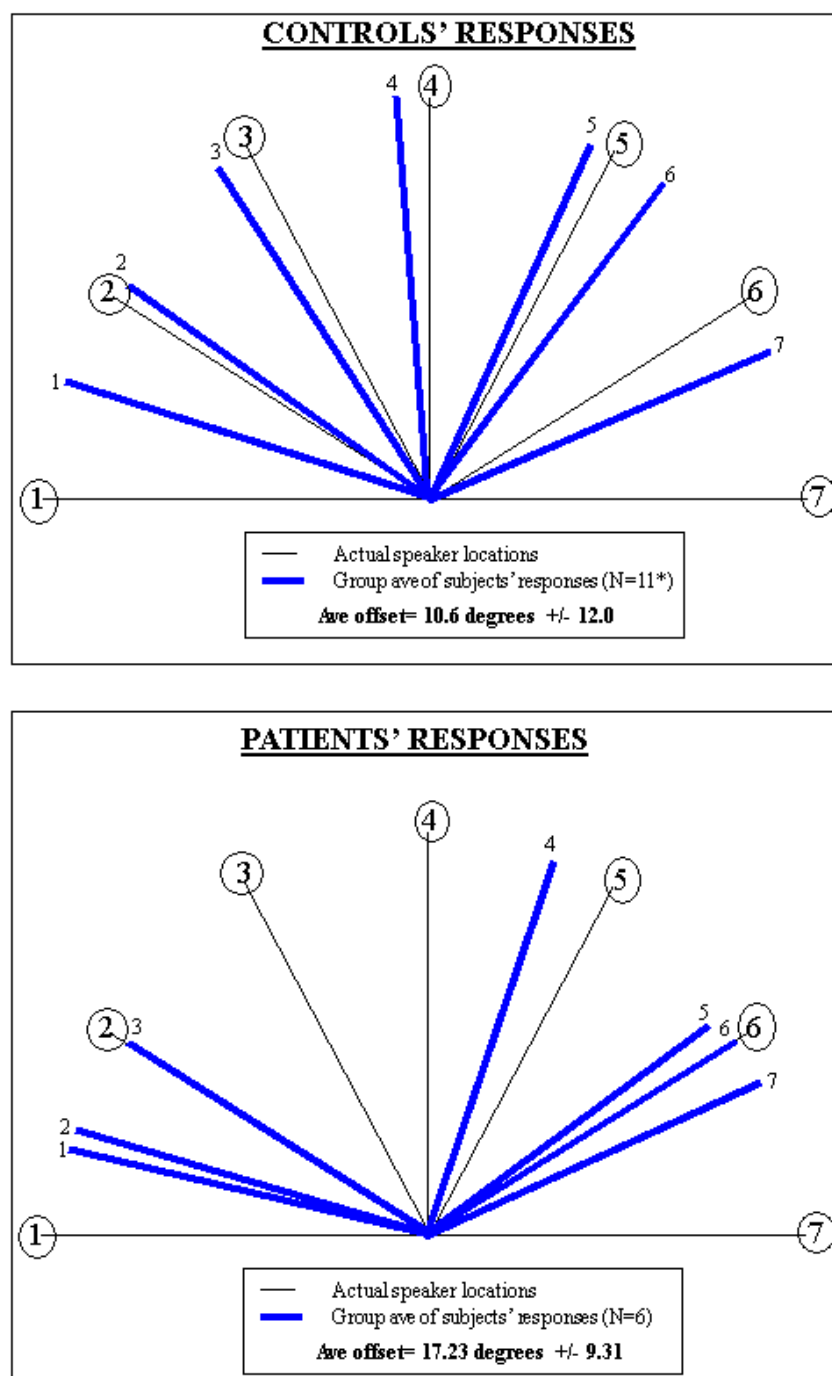
Where task: For the sound localization task, all responses across participants were averaged for each of the seven speaker locations (see **Figure 1**). The average offset of responses for all seven locations collapsed was 17.2 ± 9.3 degrees. Greater accuracy was shown for speakers in the right hemifield than left, with average offset 16.3 degrees and 18 degrees, respectively.

Electrophysiological results

Within Group

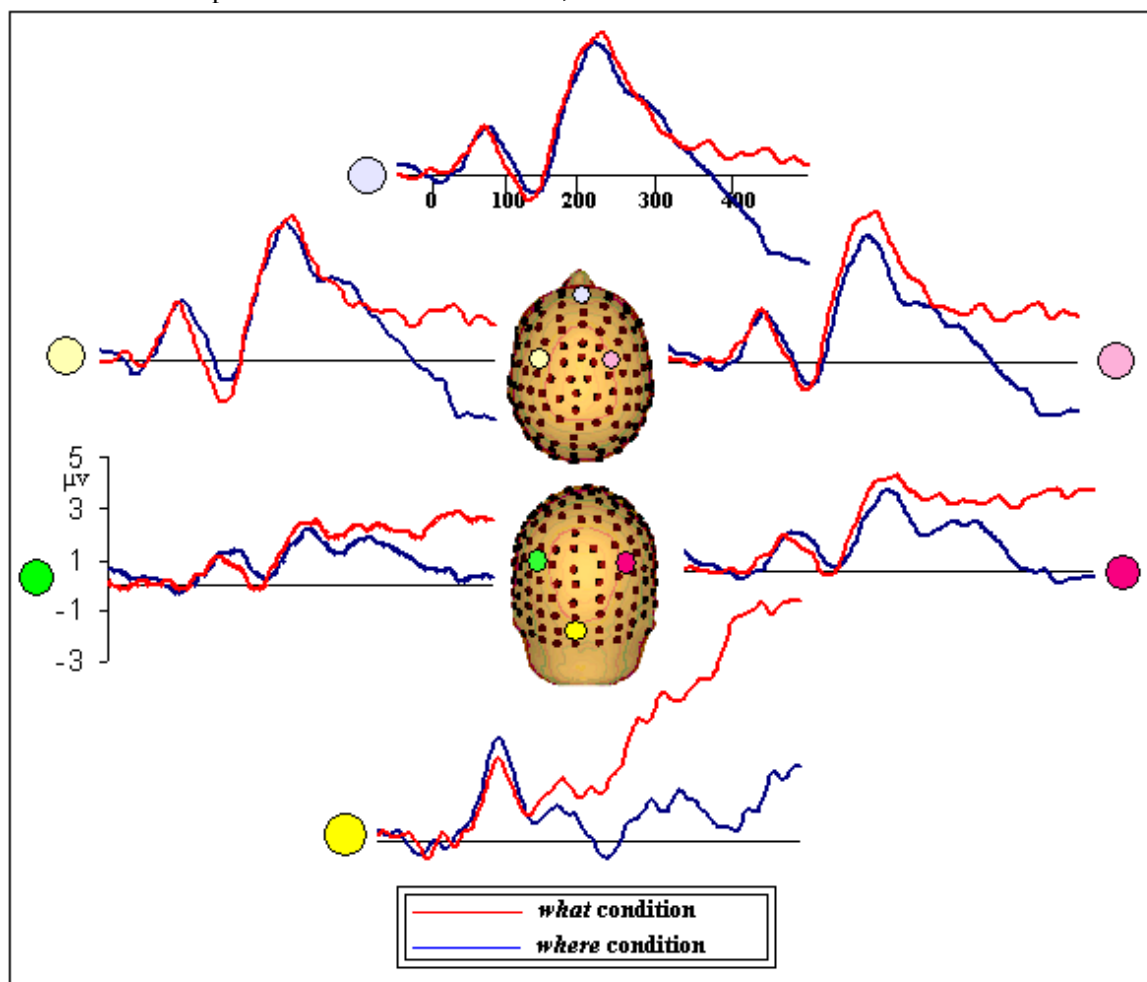
The N1 of our patient group in both conditions was similar to that of our controls, with a peak at approximately 124-128 ms. The component was broad, onsetting at approximately 70 ms and offsetting at approximately 180 ms. No significant differences were seen between *what* and *where* conditions for any component prior to the N1. Furthermore, differences in the N1 between *what* and *where* conditions, while similar in direction to that observed in controls (that is, the amplitude of the N1 generated in the

Figure 1. Behavioral results for controls (shown for comparison) and patients in the *where* condition. The figure shows in blue the average for the subjects' responses to each stimulus location. In black are the actual speaker locations.



what condition was greater than that of the *where* condition), did not reach the level of statistical significance (see **Figure 2**). Furthermore, a statistical cluster plot comparing conditions within the patient group failed to find any regions of significance.

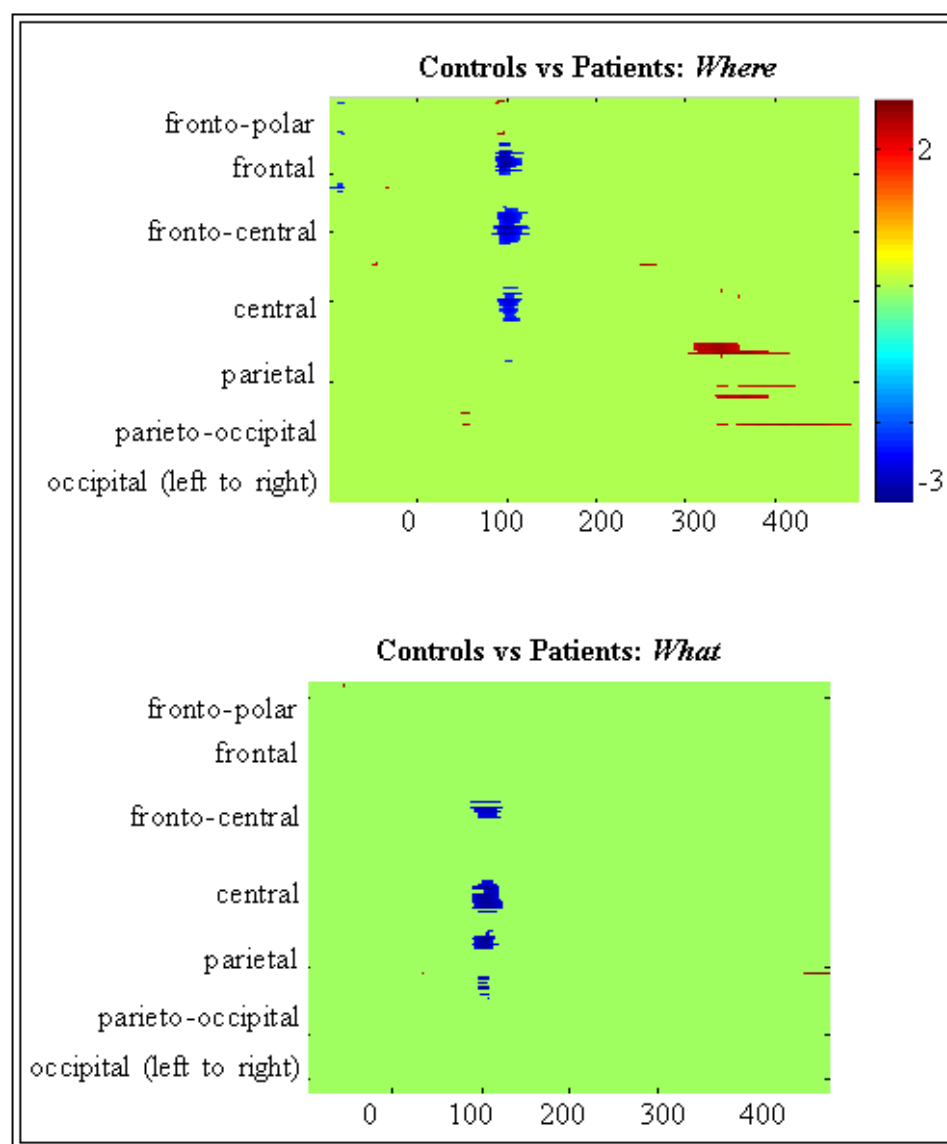
Figure 2. Group averaged waveforms from a subset of scalp electrodes from patients (N=6). Blue traces indicate responses to the *where* condition, red to the *what* condition.



Between Groups

Patients were compared to controls within each condition to determine whether significant differences between the groups could be observed. We computed a between-group statistical cluster plot as described in **Chapter 3** (see Methods, Chapter 3). This served as a hypothesis-generating tool; it provided us with a snapshot of where (in terms of scalp regions) and when (in terms of the timecourse of evoked potentials) significant differences occurred between groups in each condition. For the *where* condition, we observed differences that were concentrated over frontal, frontocentral and central scalp at approximately 100 ms (see **Figure 3**). We conducted a posthoc ANOVA over the 90-160 ms window (the N1) to better characterize this effect. Three frontocentral electrodes where the cluster plot indicated effects were maximal were selected in each hemisphere. A trend toward significance for main effect of group was found ($F_{1,16} = 3.70, p=0.073$). No effects of hemisphere or group by hemisphere were found. For the *what* condition, significant differences between patients and controls also emerged at approximately 100 ms, but were concentrated over frontocentral, central, and parietal regions. An ANOVA over the 90-160 ms window utilizing three central electrodes from each hemisphere found no significant effect of group ($F_{1,16} = 1.931, p=0.184$), hemisphere, or group by hemisphere interaction.

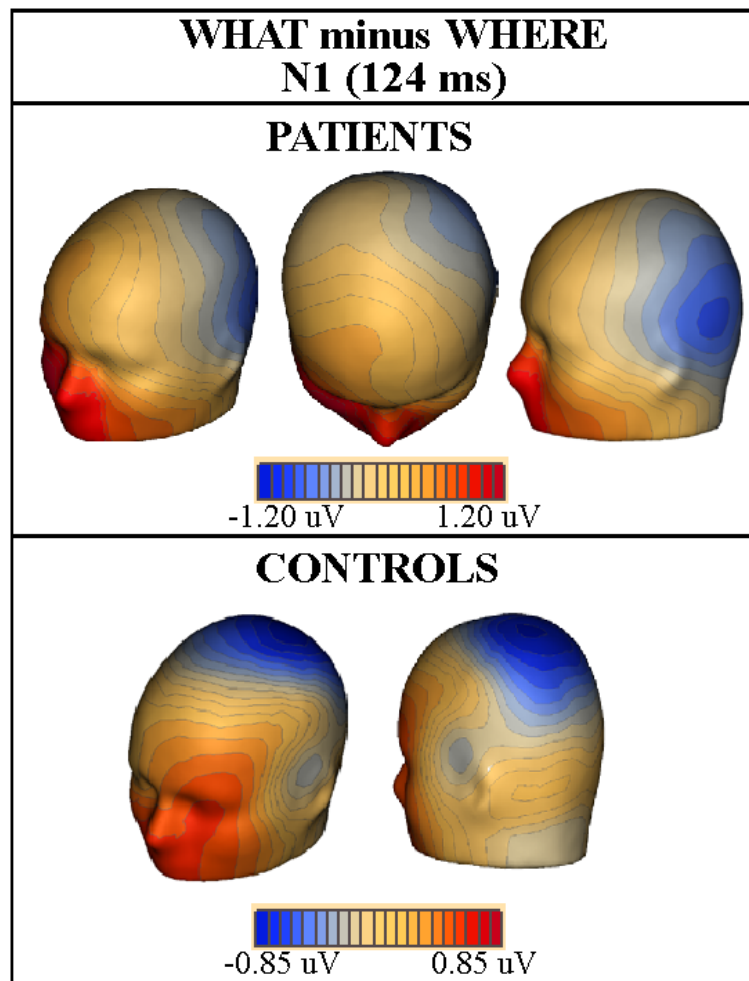
Figure 3. Statistical cluster plot of the results of the point-wise running two-tailed t tests comparing the amplitudes of patients' and controls' auditory evoked potentials in the *what* and *where* conditions. Time with respect to stimulus onset is presented on the x axis and topographic regions of 168 electrode positions on the y axis. Color corresponds to t values. Periods of significant difference are only plotted if a strict alpha criterion of $p < 0.05$ was exceeded for at least five consecutive data points. Note: controls ($N=12$), patients ($N=6$).



Topographic Maps

Topographic maps for the N1 (124 ms) are displayed in **Figure 4**. A difference wave was used here (*what* minus *where*). Maps for the controls display a pattern suggesting underlying neural generators distinct from those of the patients.

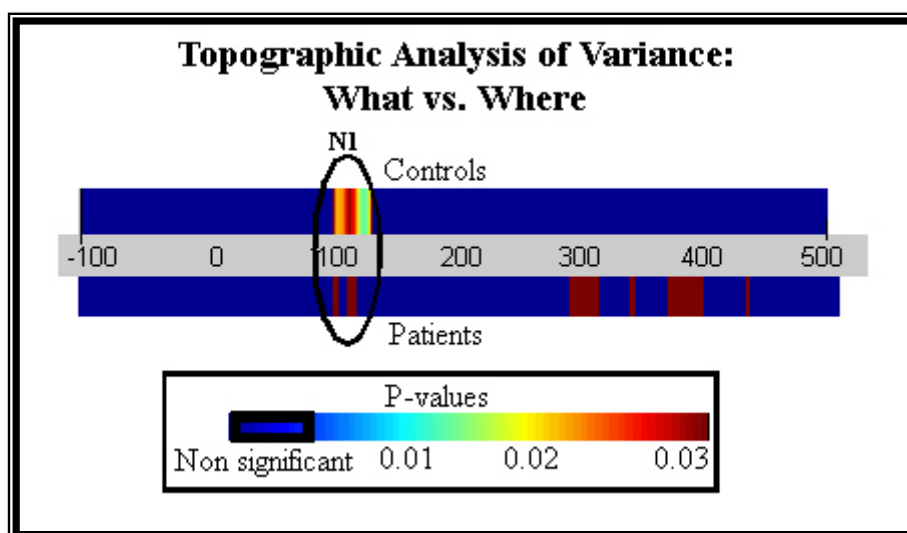
Figure 4. Topographic map of the differences between *what* and *where* conditions. For comparison, control topographic maps are included.



Topographic Modulation Analysis

Consistent with the control group results, the global dissimilarity that was computed allowed us to identify a distinct period of statistically significant differences in topographic modulations between the *what* and *where* conditions over the N1 period, indicative of the activation of distinct configurations of intracranial brain generators for each experimental condition (see **Figure 5**). As with the control group, this period was notably the only period of divergence between conditions.

Figure 5. Statistical plot of topographic modulations. Note area of significance coincident with the N1 component at approximately 100 ms; this area is consistent with that seen in the normative sample.



Dipole source analysis

The 8-dipole solution that was generated for the control group (**Chapter 3**) was applied to the patient group to determine whether it provided a reasonably good fit for the data. For the *what* condition, 76.9% of the variance was explained; for *where*, 83.6%. When the solution was applied to the difference wave (*what* minus *where*), 59.5% of the

variance was explained. A simple 2-dipole solution for the difference wave utilizing a symmetrically constrained pair fit to the N1 period (114-134) modeled generators in insular cortex ($x=32$, $y=-22$, $z=26$), and explained 67.0% of the variance. It is important to note that these models are highly susceptible to noise; therefore, results should be interpreted cautiously, given only 6 subjects in this model, and the high degree of inter-subject variability that was noted in the behavioral performance of our group.

Discussion

Patients have shown decrements in early (mid-latency) auditory evoked potentials in the simplest of auditory tasks: passive listening to simple tone-pips (Leavitt et al., 2007). However, it was interesting to us to delve further into the organization of this dysfunction, and we sought to determine whether there is an analogous case in the auditory system to that observed in the visual system of patients with schizophrenia. That is, differential impairment of the dorsal and ventral streams, the putative *where* and *what* pathways of the auditory system. We therefore utilized a paradigm that successfully enabled us to differentially tap these auditory pathways in a control sample (as detailed in **Chapter 3**), to test whether patients would show electrophysiological and behavioral evidence of divergent performance on functionally distinct tasks of sound localization versus sound object identification.

As a pilot study utilizing a small sample ($N=6$), we were clearly underpowered to find significant effects. However, there is a suggestion in our results ($p=0.07$) that a between-task difference is emerging at a similar time point as our controls, the N1, and furthermore, that the direction of the relationship of the N1 generated in the two tasks is

similar to that seen in controls. Namely, the *what* task generates a greater amplitude N1 than the *where* task. The implications of this are not entirely clear, but it does suggest that perhaps when performing a sound object identification task, additional generators must be brought online, whereas the neural network for localizing sound is constantly engaged and therefore more “automatic.” A normative study of spatial and nonspatial auditory processing utilizing simple tones found that while there was no significant difference in accuracy between a localization task and a pitch match-to-sample task, controls responded significantly faster on the localization task (Anourova et al., 2001). This suggests a speed differential between the two processes; while subjects were similarly accurate in discerning location and sound object properties, they simply localized more quickly. This may have evolved as a survival strategy: having to respond quickly to an object’s location in space is probably more important than distinguishing a leopard from a lion.

In contrast to auditory *what/where* studies that employed noise bursts (De Santis, Clarke, & Murray, 2007) or simple tones (Anourova et al., 2001; Anurova et al., 2003) and found an inverse relationship of N1 amplitude for the tasks (that is, a greater N1 for the *where* task than for the *what* task), we think that the complexity of our stimuli is driving the direction of the differences seen here. Moreover, we believe that our paradigm more accurately depicts the way we actually engage the respective pathways as we navigate through the world, thereby providing a heretofore uncharacterized glimpse of how the human auditory system parses information.

Interpreting the models created by source localization should be done cautiously with a sample of six, as individual variance may have a disproportionate effect on the

results. Additional patients will have to be run to better inform us of potential differences between controls and patients in putative generators engaged in tasks of sound localization and sound object recognition.

Furthermore, and perhaps most crucially, in order to identify electrophysiological differences between processing in the dorsal and ventral auditory pathways, it is first necessary for participants to be involved in behaviorally valid tasks. A critical question to be raised here is whether these patients were actually engaged in distinct tasks of localizing and identifying complex auditory stimuli. Of the six subjects tested, only two appeared to understand the instructions in the *what* task, based on performance as well as questioning of the subjects during and after testing. On the *what* task, a number of respondents continued to draw lines in the direction of the stimulus, despite repeated reminders to attend only to the identification of each sound, not its location. The *where* task may have been somewhat easier for most patients to grasp: their group-averaged performance suggests seven distinct points in space, albeit demonstrated with much poorer accuracy than controls.

Based on the tester's observation of behavioral responses, four of the patients (not the same four who failed to understand the directions) seemed to perseverate from one task to the other, getting "stuck" either in localizing mode or identifying mode, depending on which task they completed first. It is possible that increasing the separation of the conditions in time (e.g., running them on separate days) would be a more effective way to tap separate processes and avoid confounding them, particularly with patients who may have more difficulty understanding the task instructions to begin with. Again, this

was not done here in order to prevent subject attrition. For a subsequent study, however, it may be preferable.

It is interesting to note one striking contrast we observed between the behavioral performance of our patients and controls on the localizing task. Controls demonstrated a pattern of auditory localization that mirrors the pattern of pseudoneglect in the visual system; that is, the leftward attentional bias that occurs in normally functioning individuals causing them to bisect lines slightly to the left of their true center. Patient responses, however, were the exact opposite, and mirrored what is seen in the disorder known as spatial neglect. This may provide us with interesting questions for future research. Also notable in regards to the behavioral results of patients is that in terms of their ability to localize sound, their performance does not appear to be hindered by a lack of volition as evidenced by a clear gradation of responses from one speaker location to the next, suggestive of the fact that they were indeed discerning seven distinct locations albeit with less spatial accuracy than controls.

Conclusions

Based on these initial pilot data, the pattern of electrophysiological differences between explicit tasks of sound localization and sound object recognition in patients appears to be largely similar to controls. That is, the initial onset of the difference coincides with the onset of the N1 auditory component. Furthermore, the direction of the difference in waveforms appears similar to controls, with N1 amplitude in the sound object recognition condition greater than sound localization. More patients will have to

be included to determine whether this trend reaches significance. Behaviorally, the feasibility of the task for patients will need to be more carefully assessed.

Thus far, these results do not provide evidence for our initial hypothesis of relatively intact ventral pathway function with greater decrements of dorsal pathway reliant function in the auditory sensory processing system of patients with schizophrenia. However, these data should be considered as pilot data and we should use caution in interpreting them. The paradigm may be a useful means of characterizing the dorsal and ventral auditory pathways in patients, and additional subjects should be run. Furthermore, as the only study yet undertaken to functionally tap these distinct auditory pathways in patients with schizophrenia, it holds important implications for our understanding of how abnormal processing here may translate to auditory hallucinations at a higher level.

References

- Anourova, I., Nikouline, V. V., Ilmoniemi, R. J., Hotta, J., Aronen, H. J., & Carlson, S. (2001). Evidence for dissociation of spatial and nonspatial auditory information processing. *Neuroimage*, 14(6), 1268-1277.
- Anurova, I., Artchakov, D., Korvenoja, A., Ilmoniemi, R. J., Aronen, H. J., & Carlson, S. (2003). Differences between auditory evoked responses recorded during spatial and nonspatial working memory tasks. *Neuroimage*, 20(2), 1181-1192.
- Balogh, D. W. (1979). A study of schizophrenics' ability to localize the source of a sound. *J Nerv Ment Dis*, 169, 484-487.
- Balogh, D. W., & Leventhal, D. B. (1982). The use of temporal and amplitude cues by schizophrenics, psychiatric controls, and aged normals in auditory lateralization. *J Nerv Ment Dis*, 170(9), 553-560.
- Butler, P. D., Zemon, V., Schechter, I., Saperstein, A. M., Hoptman, M. J., Lim, K. O., et al. (2005). Early-stage visual processing and cortical amplification deficits in schizophrenia. *Arch Gen Psychiatry*, 62(5), 495-504.
- de Gelder, B., Vroomen, J., Annen, L., Masthof, E., & Hodiament, P. (2003). Audio-visual integration in schizophrenia. *Schizophr Res*, 59(2-3), 211-218.
- De Santis, L., Clarke, S., & Murray, M. M. (2007). Automatic and intrinsic auditory "what" and "where" processing in humans revealed by electrical neuroimaging. *Cereb Cortex*, 17(1), 9-17.
- First, M. B., Frances, A. J., Pincus, H. A., Vettorello, N., & Davis, W. W. (1994). DSM-IV in progress. Changes in substance-related, schizophrenic, and other primarily adult disorders. *Hosp Community Psychiatry*, 45(1), 18-20.
- Guterman, Y., & Klein, E. (1991). The role of head movement and pinnae in auditory localization in schizophrenia and psychosis. *Schizophr Res*, 6(1), 67-73.
- Hatashita-Wong, M., & Silverstein, S. M. (2003). Coping with voices: selective attention training for persistent auditory hallucinations in treatment refractory schizophrenia. *Psychiatry*, 66(3), 255-261.
- Leavitt, V. M., Molholm, S., Ritter, W., Shpaner, M., & Foxe, J. J. (2007). Auditory processing in schizophrenia during the middle latency period (10-50 ms): high-density electrical mapping and source analysis reveal subcortical antecedents to early cortical deficits. *J Psychiatry Neurosci*, 32(5), 339-353.
- McGhie, A. a. C., J. (1961). Disorders of attention and perception in early schizophrenia. *Br J Med Psychol*, 34, 103-116.

- Michie, P. T., Fox, A. M., Ward, P. B., Catts, S. V., & McConaghy, N. (1990). Event-related potential indices of selective attention and cortical lateralization in schizophrenia. *Psychophysiology*, 27(2), 209-227.
- Olsson, O., & Nielzen, S. (1999). Contralateral induction by frequency spectrum in hallucinating schizophrenics. *Psychiatry Res*, 87(1), 65-75.
- Ross, L. A., Saint-Amour, D., Leavitt, V. M., Molholm, S., Javitt, D. C., & Foxe, J. J. (2007). Impaired multisensory processing in schizophrenia: deficits in the visual enhancement of speech comprehension under noisy environmental conditions. *Schizophr Res*, 97(1-3), 173-183.
- Salisbury, D. F., Shenton, M. E., Griggs, C. B., Bonner-Jackson, A., & McCarley, R. W. (2002). Mismatch negativity in chronic schizophrenia and first-episode schizophrenia. *Arch Gen Psychiatry*, 59(8), 686-694.
- Todd, J., Michie, P. T., & Jablensky, A. V. (2003). Association between reduced duration mismatch negativity (MMN) and raised temporal discrimination thresholds in schizophrenia. *Clin Neurophysiol*, 114(11), 2061-2070.

CHAPTER 5

The binocular effect: Brief monocular deprivation as an assay of short-term plasticity of visual sensory processing in patients with schizophrenia.

Abstract:

Visual sensory processing deficits as measured by visual evoked potentials (VEPs) in patients with schizophrenia have been well established in the literature, with the robust and replicable P1 deficit receiving a great deal of attention. Notably, a recent study of first degree relatives conducted by our group determined this deficit to be endophenotypic. However, due to vast inter-individual variability in patients, we sought to develop an electrophysiological marker that would enable us to more reliably identify the disease. Our goal here was to tap a second order effect of the P1 deficit; therefore, we developed a visual challenge task utilizing monocular deprivation such that we could better characterize these known early visual processing deficits, while also finding evidence that will help explain why higher order functions such as binocular depth perception are impacted. This, in turn, could implicate a dysfunction in underlying GABAergic neurochemical systems involved in ocular dominance plasticity. Twenty chronic schizophrenia patients and twenty age-matched controls served. We recorded VEPs as participants viewed visual stimuli with both eyes for 9 minutes, then using an eye patch we recorded VEPs as participants viewed visual stimuli monocularly for 9 minutes, first with the left eye alone, then with the right eye alone. In our sample, we replicated the P1 deficit. On the monocular deprivation (MD) challenge task, controls exhibited an effect that patients failed to demonstrate; that is, the P1 amplitude elicited in controls binocularly was less than the sum of the two non-occluded eyes in the eye covered

condition. In patients, this between-condition difference was nonsignificant. These results suggest that the compensatory mechanism allowing healthy individuals to generate robust VEPs in the context of monocular deprivation appears not to be effectively activated in patients with schizophrenia. The potential utility of this metric as part of a multivariate endophenotype is discussed.

Introduction

Basic visual sensory processing deficits in patients with schizophrenia have now been consistently documented in the literature (Butler et al., 2001; Doniger, Foxe, Murray, Higgins, & Javitt, 2002; Foxe, Doniger, & Javitt, 2001; Foxe, Murray, & Javitt, 2005; Lalor, Yeap, Reilly, Pearlmutter, & Foxe, 2008; Yeap, Kelly, Sehatpour et al., 2008). Further, a recent event-related potential (ERP) study from our group found the visually evoked P1 component to be an endophenotypic marker for schizophrenia (Yeap et al., 2006), insofar as healthy first-degree biological relatives of schizophrenia patients also showed an entirely similar attenuation of the P1 component (with a large effect size of 0.9 according to Cohen's criterion). Likewise, robust deficits have recently been found in first episode patients (Yeap, Kelly, Thakore, & Foxe, 2008), further supporting the notion that this deficit is related to underlying genetic risk for the disorder rather than to the progression of the disease state itself. The relationship of the P1 deficit to genetic liability was emphasized in a recent study where we found evidence that it was linked to a specific risk haplotype for schizophrenia on the dysbindin gene (DTNBP1 – Donohoe et al., 2008). Taken together, these studies point to early visual sensory processing deficits (as evidenced by the P1 component) as a potentially valuable tool in early detection efforts and to the possibility that this endophenotypic marker might expand our abilities to identify children at risk during the prodromal stages of the disorder. Unfortunately, while effect sizes in these studies are nearly always large, there is still a great deal of overlap in the distributions of P1 amplitudes between patient and control groups, limiting the clinical applicability of the measure at this juncture.

The major stumbling block here relates to a simple issue of between-subject variance in P1 amplitude. That is, even in perfectly healthy control subjects, a very large distribution of

P1 peak amplitudes is seen, such that values ranging anywhere from 1 to 16 μV are not at all unusual. Our observations across the series of studies detailed above are that patients with schizophrenia and their relatives are no different in terms of this variance. Rather, the entire distribution appears to be shifted towards lower amplitudes and the effects that have been found in the studies described are always based on group level analyses. Thus, while many of these studies have found patient P1 amplitude to be less than half of that seen in control subjects when the group means are compared, what this means at the individual subject level is that those patients with P1s falling in the upper half of the distribution fall well within the “normal” distribution. The first major motivation for the present study, then, was to try to develop a tool that would provide us with greater diagnostic sensitivity than the simple first-order P1 deficit, thereby allowing us to more reliably identify sensory processing deficits related to the disease. Our strategy was to tap into a second-order “dynamic” effect of early visual processing mechanisms that would tax the system further, hopefully enabling us to more effectively separate the distribution of patients from that of controls.

To this end, we sought a paradigm that would assay short-term plasticity within early visual cortices during the P1 processing timeframe. Monocular deprivation (MD) is one such method that has been used to study early cortical plasticity within the visual system. In 1977, Tyler and Kaitz (1977) determined that by covering one eye of healthy human subjects for several hours, it was possible to significantly increase the amplitude of the visual evoked response evoked through stimulation of the non-occluded eye. That is, immediately following eye-occlusion, the monocularly-derived VEP amplitude drops relative to binocular viewing. What Tyler and Kaitz showed was a recovery function such that the monocularly derived VEP gained in amplitude over the following 2-6 hours. There is also considerable

evidence in the literature for the nonlinear nature of binocular interactions in humans (Apkarian, Nakayama, & Tyler, 1981; Baitch & Levi, 1988; Zemon, Pinkhasov, & Gordon, 1993); that is, when the VEPs elicited from monocular viewing of stimuli are summed together, this results in a “synthetic” response that is of greater amplitude than to the VEP evoked during binocular viewing of the same stimuli (Left eye alone + Right eye alone > Both eyes together). The implication is that during binocular viewing, there is substantial interaction between monocular dominance columns, perhaps due to cross-inhibitory mechanisms (Hensch & Stryker, 2004). We reasoned that assaying a second-order effect of this type might very well prove an effective means of amplifying previously characterized differences in basic visual sensory processing in patients.

The use of a paradigm to assay binocular interactions in schizophrenia was also considered a fertile target for exploration given recent evidence for their impairment in this population (Schechter et al., 2006). Ocular dominance columns in visual cortex segregate cells that are selective for left eye, right eye, or binocular stimuli (Hubel, 2008). While the exact functional purpose of this columnar organization is not fully known, it is highly likely that one of its functions is in the computation of stereopsis, or depth perception. While 4-5% of the general population lack stereopsis (Hubel, 2008), a recent finding from our institute determined that patients with schizophrenia have a marked deficit in binocular depth perception (Schechter et al., 2006), suggesting that the interaction of ocular dominance columns in the visual cortex of patients is compromised. This, in turn, holds implications for the underlying neurochemical systems involved. While the usual suspects in schizophrenia are dopamine and glutamate, the present study may afford us an opportunity to better characterize the potential importance of gamma-aminobutyric acid (GABA). In the visual

system, there is evidence to support the vital role played by GABA in intra-columnar inhibition. Animal studies employing long-term monocular deprivation preparations have demonstrated this dependence (e.g., Mower & Christen, 1989; Burchfiel & Duffy, 1981). Although the present investigation utilized short-term deprivation, a finding of impaired binocular interactions in patients with schizophrenia may hold implications for the integrity of GABAergic neural systems.

There is precedence for using visual manipulations that implicate cortical plasticity to investigate psychiatric illness. Pettigrew and Miller (Pettigrew & Miller, 1998) utilized binocular rivalry to examine the underlying pathophysiology in bipolar disorder. These researchers describe binocular rivalry as the “alternating perceptual states that arise when viewing different images presented separately to each eye in the same retinal position.” Bipolar patients were slower to switch from one perceptual state to the other than healthy controls, and Pettigrew and Miller attributed this to what they termed ‘sticky’ inter-hemispheric switches - a feature of their underlying pathophysiology that may prove to be a hallmark of the disease. It is noteworthy that our group recently found visual P1 deficits in a cohort of euthymic bipolar patients that mimicked those seen in schizophrenia (Yeap, Kelly, Reilly, Thakore, & Foxe, submitted), suggesting that this deficit results from shared genetic risk for psychotic disorders more generally.

Here, we utilized an MD paradigm similar to that of Tyler and Kaitz (1977), though a substantially abbreviated version that allowed us to capture dynamic effects of MD in just 25 minutes, as compared to 2-6 hours. Developing tests that are easily administered over a relatively short period will be essential if these tests are to have genuine clinical utility. We collected high-density VEPs from participants while they viewed simple isolated check

stimuli both binocularly and monocularly. Our predictions were straightforward. Once input to one or the other eye is removed (using a simple eye-patch), the expectation is that early VEP amplitude will diminish immediately thereafter, but that a relatively rapid recovery of amplitude will be evident in the following minutes as the visual system begins to compensate for missing input. Our main hypothesis here is that this rapid short-term plasticity will be less effective in patients with schizophrenia.

Methods

The procedures of this study were approved by the Ethics Committee of St. Vincents Hospital, Fairview, Dublin, and the Institutional Review Board of the City University of New York.

Subjects

Informed consent was obtained from 20 (4 female) patients with schizophrenia, aged 28-63 (mean = 41.6 ± 12.2 years), from the St. Vincent's Hospital Catchment Area in Fairview, Dublin. The mean score on the BPRS for the patients was 39.5 ± 8.6 and 33.1 ± 16.8 on the SANS. Control subjects comprised 20 (4 female) paid volunteers aged 19-61, (mean = 39.0 ± 15.2 years). The mean age of patients and controls did not differ significantly ($p = 0.48$). 17 of the 20 patients and 18 of the 20 controls were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). All subjects reported normal or corrected-to-normal vision; where possible, this was corroborated by medical records. Controls were free of any psychiatric illness or symptoms by self-report using criteria from the SCID-NP (First, Frances, Pincus, Vettorello, & Davis, 1994).

Patients met the following inclusion/exclusion criteria: Inclusion: 1) current DSM-IV-defined diagnosis of schizophrenia. A best estimate diagnostic approach was utilized in which information from the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) (First, Frances, Pincus, Vettorello, & Davis, 1994) was supplemented by information from family members, psychiatrists, and medical records to generate a diagnosis, 2) ages 18 to 65, 3) male or female, 4) competent and willing to sign informed consent. Exclusion: 1) organic brain disorder, mental retardation, or significant medical illness, 2) current substance-induced psychotic disorder or a psychotic disorder due to a general medical condition determined by DSM-IV criteria, 3) significant risk of suicidal or homicidal behavior, 4) any history of visual impairment beyond corrected to normal vision, 6) any additional Axis I diagnoses.

Normal controls met the following inclusion/exclusion criteria: Inclusion: 1) matched for age to patients with schizophrenia, 2) any race, 3) absent any current Axis I or Axis II disorder or mood or psychotic disorder for the last 5 years as assessed by the SCID-I/NP (i.e., Non-Patient version), 4) no current or past history of psychotropic medication usage, 5) no family history of psychotic illness, 6) age 18 to 65, and 7) willing to sign informed consent. Exclusion: 1) organic brain disorder, mental retardation, or significant medical illness, 2) significant risk of suicidal or homicidal behavior, 3) participants with prior intermittent alcohol or substance use were not excluded unless they met DSM-IV criteria for current alcohol or drug dependence in the last 6 months, 4) any history of abnormal vision beyond corrected to normal vision.

For all patients, demographic information was collected including age, sex, and illness duration (See **Table 1**). Symptom ratings were analyzed using the Brief Psychiatric

Rating Scale (BPRS) and the Scale for the Assessment of Negative Symptoms (SANS) (Lindenmayer, Bernstein-Hyman, & Grochowski, 1994). Doses of anti-psychotic, anti-cholinergic and adjuvant medications (e.g., anti-depressants, sedative/hypnotics, mood stabilizers, anti-convulsants) were recorded. Anti-psychotic doses were translated into chlorpromazine equivalents using the best available literature at the time of data analysis for conversion of dose levels of newer anti-psychotics (e.g., sertindole, seroquel). A limitation of the present study is that all patients were receiving medication at the time of testing. However, visual processing deficits have been found in both medicated and unmedicated patients (e.g. Braff & Saccuzzo, 1982; Butler, Harkavy-Friedman, Amador, & Gorman,

Table 1. Demographic and Clinical Characteristics of Schizophrenia Patient Group (N=20).

Neuroleptics: Atypical/Typical/Both	12/4/4
Chlorpromazine (CPZ)-equivalent $\pm$ SD, daily (mg)	564 $\pm$ 423
Education $\pm$ SD (using SCID education scale 1-8)	5.1 $\pm$ 2
Illness Duration $\pm$ SD	16.1 $\pm$ 9
BPRS Positive Symptom $\pm$ SD	39.5 $\pm$ 9
SANS total all items except global at baseline $\pm$ SD	33.1 $\pm$ 17
Visual Hallucinations: past/ present/none	4/1/15

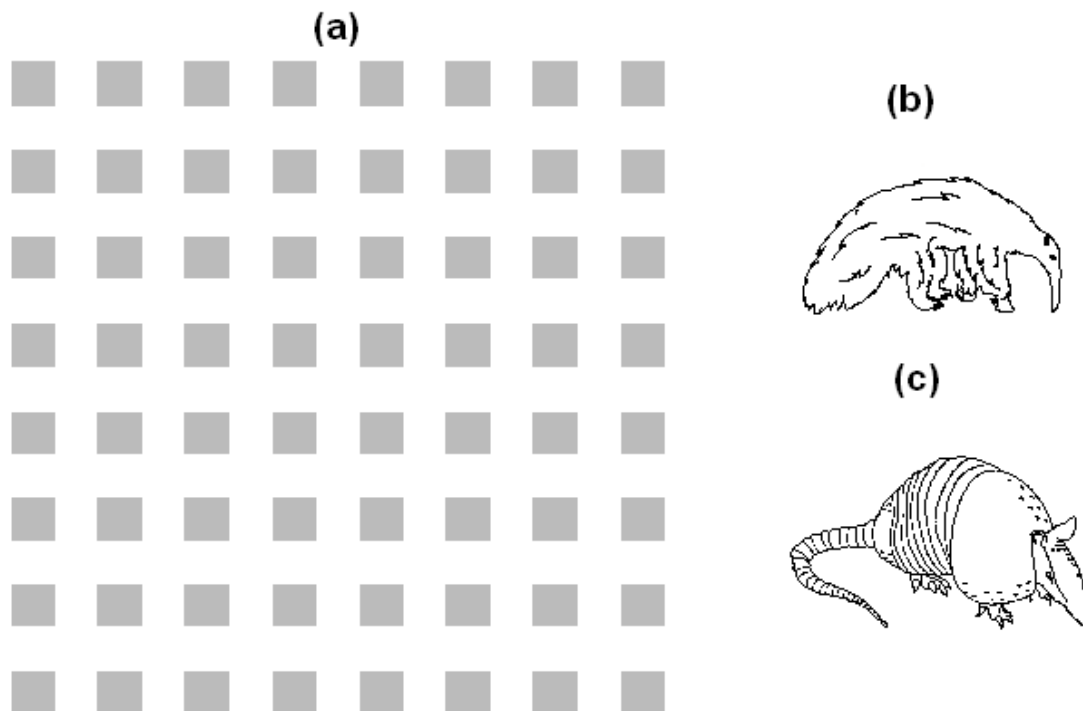
1996; Harvey, Docherty, Serper, & Rasmussen, 1990; Cadenhead et al., 1997), as well as in (unmedicated) first-degree relatives of patients with schizophrenia (Yeap et al., 2006; Green et al., 1997; Chen et al., 1999a; Keri et al., 2004). Medication effects, length of illness, and symptom severity should all be taken into consideration as potential confounds when conducting research with schizophrenia patients. However, evidence in the literature supports

the notion that these factors do not impact VEPs generated at such early latencies as the P1 (see, for example, Jibiki, Takizawa, & Yamaguchi, 1991).

Stimuli and task

Subjects were seated in a comfortable chair in a dimly illuminated, sound-attenuated room and asked to keep head and eye movements to a minimum. In each experimental block, subjects were presented with approximately 100 isolated-check images, gray on a white background ($4^\circ \times 4^\circ$ visual angle) at 64% contrast and 40 line drawings of 2 kinds of animal (2.4° wide $\times$ 1.8° high) on a white background. A different animal pair was randomly chosen for each block, from a possible 22. The isolated-check stimuli and one pair of animal stimuli are shown in **Figure 1**.

Figure 1. The centrally presented visual stimuli used in the task. Event-related potential waveforms were derived for the isolated-check nontarget stimulus (A) while target discrimination was performed on the basis of infrequently presented animal line drawings (B and C).



All subjects completed 9 blocks, each lasting 3 minutes. These consisted of 3 blocks wherein the participant viewed stimuli with both eyes, 3 blocks of occlusion (an eye patch) of one eye, and 3 blocks of occlusion of the other eye. First occluded eye was counterbalanced for order in each participant. Stimuli were presented centrally on a computer monitor in random order, with the monitor located 160cm directly in front of the seated subject. The timing of the presentations was such that each image appeared for 60 ms with a variable inter-stimulus interval (ISI) between 740 and 1540 ms (randomly in steps of 200ms) during which there was a blank white screen. The target animal was displayed at the start of the task and subjects were asked to respond each time this animal was presented by pressing a button with their right thumb. They were told only to respond to target animals and to try to withhold responses to any other animal presented. The target and non-target animals were presented with equal probability, ensuring that a subject could not rely on the exogenous alerting nature of any non-checkerboard stimulus to respond. Furthermore, the task of discrimination was made difficult by pairing similar-looking animals, e.g. dolphin and whale. The use of this task ensured that subjects were actively observing the stimuli. Only ERPs to the standard checkerboard stimuli were analyzed here.

Data acquisition and statistical analysis

Continuous EEG was acquired through the ActiveTwo Biosemi™ electrode system from 72 scalp electrodes, digitized at 512 Hz with an open pass-band from DC to 150 Hz. For analysis and display purposes, data were subsequently filtered with a 0-phase-shift 40 Hz low-pass filter (24 dB/octave) and baseline corrected after acquisition. No high-pass filter was applied. With the Biosemi system, every electrode or combination of electrodes can be assigned as the “reference”, and this is done purely in software after acquisition. BioSemi

replaces the "ground" electrodes used in conventional systems with two separate electrodes: Common Mode Sense (CMS) active electrode and Driven Right Leg (DRL) passive electrode. These 2 electrodes form a feedback loop, which drives the average potential of the subject (the Common Mode voltage) as close as possible to the ADC reference voltage in the AD-box (the ADC reference can be considered as the amplifier "zero"). For a detailed description of the referencing and grounding conventions used by the Biosemi active electrode system, the interested reader is referred to the following website:

<http://www.biosemi.com/faq/cms&drl.htm>. All data were re-referenced to the nasion after acquisition, for analysis. EEG was averaged off-line. Data were epoched (-100 ms pre-stimulus to 500 ms post-stimulus) and then averaged. Baseline was defined as the mean voltage over -100 to 0 ms preceding the onset of the stimulus. Trials with blinks and large eye-movements were rejected offline on the basis of horizontal and vertical electrooculogram recordings. An artifact rejection criterion of ± 100 μ volts was used at all other electrode sites to exclude periods of high EMG and other noise-transients. From the remaining artifact-free trials, averages were computed for each subject. The average epoch acceptance rate for the patients was $71 \pm 17.6\%$, and for the control group $75 \pm 20.0\%$. These averages were then visually inspected for each individual to ensure that clean recordings with sufficient numbers of trials were obtained and that no artifacts were still included. Bad channels were interpolated using BESA software. Data were ultimately averaged across all subjects (grand mean averages) within a given group (patient or control) for visual comparison at the group level and for display purposes. The reader should note that throughout this paper, we use the familiar nomenclature of the modified 10-20-electrode system to refer to the positioning of

electrode sites ("American Electroencephalographic Society guidelines for standard electrode position nomenclature," 1991).

Analysis strategy

For each electrode, the data from all subjects within each group (patients and controls) were collapsed into a single average waveform for all three conditions (binocular, left eye covered, right eye covered). These group-averaged waveforms were then visually inspected across all scalp-sites and the P1 and N1 components of the visual evoked potential (VEP) were identified. The timing and scalp topographies of the components here are highly consistent with those found in the literature (Foxe & Simpson, 2002; Picton, Hillyard, Krausz, & Galambos, 1974). Our primary analysis was motivated by a specific hypothesis, based on previous research by our group, regarding a substantial reduction in early visual sensory processing (i.e. the P1 processing period) in patients with schizophrenia and their healthy first-degree relatives (Yeap et al, 2006). As revealed in Yeap et al, 2006, this component represents an endophenotypic marker for the disease. Our analysis was done in two stages: first, we analyzed the P1 to determine whether we had a replication of the P1 deficit in our sample. For this stage of the analysis, we recorded P1 peak amplitudes from the scalp electrodes where the component was maximal; three representative electrodes were selected within the left (PO7/PO3/O1) and right (PO8/PO4/O2) hemispheres for a total of six electrodes; an average of these six electrodes was calculated for each participant. It is important to note that the latency of this P1 peak was variable, and by hand picking the peaks we reduced any influence of this variance. A mixed design ANOVA was conducted with factors of group (controls vs. patients) and region (left vs. right) to compare P1 amplitudes.

Having first established that the P1 processing deficit was again evident in our cohort of schizophrenia patients, we then moved to the assessment of binocular interactions. Since research into binocular interaction effects using VEPs is very sparse, and the early componentry has not been explicitly isolated for such effects (to our knowledge), we had no specific way to predict precisely when during initial sensory processing we would see non-linear effects. On the other hand, we reasoned that binocular interactions must surely occur during the earliest sensory processing timeframe since work from our lab has shown that even trans-collosal inter-hemispheric interactions occur during the P1 processing time-frame (Murray, Foxe, Higgins, Javitt, & Schroeder, 2001). As such, we used the pattern of “normal” responses from our control group to define the window for testing the earliest observable binocular effects. The binocular effect (BE) in visual evoked potentials is defined here as any deviation from the predictions of a model which assumes two independent populations of neurons whose outputs are, in the far field, simply additive. Monocular responses were added (Left eye alone and Right eye alone) to yield the model's prediction of binocularly evoked response; this trace is then subtracted from the actual binocular response to yield a difference trace which is considered to represent BE, and which we refer to as the “modulation index.” We henceforth refer to the summed waveform as SUM, and the binocularly evoked waveform as BASE. Inspection of the waveforms revealed a clear divergence between the SUM and BASE responses that appeared to onset just as the P1 component peaked (see **Figure 2**). This apparent effect then continued through the falling phase of the P1. We therefore defined the window for statistical testing as a 20ms bin (from 95-115 ms) with an onset at the average peak latency of P1 for patients and controls. These area measures were then submitted to a repeated measures analysis of variance (using SPSS

software, Chicago, IL) with between-subjects factor of group (patients vs. controls) and within-subjects factors of region (left/right) (comprising electrodes O1/PO7/PO3 and O2/PO4/PO8 covering the left lateral occipital and right lateral occipital visual scalp regions, respectively) and condition (SUM vs. BASE). All tests were two-tailed with a preset α -level of $p < 0.05$.

Following our primary analysis of P1 amplitude and the binocular effect, it was of interest to further investigate spatio-temporal properties of any potential differences between groups, using the statistical cluster plot method. This procedure has been used effectively in post-hoc analyses as a means to fully explore complex datasets and generate pointed follow-up hypotheses (e.g. Molholm et al., 2002; Wylie et al., 2003). For each group, point-wise one-tailed Student t-tests (here between conditions) were calculated at each time-point for all electrodes, and a color map was subsequently generated marking time-points on each electrode for which the t-value exceeds that corresponding to a 0.05 p-value. All non-significant points are represented as deep red regions.

Results

Behavioral results

In the binocular, left eye alone, and right eye alone conditions, the mean target hit rates were all $>80\%$ and did not significantly differ for controls and patients. These rates were taken to indicate that subjects were actively observing the stimuli.

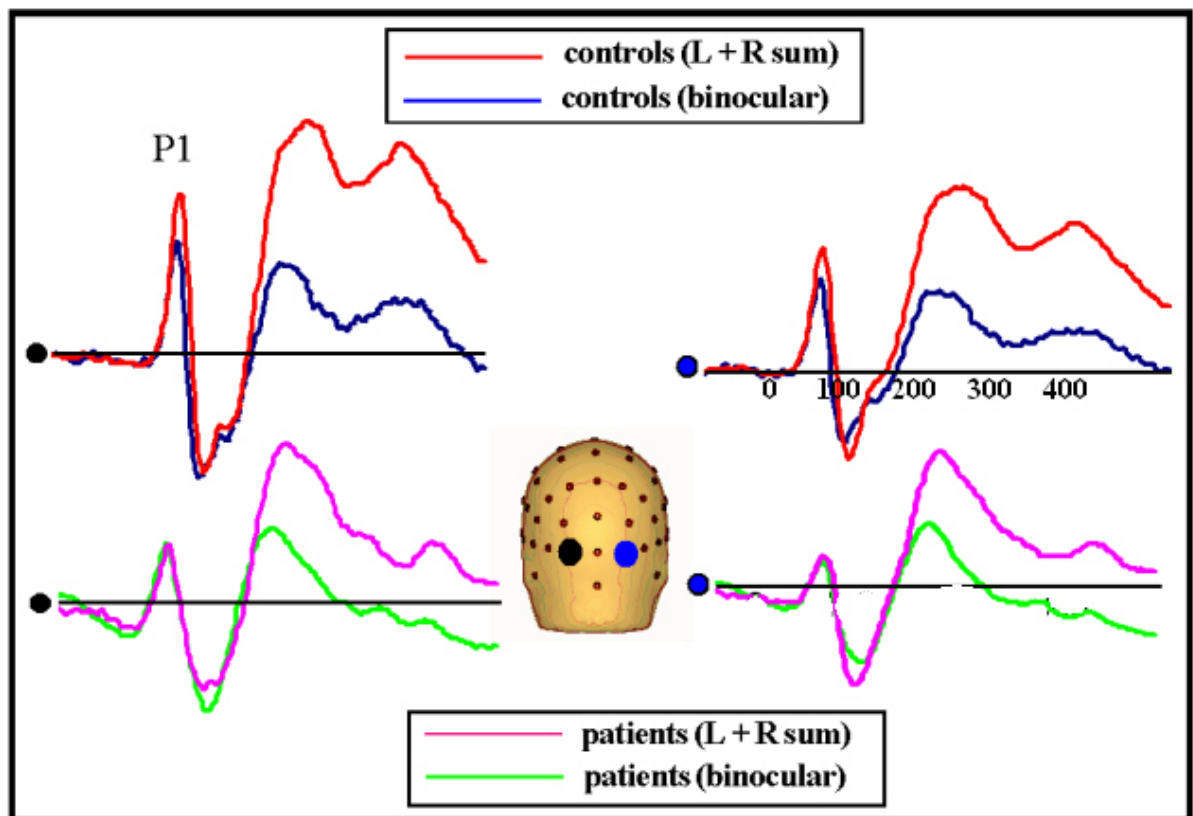
Electrophysiological results

Replicating the visual P1 deficit

We begin with a description of the P1, our component of interest, observed in the data of our 20 controls and 20 patients. The P1 peak for our control group in the binocular

condition was found at approximately 93 ms, and was maximal over parieto-occipital and occipital regions. In patients, the P1 peak was found at 97 ms over the same regions. In both groups, the P1 peak in the SUM condition was shifted to the right by 2 ms (95 and 99 ms, respectively) (see **Figure 2**).

Figure 2. Waveforms from two representative occipital electrodes (PO3 and PO4) are shown for controls and patients. Top pairs (red and blue) are from 20 control subjects, bottom pairs (pink and green) are from 20 patients.



A mixed 2x2 ANOVA was conducted with a between group factor (patients vs. controls), and within group factor of hemisphere (left vs. right). The P1 peak was identified at each site for each subject¹, and an average of the three electrodes was calculated for each

¹ It is important to note that in four controls and four patients, a P1 could be identified in only one hemisphere. The hemisphere of absent P1 was not systematic. These subjects were eliminated from our P1 2x2 ANOVA.

hemisphere. A robust main effect of group ($F(1,31)= 7.148$, $p=0.01$) was found, as was a significant interaction of group by hemisphere ($F(1,31)= 4.794$, $p=0.036$).

To examine the interaction between group and hemisphere further, protected *t*-tests were carried out for each hemisphere separately. We used P1 amplitude, averaged across three electrodes in the left hemisphere and three electrodes in the right hemisphere, as our dependent variable. A significant difference was found between controls and patients for both the left ($p=0.01$) and the right ($p=0.002$) hemispheres. For controls, the average P1 amplitude on the left was $5.92\mu V \pm 2.67$, on the right 6.72 ± 2.90 . For patients, these values were 3.59 ± 2.51 (left) and 3.35 ± 2.51 (right). As such, the interaction effect was driven by the fact that the difference between groups was greater over the right hemisphere than the left.

Figure 3 is a scatterplot of P1 amplitudes for the controls and patients. In **Figure 4a**, we collapsed across left and right hemifields to obtain a single metric of P1 amplitude; the values for 16 controls and 16 patients are displayed in a scatterplot. Topographic maps of the P1 peak for each group are displayed in **Figure 4b**, with a subtraction map showing the differences between groups that are represented predominantly by a negativity seen over occipital cortices.

Figure 3. In the binocular condition, a robust P1 deficit was seen for patients with schizophrenia (N=16) compared to controls (N=16) in both the left and right hemispheres ($p=0.0095$ and $p=0.002$, respectively).

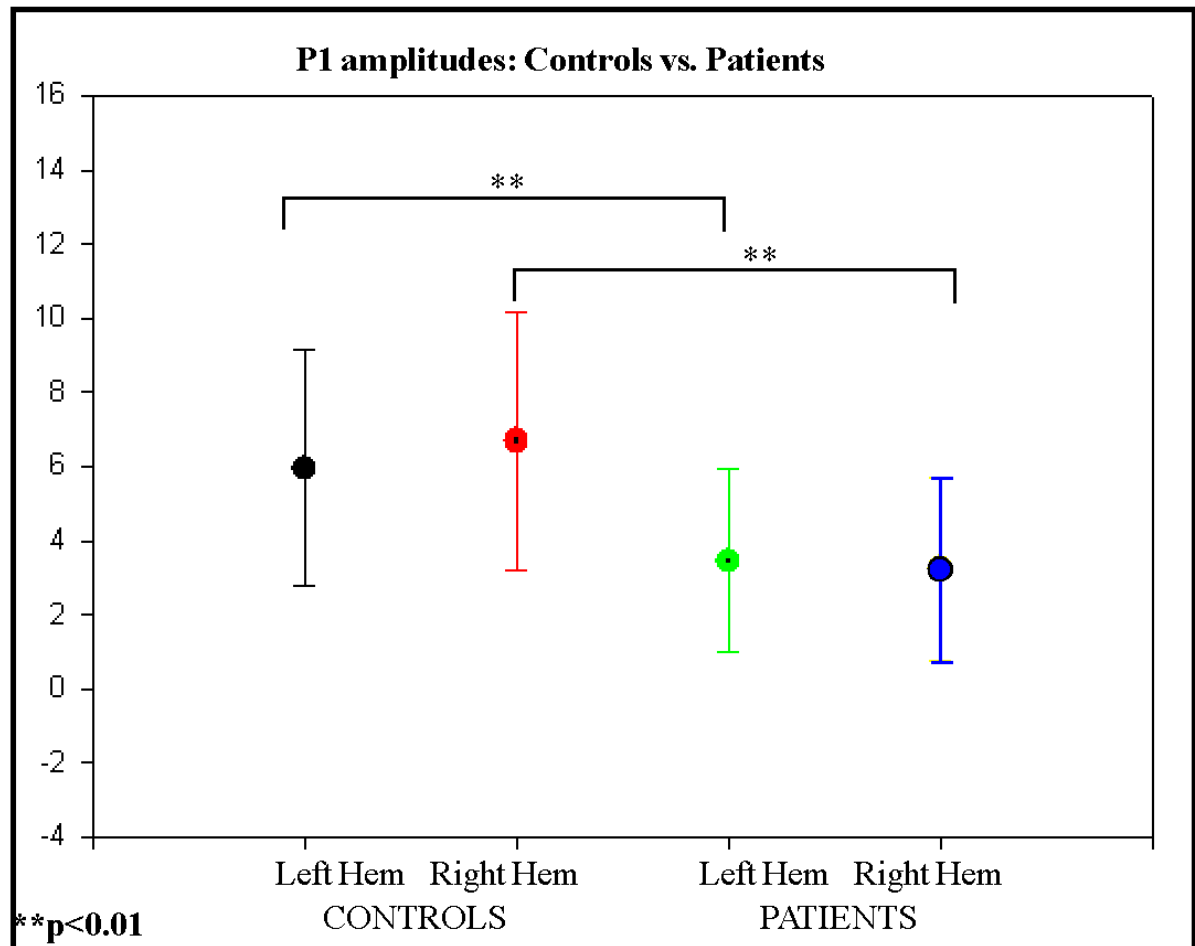
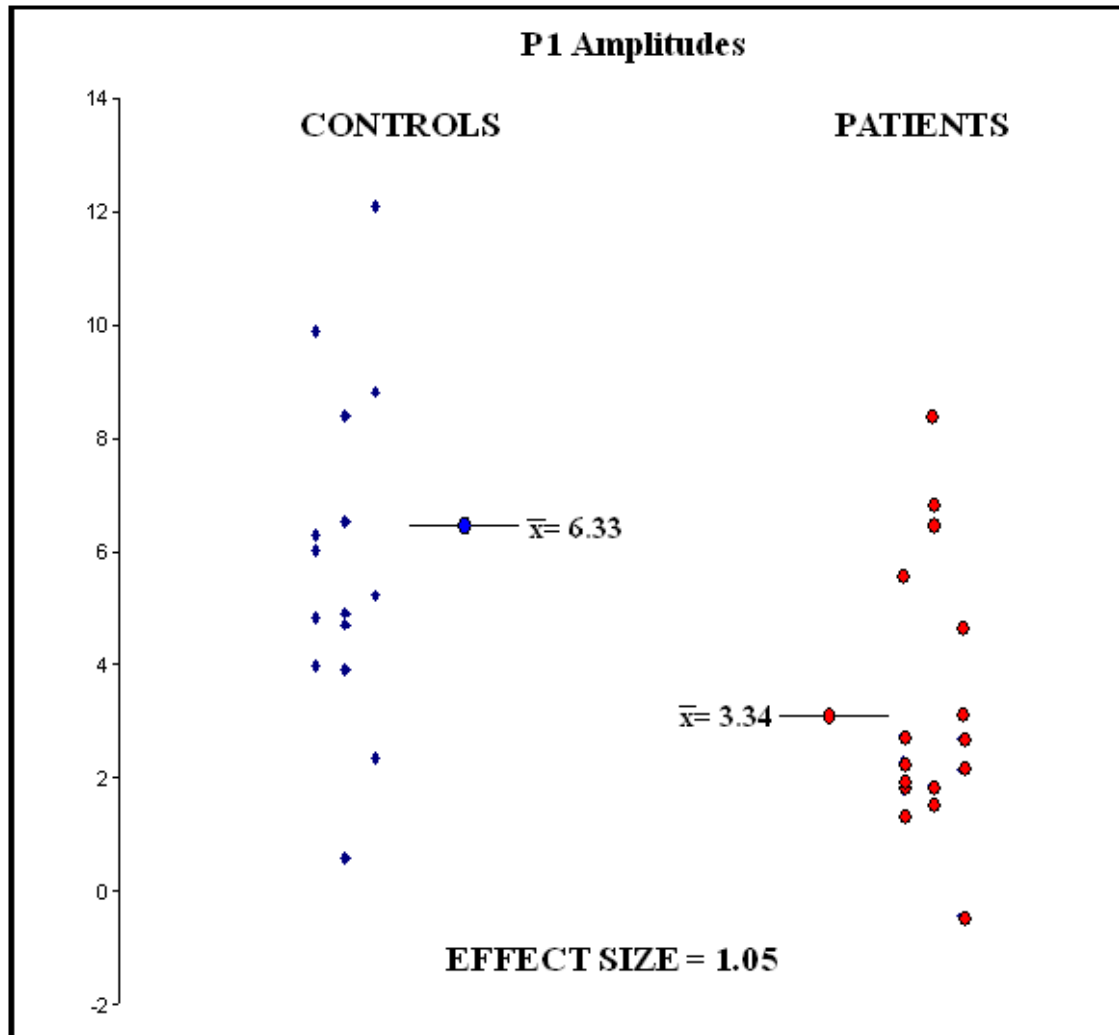


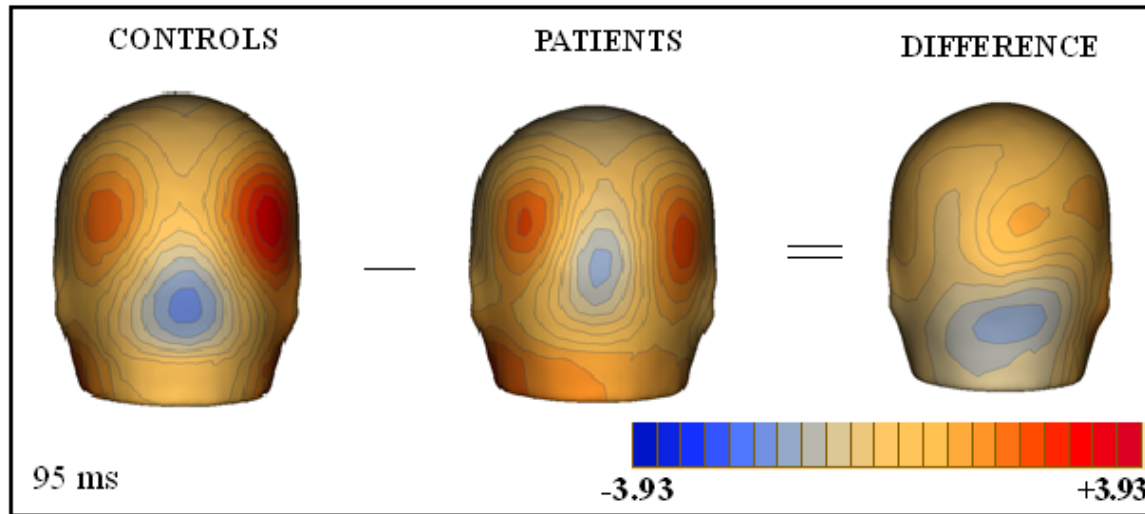
Figure 4a. Scatterplot displaying P1 amplitude of each participant; averages were taken after collapsing over left and right hemisphere electrodes. Controls' values are shown in blue (n=16), patients in red (n=16). The average of the controls' P1 amplitude was 6.33; patients' was 3.34. The effect size of the difference (using Cohen's d) is 1.05.



The Binocular effect: Characterizing inter-ocular plasticity

By visually examining the ERPs of both groups at sites where the P1 was maximal, we observed a striking non-linearity in the control group for their summed EPs (left eye alone + right eye alone, or SUM) compared to their binocularly evoked EPs (BASE) (see **Figure 2**). We termed this non-linearity our “binocular effect”; named as such, it recalls its more studied auditory analogue, the binaural effect (see e.g., Dobie & Norton, 1980). To

Figure 4b. Topographic maps for controls and patients for the average P1 peak latency for the two groups, 95 ms, and a subtraction topography.



explore potential group differences in the binocular effect, a 2x2x2 ANOVA was performed with factors of group (patients vs. controls), condition (BASE vs. SUM) and hemiscalp (left vs. right). A significant interaction of group by condition was found ($F(1,38)=4.526$, $p=0.04$). Follow up t-tests revealed a significant effect of condition over both the left and right occipital scalp in controls ($p=0.002$ and $p=0.034$, respectively). Patients on the other hand, failed to exhibit a significant effect of condition over either hemisphere ($p=0.93$ and $p=0.90$). A main effect of hemisphere was also found ($F(1,38)=4.769$, $p=0.035$), simply reflecting the fact that the P1 was greater over the right than the left hemisphere in both groups during this processing period. No other main effects or interactions were reliable.

Figure 5 displays the modulation index. Each point on the scatterplot is a subject's single value for SUM minus BASE, thereby providing a snapshot of the degree to which each subject exhibited the binocular effect.

Figure 6 displays waveforms and topographic maps highlighting the binocular effect for controls and patients. In the top panels, waveforms taken from a representative occipito-parietal electrode site (PO3) highlight the non-linearity for controls between conditions, BASE (blue) versus SUM (red), that emerges between approximately 90 and 120 ms. In contrast, a comparison of the patient waveforms from the same electrode site fails to demonstrate any obvious non-linearity during the same time period for these subjects (these effects can also be seen in the waveforms displayed in **Figure 2**). Calculation of the difference waves for each group, that is SUM minus BASE, accentuates the relative lack of effect for patients compared to controls during this time frame. In the bottom panels, topographic maps are displayed. These were computed for the base binocular condition and for the difference wave (the binocular effect) for both subject groups. In controls, the topography of the P1 is evident as a pair of bilateral positive foci over lateral occipital scalp.

Figure 5. Modulation index for the binocular effect: each point in the scatterplot is a single value for a participant. Values were derived by subtracting BASE from SUM. Controls are shown in blue, patients in red. Using Cohen's d, the effect size of the difference is 0.67.

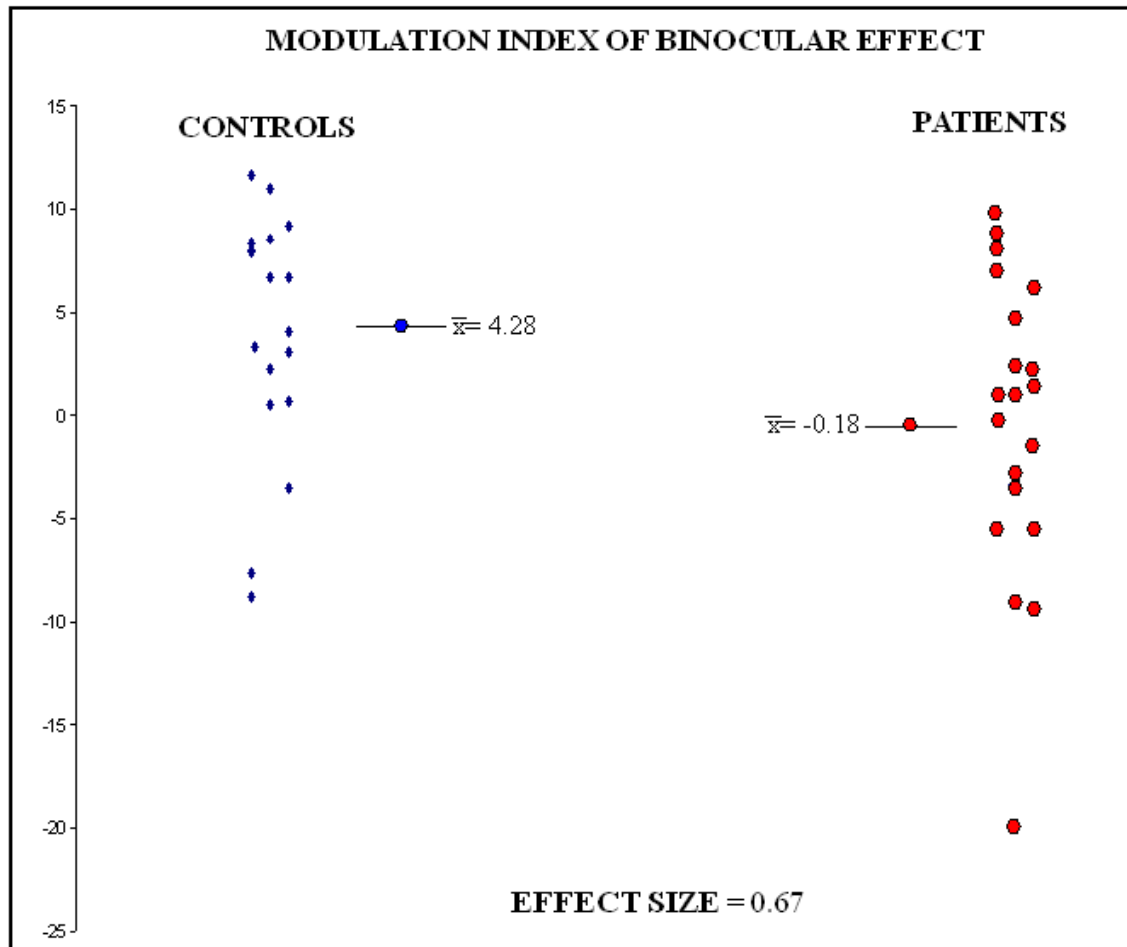
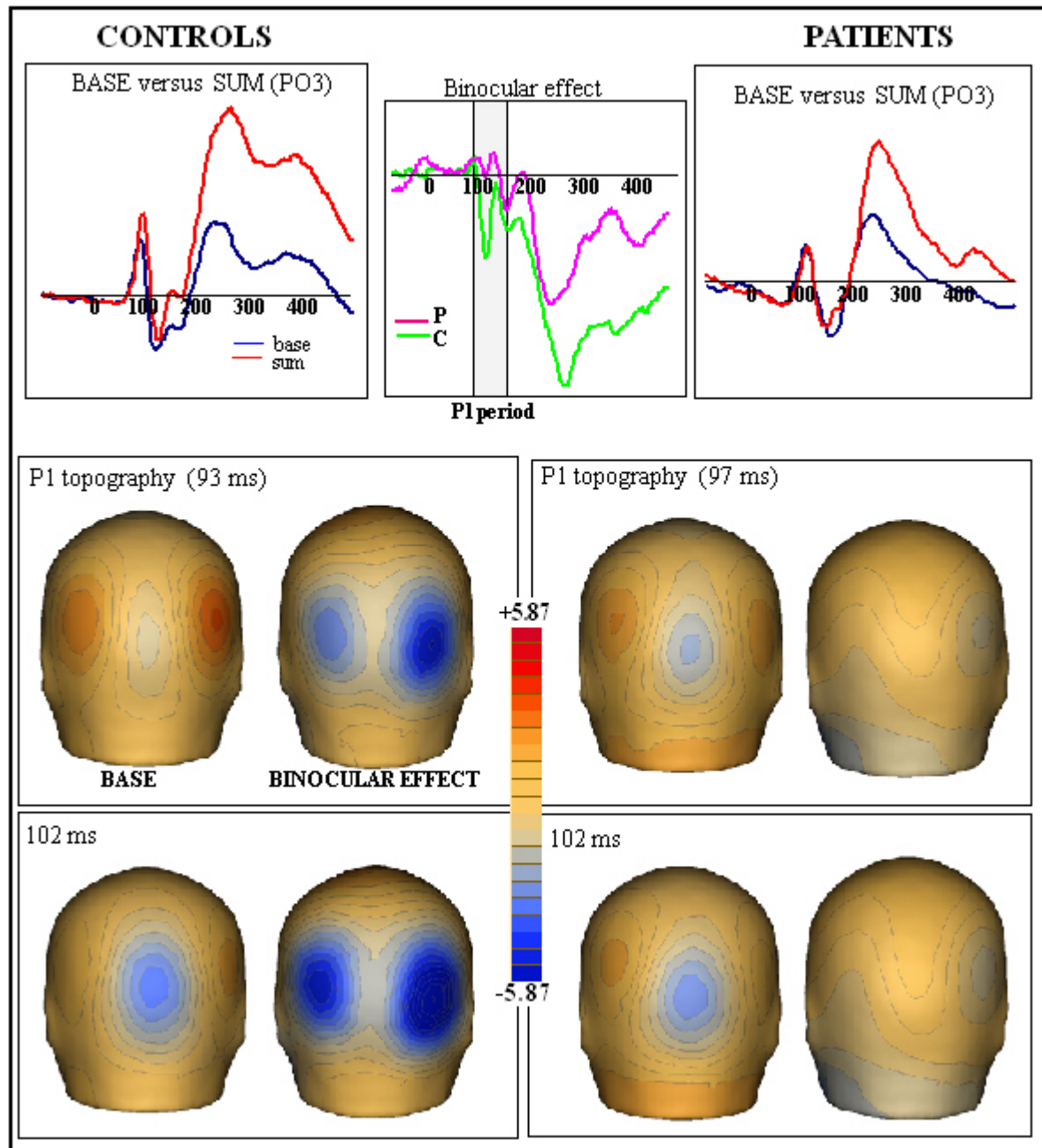


Figure 6. The binocular effect is characterized with difference waveforms and topographic maps. Control data are displayed on the left, patients on the right.

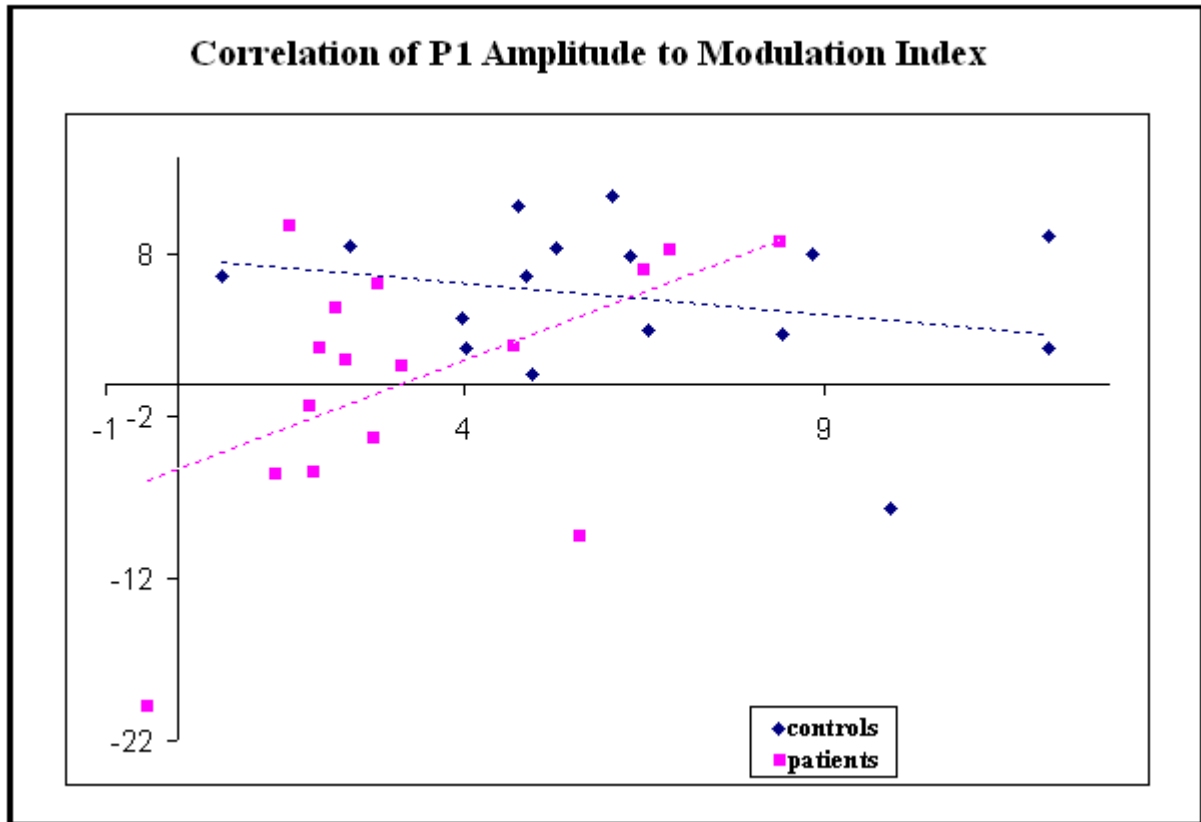


Top panel: Waveforms in the top panel were taken from electrode PO3; shown here are waves for BASE (blue) and SUM (red). Difference waves (the binocular effect, SUM minus BASE) are displayed in the middle top panel; controls' waveform is green, patients' pink. The P1 period has been highlighted to accentuate the relative lack of effect for patients, whereas controls demonstrate a distinct effect in this time frame. **Bottom panel:** In the bottom panel, topographic maps are displayed for baseline and for the difference wave (the binocular effect). Note that the scale remains consistent for all topographic maps. The distinct topographic shift seen during the P1 time period for controls between conditions is not present in the topographies of patients.

The difference maps showing the binocular effect also show bilateral foci over occipital scalp, although the distribution of this effect is not coextensive with the P1 topography. Rather, the binocular effect has a more medial distribution, indicating that the generators of the effect are not fully overlapping with the generators of the P1. The more medial distribution likely indicates greater contributions from hierarchically early retinotopic visual regions. In patients, the P1 period is represented by topographic maps that are relatively similar to those of the controls although clearly with lower signal amplitude (i.e. the P1 deficit). However, the maps of the binocular effect in patients, such as it is, show a near complete absence of amplitude during this processing period and there is no hint of the strong bilateral distribution seen in control subjects. The bottom-most panels display maps at 102 ms since this was the time point at which the binocular effect had its peak amplitude in control subjects. Again, the effect is notably absent in patients.

In order to test whether a relationship between P1 amplitudes and the binocular effect could be detected, we conducted correlation analyses. The main goal here was to assess whether those patients with the greatest P1 deficits were those who also showed the lowest binocular modulation index – that is, to assess whether the binocular effect and P1 generation might be related. A correlation coefficient was computed for P1 amplitudes (collapsed averages for left and right hemispheres of each subject) and modulation index values. In controls, there was no correlation ($r = -0.26$; $p = 0.165$); however, a significant positive correlation between these two measures was found for the patients ($r = 0.515$; $p = 0.02$). Correlation scatterplots for patients and controls are overlaid in **Figure 7**.

Figure 7. Scatterplot is displayed showing correlations for each subject of P1 amplitude to modulation index. The x-axis displays values for P1 amplitudes; y-axis displays modulation indices. The P1 values used here are collapsed averages of left and right hemisphere amplitudes. Controls are blue (n=16), patients pink (n=16).



Following the logic of multivariate endophenotype as described by Price et al.(2006), we combined our two metrics, P1 amplitude and binocular modulation index, to determine whether this would result in a greater overall effect size. Our hope was that taken in concert, these measures would have greater overall diagnostic predictive value than taken singly. In this approach, the two metrics were first treated as individually independent variables, with subjects our dependent variable. Univariate logistic regression (cut 0.5) was used to determine a regression model that maximally separates patient and control groups on the basis of each feature alone. Multivariate logistic regression (cut 0.5) was then used to

develop a composite regression model that was compared with the univariate models. Overall predictor values were obtained for each metric individually. This indicated the ability of each measure to correctly classify patients and controls. P1 amplitude predicted group membership with 71.9% accuracy, the binocular effect modulation index with 65.6%, and both measures taken together were 75% accurate as predictors. Full results of the analyses are displayed in **Table 2**.

Table 2. Coefficients of univariate logistic regression models that were evaluated: Univariate models for two features, then a multivariate model incorporating both features.

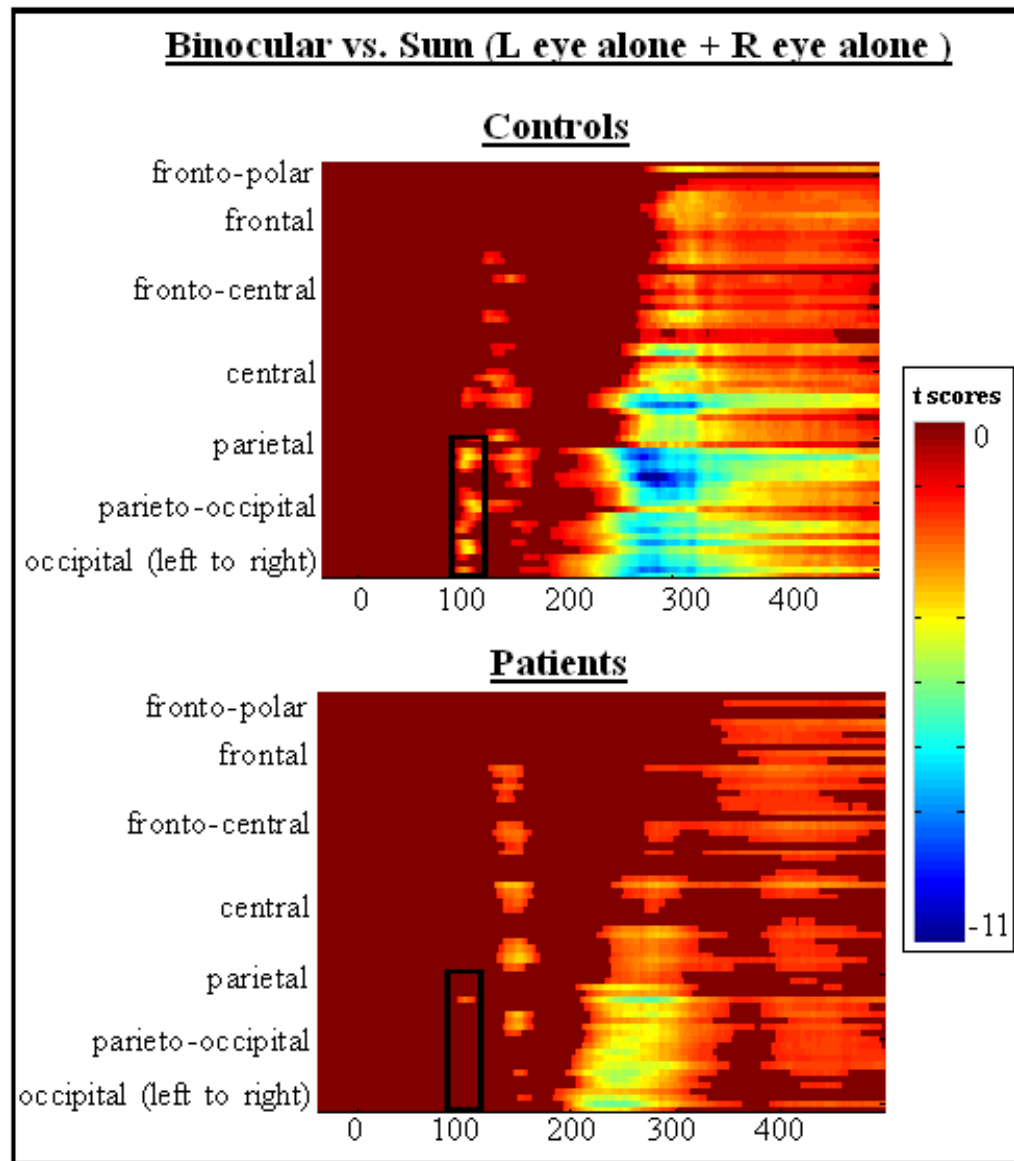
Model Predictor	B	SE	Wald Statistic	df	p	Exp(B)	Overall predictor value
P1 Amplitude	-.394	.165	5.735	1	0.017	.674	71.9%
P1 Constant	1.841	.838	4.830	1	0.028	6.304	
Binoc Effect	-.139	.073	3.585	1	0.058	.871	65.6%
Binoc Effect Constant	.462	.474	0.950	1	0.330	1.588	
Multivariate P1 amp	.364	.167	4.763	1	0.029	1.440	75%
Multivariate Binoc Effect	.127	.081	2.460	1	0.117	1.135	

All models were generated based on 16 patient and 16 control subjects.

In **Figure 8**, the statistical cluster plots display between-condition differences (BASE vs. SUM) for each group. Examination of these plots made clear that there were four major clusters of interest. The first of these was, of course, the one of primary interest to us, as it encapsulates the binocular effect. This is highlighted with a black box in Figure 8. In controls, this cluster emerged at approximately 90 ms, and was restricted largely to posterior scalp (i.e. parietal, parieto-occipital, and occipital regions). In patients, effects in this period are notably absent; consistent with the complete absence of any binocular effect in patients as

discussed above. The second significance cluster emerges for both groups at approximately 140-160 ms. A comparison with waveforms shows this cluster to correspond generally with the N1 component for both groups (see **Figure 2**), and the effect appears largely similar for both groups. A third pronounced cluster onsets at approximately 200 ms; waveform comparison shows that this cluster corresponds to the first of two broad positive components elicited in both groups. Whereas this significance cluster in patients is largely confined to central, parietal and occipital regions, in controls it may extend more frontally as well. The cluster plots show that this effect is highly robust for both groups, although it is also clear that it is more so the case in controls. The final cluster is a much more broadly distributed effect that appears to have its onset between 300 and 400 ms and extends to the end of the sampled epoch. In controls it is less distinct as a separable cluster than in patients, but again comparing cluster plots to waveforms revealed that this is largely coincident with the final positivity onsetting between 300-400 ms. Again, the cluster plots suggested that this later period was also more robust in controls than patients. We were interested to determine whether these later two periods would show significant group by condition interactions and therefore submitted these time-windows to a pair of post-hoc ANOVAs. For the 200-300 ms period, a main effect was found for condition ($F(1,38)= 78.636, p<0.000$), but not for group ($F(1,38)= .414, p=0.524$). A group by condition interaction did not attain conventional levels of significance although a trend is evident ($F(1,38)= 3.495, p= 0.069$), and this effect may represent a good candidate for future investigation and replication. We also tested both groups for the time period 300-400 ms; here, main effects of group ($F(1,38)= 7.774, p=0.008$) and condition ($F(1,38)= 11.131, p=0.002$) were found, but there was no significant interaction of group by condition ($F(1,38)= 0.883, p=0.354$).

Figure 8. Statistical cluster plot of the results of the point-wise running one-tailed t tests comparing the amplitudes of participants' VEPs in BASE vs. SUM conditions. Time with respect to stimulus onset is presented on the x axis and topographic regions of 72 electrode positions on the y axis. Color corresponds to t values. Periods of significant difference are only plotted if a strict alpha criterion of <0.05 was exceeded for at least ten consecutive data points. The P1 period has been outlined with a black box for each group.



Discussion

The primary goals of the present investigation were twofold. First, we sought to develop a simple-to-execute test of early visual processing that might prove a more sensitive measure than the already established P1 deficit, which our group has shown to be an endophenotypic marker for schizophrenia (Yeap, 2006). To that end, we developed a challenge task from which a binocular modulation index could be derived. It was our hope that this index would afford us greater diagnostic sensitivity than the visual P1 deficit. The second goal was a basic neuroscience issue, to determine whether short-term cortical plasticity was intact in this population and whether basic sensory-level integration of binocular inputs was normal in this group. If not, this would provide further evidence for fundamental visual sensory processing deficits in this population and might explain why recent work has shown deficits in basic depth perception (Schechter et al., 2006).

Here, we first replicated the P1 deficit in our patient sample, again with a large effect size (1.05). In terms of the binocular effect, while our patients exhibited a significant decrement, the effect size achieved was only in the medium range (0.67). Therefore, our goal of developing a more sensitive metric was not met. On the other hand, a correlation analysis revealed that those patients with the weakest binocular effect were those patients also showing the greatest P1 deficit. Coupled with the complete lack of correlation between these metrics in controls, this finding is intriguing. First, the absence of any relationship between P1 and the binocular effect in controls clearly indicates that separable processes drive them. This dissociability is emphasized by the fact that the P1 and the binocular effect have distinct topographic distributions and they also have quite different, if overlapping, timecourses. Why then do we find significant correlation in the patients? The clear implication is that both

metrics simply index a more general set of visual processing deficits in this population. An ideal scenario from a diagnostic perspective would be that these two metrics could both be identified as endophenotypic. While we already know this to be the case for the P1 deficit, it remains to be seen whether the same is true of the binocular effect. As such, combining these two easily obtained metrics as part of a so-called multivariate endophenotype (see Price et al., 2006) could be an effective strategy in developing a useful and sensitive diagnostic clinical tool. The result of combining P1 and the binocular effect here in this small group was disappointing though in that the ability of a combined measure to correctly classify patients and controls into separate groups increased only modestly to 75%, from 71.9% when the P1 measure was used in isolation. Nonetheless, while this modest improvement may yet be useful when a greater number of measures are combined.

While inter-individual variance of the binocular effect precludes its use as a single clinical marker, it may yet be useful for future research to parse deficits in basic sensory processing with an intra-individual strategy in mind. For example, since patients with schizophrenia have shown impaired binocular depth perception (Schechter et al., 2006), it could well be the case that a closer examination of the patients in the present study whose modulation index was the lowest would reveal a specific profile of visual sensory impairment that may enable us to begin to tease apart some fundamental trait-level processing deficits, that in turn allow us to classify a sub-group of patients that share specific risk genetics. That is, the patients who failed to show the binocular effect (i.e. had a modulation index of zero or less) may also be those individuals who lack stereopsis, although this remains to be explicitly tested. Further, there may be a link between these deficits and deficits of the visual biological motion processing system, which has already been shown to be impaired in schizophrenia

(Kim, Wylie, Pasternak, Butler, & Javitt, 2006). Linking a cluster of subclinical traits together in such a way may prove to be valuable in allowing us to target the presence of schizophrenia in a prodromal population. Even weakly endophenotypic markers for schizophrenia may still prove very useful as elements of a battery of metrics for risk assessment. That is, compilation of a set of measures, some with high sensitivity but low specificity and others with high specificity but low sensitivity, may prove to be an excellent multivariate strategy for assessing risk, a strategy that has already been applied with some success by Price et al. (2006).

Returning to the basic finding of a binocular interaction deficit in schizophrenia during early sensory processing, it is of interest to consider what the underlying neurophysiological mechanisms that are awry might be. As detailed in our introduction, the major neurotransmitter system implicated in early binocular interactions is the GABAergic system (Mower & Christen, 1989; Burchfiel & Duffy, 1981), although the picture is surely more complicated than a single transmitter system. Thus far, what we know about the effects of monocular deprivation is largely informed by animal models, usually involving long-term deprivation (e.g., Mower & Christen, 1989, Yan, Mazow, & Dafny, 1995, Prusky, Alam, & Douglas, 2006, He, Hodos, & Quinlan, 2006; Pham et al., 2004). In a study employing adult mice, an enhancement of vision in the non-deprived eye was observed after monocular deprivation (Prusky et al., 2006). Specifically, the spatial frequency sensitivity of the optokinetic response in the non-deprived eye increased gradually over five days of deprivation. Eye opening led to a gradual decline; however, enhanced sensitivity was maintained for 5-6 days before baseline levels were resumed. This remarkable plasticity showed learning-like properties, with maximal effects seen in animals that had active testing

experience throughout deprivation. Furthermore, the duration of enhanced sensitivity after deprivation was extended by increasing the length of deprivation, and by repeating deprivation. Hubel and Wiesel (1970) observed that monocular deprivation during a critical period in kittens induced a shift in ocular dominance toward the non-deprived eye. Other work with animal models has suggested that over the course of postnatal development, there is a decrease in the level of ocular dominance plasticity as a result of an increase in the strength of GABAergic inhibition relative to glutamatergic excitation (as reviewed in He et al., 2006). These neurochemical systems have yet to be fully characterized in human subjects, much less in patients with schizophrenia. However, developing paradigms to do so may be valuable in enabling us to establish deficits that implicate specific underlying pathophysiology in schizophrenia.

Conclusions

The aim of the present study was to construct a paradigm that would sufficiently challenge early visual processing mechanisms, in the hope that we could unmask decrements in the visual evoked potentials of individuals with schizophrenia above and beyond those already identified. We developed a paradigm to assay short-term plasticity within early visual cortices during the P1 processing timeframe, employing monocular deprivation. We reasoned that evaluating a second-order effect of this type might very well prove an effective means of amplifying previously characterized differences in basic visual sensory processing in patients. Our overarching hypothesis was that compensatory mechanisms in the visual system of controls would allow for a relatively rapid recovery of VEP amplitude in the presence of

monocular deprivation, but that this rapid short-term plasticity would be less effectively engaged in patients with schizophrenia.

Controls exhibited a robust binocular effect; that is, when we added the evoked response elicited from viewing with one eye to that of the other eye and compared this sum to the waveform resulting from stimulation of both eyes together, we observed a nonlinear response (i.e., the sum of the parts was greater than the whole). Presumably, a compensatory mechanism related to ocular dominance plasticity was engaged in control subjects to effectively “boost” the response from the non-occluded eye such that the resultant monocular VEPs were nearly of the same amplitude as those evoked in the binocular condition. Patients, on the whole, failed to exhibit this binocular effect, suggesting that they were not engaging in the same process of cortical plasticity that allowed controls to generate robust EPs in the absence of input from the full visual field (i.e., both eyes). This may hold important implications for the integrity of underlying neural networks involved in intra-columnar inhibition, that is, GABAergic networks. Further research specifically tapping these neurochemical systems in patients is therefore warranted. Additionally, it will be of interest to determine in a future study whether there is a direct correspondence between the binocular effect modulation index, lack of stereopsis, and biological motion processing deficits in patients with schizophrenia. To extrapolate, it may be very informative to determine whether a link exists between individuals demonstrating deficits in these basic visual sensory processing indices and in a metric of basic auditory sensory processing that has been shown to be impaired in schizophrenia.

References

- American Electroencephalographic Society guidelines for standard electrode position nomenclature. (1991). *J Clin Neurophysiol*, 8(2), 200-202.
- Apkarian, P. A., Nakayama, K., & Tyler, C. W. (1981). Binocularity in the human visual evoked potential: facilitation, summation and suppression. *Electroencephalogr Clin Neurophysiol*, 51(1), 32-48.
- Baitch, L. W., & Levi, D. M. (1988). Evidence for nonlinear binocular interactions in human visual cortex. *Vision Res*, 28(10), 1139-1143.
- Braff, D. L., & Saccuzzo, D. P. (1982). Effect of antipsychotic medication on speed of information processing in schizophrenic patients. *Am J Psychiatry*, 139(9), 1127-1130.
- Burchfiel, J. L., & Duffy, F. H. (1981). Role of intracortical inhibition in deprivation amblyopia: reversal by microiontophoretic bicuculline. *Brain Res*, 206(2), 479-484.
- Butler, P. D., Harkavy-Friedman, J. M., Amador, X. F., & Gorman, J. M. (1996). Backward masking in schizophrenia: relationship to medication status, neuropsychological functioning, and dopamine metabolism. *Biol Psychiatry*, 40(4), 295-298.
- Butler, P. D., Schechter, I., Zemon, V., Schwartz, S. G., Greenstein, V. C., Gordon, J., et al. (2001). Dysfunction of early-stage visual processing in schizophrenia. *Am J Psychiatry*, 158(7), 1126-1133.
- Cadenhead, K. S., Geyer, M. A., Butler, R. W., Perry, W., Sprock, J., & Braff, D. L. (1997). Information processing deficits of schizophrenia patients: relationship to clinical ratings, gender and medication status. *Schizophr Res*, 28(1), 51-62.
- Dobie, R. A., & Norton, S. J. (1980). Binaural interaction in human auditory evoked potentials. *Electroencephalogr Clin Neurophysiol*, 49(3-4), 303-313.
- Doniger, G. M., Foxe, J. J., Murray, M. M., Higgins, B. A., & Javitt, D. C. (2002). Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. *Arch Gen Psychiatry*, 59(11), 1011-1020.
- Donohoe, G., Morris, D. W., De Sanctis, P., Magno, E., Montesi, J. L., Garavan, H. P., et al. (2008). Early visual processing deficits in dysbindin-associated schizophrenia. *Biol Psychiatry*, 63(5), 484-489.
- First, M. B., Frances, A. J., Pincus, H. A., Vettorello, N., & Davis, W. W. (1994). DSM-IV in progress. Changes in substance-related, schizophrenic, and other primarily adult disorders. *Hosp Community Psychiatry*, 45(1), 18-20.

- Foxe, J. J., Doniger, G. M., & Javitt, D. C. (2001). Early visual processing deficits in schizophrenia: impaired P1 generation revealed by high-density electrical mapping. *Neuroreport*, 12(17), 3815-3820.
- Foxe, J. J., Murray, M. M., & Javitt, D. C. (2005). Filling-in in schizophrenia: a high-density electrical mapping and source-analysis investigation of illusory contour processing. *Cereb Cortex*, 15(12), 1914-1927.
- Foxe, J. J., & Simpson, G. V. (2002). Flow of activation from V1 to frontal cortex in humans. A framework for defining "early" visual processing. *Exp Brain Res*, 142(1), 139-150.
- Harvey, P. D., Docherty, N. M., Serper, M. R., & Rasmussen, M. (1990). Cognitive deficits and thought disorder: II. An 8-month followup study. *Schizophr Bull*, 16(1), 147-156.
- He, H. Y., Hodos, W., & Quinlan, E. M. (2006). Visual deprivation reactivates rapid ocular dominance plasticity in adult visual cortex. *J Neurosci*, 26(11), 2951-2955.
- Hensch, T. K., & Stryker, M. P. (2004). Columnar architecture sculpted by GABA circuits in developing cat visual cortex. *Science*, 303(5664), 1678-1681.
- Hubel. (2008). *Eye, Brain, and Vision*, 2008, from <http://hubel.med.harvard.edu>
- Hubel, D. H., & Wiesel, T. N. (1970). Stereoscopic vision in macaque monkey. Cells sensitive to binocular depth in area 18 of the macaque monkey cortex. *Nature*, 225(5227), 41-42.
- Jibiki, I., Takizawa, Y., & Yamaguchi, N. (1991). Visual dysfunction in treated schizophrenia suggested by visual evoked potentials from pattern-reversal stimulation. *Eur Arch Psychiatry Clin Neurosci*, 241(1), 61-64.
- Kim, D., Wylie, G., Pasternak, R., Butler, P. D., & Javitt, D. C. (2006). Magnocellular contributions to impaired motion processing in schizophrenia. *Schizophr Res*, 82(1), 1-8.
- Lalor, E. C., Yeap, S., Reilly, R. B., Pearlmuter, B. A., & Foxe, J. J. (2008). Dissecting the cellular contributions to early visual sensory processing deficits in schizophrenia using the VESPA evoked response. *Schizophr Res*, 98(1-3), 256-264.
- Lindenmayer, J. P., Bernstein-Hyman, R., & Grochowski, S. (1994). Five-factor model of schizophrenia. Initial validation. *J Nerv Ment Dis*, 182(11), 631-638.
- Magno, E., Yeap, S., Thakore, J. H., Garavan, H., De Sanctis, P., & Foxe, J. J. (2008). Are Auditory-Evoked Frequency and Duration Mismatch Negativity Deficits Endophenotypic for Schizophrenia? High-Density Electrical Mapping in Clinically Unaffected First-Degree Relatives and First-Episode and Chronic Schizophrenia. *Biol Psychiatry*.

- Molholm, S., Ritter, W., Murray, M. M., Javitt, D. C., Schroeder, C. E., & Foxe, J. J. (2002). Multisensory auditory-visual interactions during early sensory processing in humans: a high-density electrical mapping study. *Brain Res Cogn Brain Res*, 14(1), 115-128.
- Mower, G. D., & Christen, W. G. (1989). Evidence for an enhanced role of GABA inhibition in visual cortical ocular dominance of cats reared with abnormal monocular experience. *Brain Res Dev Brain Res*, 45(2), 211-218.
- Murray, M. M., Foxe, J. J., Higgins, B. A., Javitt, D. C., & Schroeder, C. E. (2001). Visuo-spatial neural response interactions in early cortical processing during a simple reaction time task: a high-density electrical mapping study. *Neuropsychologia*, 39(8), 828-844.
- Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, 9(1), 97-113.
- Pettigrew, J. D., & Miller, S. M. (1998). A 'sticky' interhemispheric switch in bipolar disorder? *Proc Biol Sci*, 265(1411), 2141-2148.
- Pham, T. A., Graham, S. J., Suzuki, S., Barco, A., Kandel, E. R., Gordon, B., et al. (2004). A semi-persistent adult ocular dominance plasticity in visual cortex is stabilized by activated CREB. *Learn Mem*, 11(6), 738-747.
- Picton, T. W., Hillyard, S. A., Krausz, H. I., & Galambos, R. (1974). Human auditory evoked potentials. I. Evaluation of components. *Electroencephalogr Clin Neurophysiol*, 36(2), 179-190.
- Price, G. W., Michie, P. T., Johnston, J., Innes-Brown, H., Kent, A., Clissa, P., et al. (2006). A multivariate electrophysiological endophenotype, from a unitary cohort, shows greater research utility than any single feature in the Western Australian family study of schizophrenia. *Biol Psychiatry*, 60(1), 1-10.
- Prusky, G. T., Alam, N. M., & Douglas, R. M. (2006). Enhancement of vision by monocular deprivation in adult mice. *J Neurosci*, 26(45), 11554-11561.
- Schechter, I., Butler, P. D., Jalbrzikowski, M., Pasternak, R., Saperstein, A. M., & Javitt, D. C. (2006). A new dimension of sensory dysfunction: stereopsis deficits in schizophrenia. *Biol Psychiatry*, 60(11), 1282-1284.
- Tyler, C. W., & Kaitz, M. F. (1977). Binocular interactions in the human visual evoked potential after short-term occlusion and anisometropia. *Invest Ophthalmol Vis Sci*, 16(11), 1070-1073.
- Yan, H. Q., Mazow, M. L., & Dafny, N. (1995). Monocular visual deprivation at the critical period modulates photic evoked responses. *Brain Res Bull*, 36(6), 545-548.

- Yeap, S. (2006). Are early visual processing deficits endophenotypic for schizophrenia? A high-density electrical mapping study in clinically unaffected first-degree relatives. *Arch Gen Psychiatry*.
- Yeap, S., Kelly, S. P., Reilly, R. B., Thakore, J. H., & Foxe, J. J. (submitted). Visual sensory processing dysfunction as a common endophenotype for bipolar disorder and schizophrenia.
- Yeap, S., Kelly, S. P., Sehatpour, P., Magno, E., Garavan, H., Thakore, J. H., et al. (2008). Visual sensory processing deficits in Schizophrenia and their relationship to disease state. *Eur Arch Psychiatry Clin Neurosci*.
- Yeap, S., Kelly, S. P., Sehatpour, P., Magno, E., Javitt, D. C., Garavan, H., et al. (2006). Early visual sensory deficits as endophenotypes for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives. *Arch Gen Psychiatry*, 63(11), 1180-1188.
- Yeap, S., Kelly, S. P., Thakore, J. H., & Foxe, J. J. (2008). Visual sensory processing deficits in first-episode patients with Schizophrenia. *Schizophr Res*, 102(1-3), 340-343.
- Zemon, V., Pinkhasov, E., & Gordon, J. (1993). Electrophysiological tests of neural models: evidence for nonlinear binocular interactions in humans. *Proc Natl Acad Sci U S A*, 90(7), 2975-2978.

CHAPTER 6

Conclusion

Schizophrenia is a disease that exacts a devastating toll on the individuals and families of the individuals it affects. While a substantial amount of research has focused on the overt symptoms that are a hallmark of the disease, the work described here takes a very different stage of processing in the brain as its starting point; that is, the earliest discernible time points of basic sensory processing. By employing electrophysiology, it is possible to characterize deficits that are present from the very initial afference to primary regions of sensory processing, and indeed, even earlier. Individuals with schizophrenia have complex symptom profiles, manifesting a vast variety of negative and/or positive symptoms, and this inter-individual variance continues to confound researchers and diagnosticians alike. What these findings of early sensory deficits make clear is that by scrolling back to the most basic elements of all subsequent higher-order processing, the very foundations of the brain show evidence of diffuse impairment. It may very well be the case that by examining these origins, we are tapping a strategy that has the potential to more accurately pinpoint one aspect of neural dysfunction which underlies this debilitating illness.

Study 1 provided a detailed, comprehensive description of the auditory middle latency responses for a normative sample. In addition, this period of evoked componentry was examined for a schizophrenia patient sample, thereby enabling us to make detailed comparisons. Deficits in the patients were carefully and comprehensively delineated. Evidence of dorsal/ventral distinctions within the patient sample emerged, showing that not only do the very earliest stages of auditory sensory processing in cortex show impairment, but providing evidence of impairment during subcortical processing. This

provided impetus for a closer examination of the ‘what/where’ auditory pathways that served as Study 2.

In Study 2, the underlying neural substrates of sound localization and sound object recognition were investigated in a normative sample. Our findings are intriguing in that they represent a departure from a handful of studies in the literature, which found a difference in auditory evoked componentry elicited during dedicated tasks of ‘what’ and ‘where’ that coincided with the auditory N1 component. We also found a difference during this time frame; however the relative direction of the effect was inverted in our data. Specifically, it was our ‘what’ task that elicited a greater N1, whereas in other studies it was consistently the ‘where’ task that did so. We attribute this to greater demands of the ecologically valid task we employed: natural animal calls delivered from seven free-field speakers. We applied this paradigm to patients with schizophrenia. A major impetus for investigating a dorsal/ventral distinction in schizophrenia was the suggestion of a relatively intact ventral pathway provided by prior studies from our laboratory (Leavitt, Molholm, Ritter, Shpaner, & Foxe, 2007; Ross et al., 2007). Pilot data from six patients with schizophrenia provided preliminary evidence for dissociable underlying processes for tasks of sound localization versus sound object recognition. However, the patient results brought to light critical methodological considerations; namely, our results suggested that the tasks were simply too challenging for patients. Modifications to the tasks that will more enable patients to truly engage in sound localizing and sound object recognition tasks will allow us to better characterize the underlying integrity of dorsal and ventral auditory pathways for patients with schizophrenia in a future study.

Study 3 shifted the focus from auditory to visual processing deficits in schizophrenia. Given what we know of fundamental early stage visual dysfunction in this population, we created a challenge task with the aim of amplifying patient deficits such that they might be rendered more diagnostically useful. Utilizing brief monocular deprivation, substantial electrophysiological differences between patients and control subjects were shown. Specifically, patients failed to show the binocular effect. While in and of itself, the monocular deprivation effect demonstrated in patients failed to reach a large effect size, utilizing this metric as part of a battery of subclinical traits encompassing a variety of possibly linked deficits in basic sensory processing (visual and auditory) may represent a very important strategy for identifying schizophrenia in a prodromal population (as set forth by Price et al., 2006).

Directions for future research

Applying these paradigms to diagnostically delimited patient groups might enable us to begin to more specifically characterize disease subtypes. As we know, schizophrenia's heterogeneity tends to preclude straightforward findings throughout the literature (including, for example, neuroanatomical, genetic, and behavioral studies of neurocognitive deficits; for a recent review of episodic memory deficits in schizophrenia, see Leavitt and Goldberg, 2009). Focusing on patients with positive symptom cluster profiles (e.g., those with active auditory hallucinations) could represent a step toward disentangling these variable disease phenotypes. In addition to these types of delimiters, it might be informative to demographically narrow our patient groups. Factors such as

length of illness, age, and symptom severity are among many variables of interest that could be controlled in subsequent studies.

Despite the importance of the findings described here, the results do not easily lend themselves to an overarching, mechanistic model of how basic sensory processing deficits in schizophrenia occur, nor how they may impact higher order cognitive functioning. Nevertheless, we believe that a multifactorial perspective might offer a principled way to mechanistically understand basic sensory processing in schizophrenia. Given that evidence of impairments of basic sensory processing across modalities have been robust and replicable, it is perhaps frustrating that a unitary characterization of this hallmark feature of schizophrenia has not emerged. It is our hope that by further developing paradigms such as those described herein, we may gain a clearer sense of promising directions for future research.

References

- Leavitt, V.M. & Goldberg, T.E. (2009). Episodic memory in schizophrenia. *Neuropsychology Review*. in press.
- Leavitt, V. M., Molholm, S., Ritter, W., Shpaner, M., & Foxe, J. J. (2007). Auditory processing in schizophrenia during the middle latency period (10-50 ms): high-density electrical mapping and source analysis reveal subcortical antecedents to early cortical deficits. *J Psychiatry Neurosci*, 32(5), 339-353.
- Price, G. W., Michie, P. T., Johnston, J., Innes-Brown, H., Kent, A., Clissa, P., et al. (2006). A multivariate electrophysiological endophenotype, from a unitary cohort, shows greater research utility than any single feature in the Western Australian family study of schizophrenia. *Biol Psychiatry*, 60(1), 1-10.
- Ross, L. A., Saint-Amour, D., Leavitt, V. M., Molholm, S., Javitt, D. C., & Foxe, J. J. (2007). Impaired multisensory processing in schizophrenia: deficits in the visual enhancement of speech comprehension under noisy environmental conditions. *Schizophr Res*, 97(1-3), 173-183.