The Contribution of Early Sensory Deficits to Attention Impairments and Symptom Severity in Schizophrenia

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Recent evidence suggests that early primary sensory cortices and impairments in sensory processing are characteristics of schizophrenia. Early sensory processing impairments likely contribute to cognitive dysfunction and symptom severity. Attention impairments are among the most significant neurocognitive symptoms associated with schizophrenia. Performance on traditional assessments of attention requires reliance on other aspects of cognitive functioning known to be disrupted in schizophrenia, such as working memory, processing speed and perception, leaving unresolved the degree to which impaired performance truly reflects attention.

From a sensory perspective, attention involves an interaction between exogenous and endogenous networks. Exogenous processes, also referred to as attentional capture or "bottom-up" modulation, refers to stimulus-driven processes for capture of attention, even in the absence of volitional intent. Endogenous attention, also referred to as attentional allocation or "top-down" attention, refers to volitional modulation of intent and depends on processes such as attention and working memory. Although endogenous attentional processes have been extensively characterized in schizophrenia, the exogenous processing networks remains significantly understudied. Recent findings from sensory investigations demonstrate that systems underlying the exogenous network are severely compromised in schizophrenia, suggesting that loss of automatic attentional capture may be an important, but understudied aspect of the illness.

Studies of auditory discrimination of pitch, frequency and loudness consistently demonstrate early auditory processing and primary auditory cortex abnormalities in schizophrenia. Primary auditory cortex abnormalities and misattribution of sound sources have been postulated to cause hallucinations. However, few studies have examined early sensory processing associated with spatial localization and none have assessed its relationship with hallucination severity.

In the present dissertation, three studies were conducted to examine early visual and auditory sensory processing in individuals diagnosed with schizophrenia spectrum disorders. The first examined the contribution of early visual processing deficits to impaired performance on traditional assessments of visual attention. The remaining two studies examined auditory spatial localization. The relationship between spatial localization and positive symptom severity was also explored. Overall, the findings suggest that early sensory processing deficits significantly contribute to impaired performance on traditional assessments of attention and symptom severity.

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Dedication

This dissertation is dedicated to my son, Khalil, who gave me the inspiration to finish.

> "One day you will ask me which is more important? My life or yours? I will say mine and you will walk away not knowing that you are my life." — Kahlil Gibran

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Chapter 1: Background

Schizophrenia is a neuropsychiatric illness characterized by three symptom clusters: negative, positive, and cognitive[1]. Negative symptoms consist of blunted affect, lack of motivation or goal-directed behavior (referred to as “avolition”), poverty of speech (referred as “alogia”) and social withdrawal. Positive symptoms consist of hallucinations, delusions, odd behavior and thought disorder. Thought disorder refers to derailment or tangential thought processes. Cognitive symptoms are characterized by impairments in attention, working memory, and executive processing[2]. Cognitive symptoms cause the greatest functional impairment[3]. Attention impairments are considered one of the key components of neurocognitive dysfunction in schizophrenia.

There is emerging evidence that early visual [4, 5] and auditory processing [6] are impaired in individuals diagnosed with schizophrenia. Such deficits likely impact cognitive functioning and symptom severity. Intact sensory processing is necessary for accurate performance on conventional assessments of attention. Primary auditory cortex abnormalities [7-10] and perceptual deficits [11, 12] are demonstrated to be associated with positive symptom severity. In the present dissertation, early visual and auditory processing in schizophrenia was examined and the contribution of such deficits to impaired attention and symptom severity was explored.

Attention and Schizophrenia

Much of the attentional dysfunction literature in schizophrenia evolved prior to recent demonstrations of impaired sensory processing. Prior findings are based on tasks with substantial sensory processing demands, leaving unresolved the degree to which attention related performance impairments are due to dysfunction in attention and/or to sensory processing.

William James, the forerunner of modern attention research, spoke of attention as the process of:

> "Taking possession by the mind, in clear and vivid form, of one out of what seems several simultaneously possible objects or trains of thought. Focalization, concentration of consciousness are of its essence. It implies withdrawal of some things in order to deal effectively with others" (James 1890, pp 403). [13]

A major advance in the past century, however, has been the realization that attention processing does not constitute a unitary phenomenon, but instead represents concerted and competitive activity of multiple overlapping networks. Further, attentional mechanisms may differ across sensory modalities, depending upon the unique types of information that must be considered within these systems.

To date, the "attentional space" in schizophrenia has been evaluated only to a limited degree. Even within this space, however, it is not clear that all components of attention are equally impaired, if in fact, impaired at all. Many forms of attention that appear extremely effortful seem paradoxically intact, while some that require little conscious effort appear substantially impaired[14]. This paradox has been discussed recently by Luck and Gold [15] who proposed a dichotomy between control and implementation selection. Similarly, Wang and Fan [16] have stressed the potential role of executive dysfunction in apparent attention deficits in schizophrenia, while suggesting that other aspects of attentional networks, such as orienting and alerting networks, remain intact.

The present dissertation further considers this paradox from a sensory framework and points to the potential contributions of impaired sensory processing to the "attention" impairment in schizophrenia. It is postulated that early processing impairments may contribute to performance differences associated with schizophrenia on traditional attention assessments.

Connectionist Model of Attention

As it has become increasingly clear that attention is not a unitary phenomenon, alternative schemata have been developed. The Connectionist model of attention postulates that attention is comprised of two neuroanatomically distinct networks: the posterior and anterior systems. The **posterior system** is responsible for sensory perception, while the **anterior system** serves to modulate sensory processing [17]. Attention is carried out by three subsystems that perform different, but inter-related functions: alerting, orienting, and executive control.

A computational model was recently derived using a biologically realistic connectionist framework to simulate the neurological pathways involved in attention[16] (Figure 1.1). The model predicts that information is projected from the primary visual cortex to the alerting and orienting network. The purpose of the alerting network is to enhance processing, both in the orienting network and primary visual cortex. The orienting network selectively modulates processing for spatial characteristics based on input initially projected from the primary visual cortex in two ways. First, it projects back to the primary visual cortex to upregulate processing of relevant spatial characteristics; input that is subsequently projected to the object pathway. The orienting network also projects to the object pathway to enable selective processing of spatial characteristics associated with object recognition. The executive control network provides input to the orienting network and object pathway when a conflict arises in determining what input to select for further processing. Once the object pathway receives sufficient input, it projects to the output pathway to generate an appropriate response. Data derived from performance on the Attention Networking Test (ANT), an assessment designed to isolate functioning in each network[18] verified that the model accurately predicts performance.

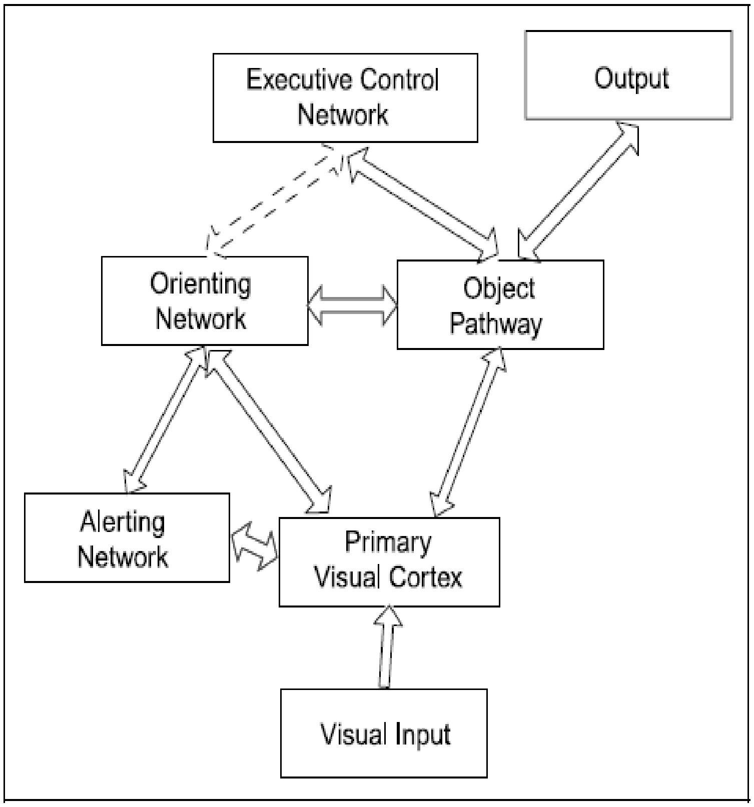


Figure 1.1 Connectionist Model of Attention

Visual input is projected from the primary visual cortex to the alerting and orienting networks. The alerting network serves to upregulate processing in the primary visual cortex and orienting network. The orienting network enhances processing of spatial information (i.e., dorsal where pathway) in the primary visual cortex and object pathway. The object pathway differentially selects relevant object characteristics (i.e., ventral, what pathway)for further processing. The executive control network projects to the orienting and object pathway to resolve conflicts in determining which stimuli to select for further processing. Selected input from the orienting network and primary visual cortex is processed in the object pathway and subsequently projected to the output area where an appropriate response is generated. (reprinted from Wang and Fan, 2007 with permission from MIT Press)

The model was also modified to "impair" the executive control network and simulated data were generated for comparison with performance on the ANT in a sample of individuals with schizophrenia. Performance between the two groups was highly correlated, leading the authors to conclude that attention impairments associated with schizophrenia are due to deficits in the executive control network [16]. In additional studies of schizophrenia using the ANT the executive control network is impaired and the alerting network appears to be intact [19-23]. With respect to the orienting network, small [19] to relatively no deficits are observed in most studies [20-23]; however, impairments have been found in studies employing other paradigms[14, 24-30]. As suggested by the Connectionist model and imaging research[31, 32], orienting can be further distinguished by whether attention modulation is required (top-down orienting) or not (bottom-up orienting). Inconsistencies in findings may be attributed to the degree of executive control involvement required for target detection. Research isolating bottom-up from top-down mechanisms suggests selective top-down orienting impairments in patients[27]; however, modulation necessary for target detection involves distinct mechanisms to select relevant input for further processing [31, 33-36]. Further, performance within networks is measured based on reaction time differences. Processing speed is consistently reduced in patients with schizophrenia[37, 38]. Failure to identify specific network differences may also be due to overall reductions in processing speed in the patient sample.

In general, the findings suggest that attention impairments characteristic of the disorder reflect a global deficit, which is attributed to impaired executive functioning. However, the executive control network involves multiple types of cognitive functioning. While the role of input is delineated by the model, the ANT is not designed to assess the contribution of early sensory processing. It remains unclear whether other mechanisms involved in attention modulation affect performance.

Cognitive Model of Attention

Recently, Luck and Gold (2008) proposed a cognitive model to further elucidate regulatory mechanisms involved in attention[15]. The model proposes that two types of attention can be functionally differentiated into **input selection** and **rule selection**. **Input selection** refers to selecting a subset of inputs for further cognitive processing. This is accomplished through facilitating processing of relevant inputs while inhibiting processing of irrelevant inputs, which is based on the Biased Competition Theory [39]. **Rule selection** is an executive control process in which an appropriate rule, or cognitive precept, is selected to determine which inputs to select for further sensory processing. Executive control is used to inhibit selection of irrelevant cognitive precepts and facilitate selection of relevant precepts. The precepts derived from rule selection serve to regulate input selection. Rule selection is accomplished by the prefrontal cortex. Information from rule selection is projected to the posterior cortical regions where input selection occurs. Input selection maps onto the anterior and posterior attention systems described in the Connectionist Model. Impaired performance on the Stroop task [40-45] suggests that deficits in rule selection are characteristic of the disorder; however, it is difficult to isolate the effects of attention from other aspects of cognitive control from such assessments.

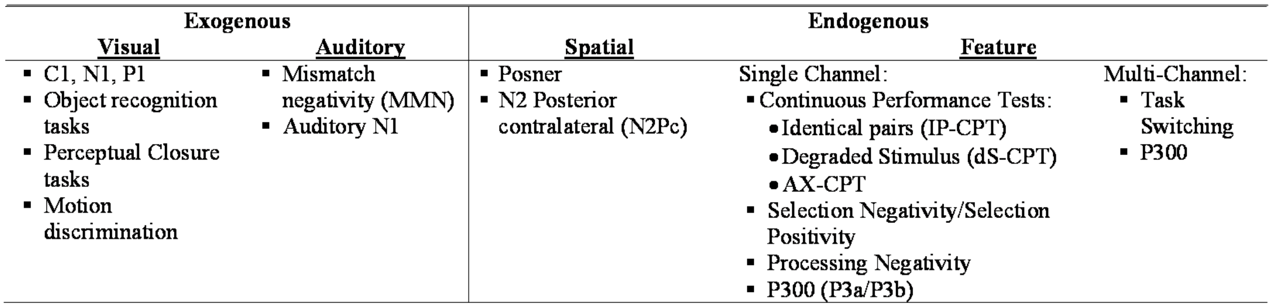
Luck and Gold propose that rule selection modulates input selection through two distinct processes: **control selection** and **implementation selection.** **Control selection** is the process of identifying inputs for further processing. It postulated to involve activity in prefrontal cortex and parietal areas. **Implementation selection** is the enhancement of processing of inputs selected from control selection, which occurs in sensory areas, such as the visual cortex. Impaired control selection in patients is previously documented [46] and has already been reviewed by Luck and Gold [15]. **Implementation selection** is associated with activity in sensory input areas and enables differential processing of selected and unselected inputs. This stage relies heavily on sensory processing. In the remaining sections, we will elaborate evidence from studies of attention and early sensory processing suggesting that impairments in implementation selection may partially account for impaired performance on attention tasks in schizophrenia.

Sensory Perspective of Attention

From a sensory point of view, attention networks can be divided into **endogenou***s* and **exogenous** depending upon whether attention allocation is volitional or stimulus driven, respectively [47-49]. Endogenous attention is further divided by the physical characteristics of stimulus used to direct focus into either **spatial**- or **feature**- based. **Spatial-based** attention refers to directing focus to a particular location within a stimulus. **Feature-based** refers to directing focus to a particular characteristic of a stimulus. In visual stimuli, this refers to color, size, shape or orientation. In auditory stimuli, examples of featured-based characteristics include loudness (i.e., intensity), pitch (i.e, frequency) or duration.

Although definitive schemata have yet to be developed, at least several subtypes of attention can be considered, based upon their relationship with sensory systems. Within each sensory system, tasks can be considered to involve single or multiple channels of sensory information; all of which, as per James[13], compete to take possession of the mind. Exogenous networks reflect pre-attentive processing and are differentiated based on sensory modality examined. Table 1 presents a summary of common paradigms used to assess exogenous and endogenous processing in auditory and visual modalities in schizophrenia.

Table 1.1. Summary of Paradigms Assessing Exogenous and Endogenous Processing in Schizophrenia



Exogenous		Endogenous		
Visual	**Auditory**	**Spatial**	**Feature**	
▪ C1, N1, P1 ▪ Object recognition tasks ▪ Perceptual Closure tasks ▪ Motion discrimination	▪ Mismatch negativity (MMN) ▪ Auditory N1	▪ Posner ▪ N2 Posterior contralateral (N2Pc)	Single Channel: ▪ Continuous Performance Tests: • Identical pairs (IP-CPT) • Degraded Stimulus (dS-CPT) • AX-CPT ▪ Selection Negativity/Selection Positivity ▪ Processing Negativity ▪ P300 (P3a/P3b)	Multi-Channel: ▪ Task Switching ▪ P300

Exogenous Processing

Although attention remains a widely discussed construct of interest in schizophrenia, relatively little research has focused on exogenous attention. Exogenous processing may be considered in two separate contexts. First, rather than being allocated volitionally, attention is “grabbed” by salient features of the environment, such as loud noises, bright lights and moving objects. Second, these bottom-up influences compete with top-down mechanisms for capture of attention. ERP components reflecting early cortical processing in both visual and auditory modalities provide evidence that deficits in sensory processing may contribute to observed performance impairments on traditional attention tasks[50].

Event Related Potentials

Event related potential (ERP) studies have been instrumental to sensory processing and attention research because of their high temporal resolution, which permits assessment of information flow within and across discrete brain regions, from the thalamus through primary and secondary sensory regions. Neural activity associated with sensory processing and attention is measured by examining the latency and amplitude of components reflecting exogenous and endogenous processing responses to visual or auditory stimuli. Comparisons of ERP activity during attended and unattended tasks allow discriminations between exogenous and endogenous processes involved in attention (either visual or auditory depending on the task) and the pattern of neural activity can be further differentiated for spatial- and feature-based attention based task requirements.

Visual Event Related Potentials

Event related potential components reflecting early visual processing include the C1, P1 and N1. The C1 [51] represents the earliest visual processing and is generated approximately 50-60 ms post stimulus presentation with activity localized in the primary visual cortex [52, 53]. The P1 (onset 70-130ms) and N1(onset 150-200ms) are generated subsequently in the extrastriate cortex and reflect dorsal and ventral visual stream processing, respectively (discussed further in Exogenous Visual Processing, page 14)[52, 54]. The P1 and N1 components are thought to reflect exogenous processing because they are produced even in the absence of attention. Amplitudes for both are, however, increased when subjects are required to attend to spatial characteristics of a visual field (referred to a “sensory gain”)[55-57], suggesting that the endogenous network modulates early sensory processing in secondary visual areas[58].

Communication between endogenous and exogenous networks is differentiated by different forms of attention. In a study using bilateral and unilateral visual stimuli for target detection, Luck et al[59], demonstrated differential modulation of the P1 and N1 components depending on task demands. Component comparisons between the tasks suggests that N1 is likely involved in orienting attention whereas P1 is involved in facilitating sensory processing of relevant visual input. Focusing on spatial characteristics of a visual scene also produces an endogenous component, referred to as the N2 posterior contralateral (N2pc) component. This is generated at 200-300ms in the contralateral occipitotemporal cortex[55, 56, 60].

Attending to features of a visual scene activates endogenous networks in other brain regions. The Selection Negativity (SN)[61] is negative deflecting endogenous component, generated in the occipito-temporal region in response to attending to features of a visual stimulus such as color[62] orientation[61, 63] and size (i.e., spatial frequency)[64, 65]. Onset occurs between 160 and 220ms. Accompanying this component is the frontal selection positivity (FSP or P2a), a positively deflecting endogenous component, with slightly earlier onset (150-200ms), which is localized in the frontal region[66]. All three components are involved in endogenous processes involved in attention; however, the N2pc reflects focused attention and the SN and P2a components reflect selective visual attention.

Auditory Event Related Potentials

Exogenous and endogenous processing associated with auditory attention has been isolated using dichotic listening[67] and distraction tasks[68-70], although distinctions between feature and spatial based attention remain unclear. Exogenous auditory components consist of the P1, N1 and Mismatch Negativity (MMN). The P1 and N1 are generated by any discernible auditory stimulus. The P1 reflects early auditory processing in the primary auditory cortex and the N1 reflects early auditory processing in both primary and secondary auditory cortices, with onset at 80-120ms [71]. The Mismatch Negativity (MMN) is also generated in secondary auditory cortical regions, with onset early as 50ms, although onset varies depending on the acoustic characteristic being processed[72-75]. While the MMN is also produced in the absence of attention[74, 76, 77], unlike the P1 and N1, it is only elicited in response to novel auditory stimulus presented within a sequence of sounds.

MMN components are often studied using the oddball paradigm. In this paradigm a tone that differs by one acoustic characteristic (i.e., pitch or frequency[78], intensity[79], duration[80] or location[81]) is presented randomly and infrequently (usually 10% of the time; referred to as the “deviant” stimuli) among repetitively presented stimuli (referred to as “standards”). MMN is calculated by subtracting the standard waveform from the deviant waveform. MMN is thought to reflect an “automatic change-detection” [82, 83] mechanism for processing the discordance between a pre-attentive sensory-memory representation of the preceding repetitively presented stimuli and the deviant stimuli[78]; often referred to as the “auditory sensory memory” (ASM) or echoic memory[84]. As such, it is thought to elicit an automatic attention switch to deviations in the auditory background. Accompanying the temporal activation is a slightly later frontal sub-component[72, 85, 86]. The sub-components are thought to reflect a tempo-frontal circuitry involved in recruitment of automatic switching of attention[68, 86]. The change detection signal generated in the temporal cortex likely triggers an automatic attention-switching response in the frontal region[68, 72, 86].

Repetitive frequently presented auditory stimuli produce small N1and P1 amplitudes. Neural activity is modulated to inhibit processing of redundant information (referred as “sensory gating” [87, 88]). In contrast, stimuli with salient features increase N1 amplitude[89]. Because of its response to novel stimuli and its close temporal and spatial proximity with the MMN, there has been debate as to whether the N1 and MMN reflect the same neural activity; however, several differences between the components have been identified(reviewed by Naatanen [82, 90]). N1 can be generated in response to an isolated auditory stimulus, whereas MMN requires the context of several previously presented stimuli to detect differences in acoustic characteristics. While N1 and MMN often overlap, onset of MMN is slightly later than N1 and the components activate separate neural populations within the supratemporal gyrus, with MMN activity being slightly anterior to N1[91-93] . Further, MMN activates specialized areas of the auditory cortex depending on the acoustic feature of deviation [94, 95] (reviewed by Alho [73]). Hence, N1 reflects response to sound onset and MMN reflects response to auditory change[96].

The distinction between N1 and MMN components is further supported by their relationships with endogenously modulated components on attention dependent tasks. In dichotic listening tasks, N1 amplitude is enhanced by attending to auditory deviant stimuli[97]. Accompanying the N1 is an endogenous negatively deflected component referred to as the Processing Negativity (PN)[67], which is observed as a slow, low-amplitude negative displacement occurring approximately 150ms post stimulus onset that persists for approximately 500ms (this varies depending the degree of difference between the deviant and standard stimuli), with activation in both temporal and frontal cortices[83, 98]. The temporal subcomponent is thought to reflect a comparison between the input and the voluntarily maintained representation of the to-be-attended stimulus (i.e., the “attentional trace”)[99, 100]. The frontal subcomponent reflects the maintenance of control processes required for selective attention[100, 101]. The relevant stimulus features are maintained in the attentional trace by the frontal PN control processes[101]. Each additional input elicits a comparison with the attentional trace, which is reflected in the PN. Greater similarities between the input and attention trace are associated with increased amplitudes and greater duration of the PN component because more time is required to identify differences [102, 103] (reviewed by Naatanen, 2011 [90]).

Attending to auditory stimuli also enhances MMN amplitude [73], which modulates later components involved in processing deviant stimuli. When a large discrepancy between the deviant and standards exists, a large MMN frontal subcomponent is elicited, which is accompanied by a subsequent P3a component. The P3a is one of the subcomponents of the P300, an endogenous component thought to reflect working memory and attention allocation necessary for stimulus discrimination. The amplitude, latency and scalp topography of the P300 differ depending on task demands, although the precise location of neural generators remains unclear (reviewed by Polich, 2007 [104]).

The P300 is divided into the P3a and P3b subcomponents, which differentially respond to targets and distracters and have different scalp topographies[105]. The P3a is elicited by novel, distracting, or complex stimuli; whereas the P3b occurs during target stimulus processing[106]. Scalp topography for the components varies depending task demands and degree of attention required[107]. The precise location of neural generators is unclear; however, ERP studies of patients with brain lesions suggest that the P3a and P3b components likely form a neural connection between the frontal and sensory cortices, with P3a being generated in the frontal region and P3b in the sensory regions (reviewed by Polich, 2007 [104]) The P3a component is elicited when sufficient attentional focus is engaged to process stimuli and the P3b occurs when attentional resources activate memory operations in the sensory cortices[108, 109]. The P3a involves switching of attention in response to deviant stimuli and is thought to reflect reorienting or covert shifting of attention[104]. Hence, the MMN frontal sub-component that occurs with the P3a likely reflects an attention switch that leads to the recruitment of endogenous processes involved in focus of attention.

To identify pre-attentive processing, the MMN can be subtracted from the waveform for unattended stimuli. The subtraction reveals an additional N2 component, which has slightly posterior topography compared to the N1. The P3a also accompanies the N2 waveform, a complex that is referred to as the N2-P3a complex. The N2-P3a complex is thought to reflect an “attention leak” because it is elicited in response to deviants in the unattended channel.

In summary, the relationships between the N1, MMN, PN, P3a and N2-P3a complex components can be used to identify exogenous and endogenous processes involved in auditory attention. The N1 and MMN involve early exogenous auditory processing that upregulates later endogenous processes. The PN component reflects endogenous processing involved in discrimination of stimulus characteristics. The P3a reflects both exogenous and endogenous re-orienting of attention directing focus on novel stimuli.

Visual Attention in Schizophrenia

Exogenous Visual Processing

In the past few decades, there has been a considerable amount of research demonstrating impairments in early visual processing in individuals with schizophrenia (for reviews, please refer to [4, 5]). With a recent increase in our understanding of the visual pathways, it has been possible to generate stimuli isolating functioning within each visual pathway to refine our understanding of the nature of the impairment characteristic of the disorder.

The visual system is divided into the **magnocellular** and **parvocellular** pathways. Specialized magnocellular and parvocellular cells in the retina project through the lateral geniculate nucleus to spatiotopically organized areas of the primary visual cortex and subsequently to higher-order cortical regions where they interact to produce a complete impression of the visual scene [110, 111]. Magnocellular cell bodies in the lateral geniculate nucleus are fewer and larger with more rapidly conducting projections. They are more sensitive to rapidly changing, low luminance-contrast, low spatial frequency (i.e., low resolution larger details of objects) aspects of visual information. Parvocellular cells are smaller, more abundant, and conduct visual input more slowly. They selectively respond to static, high contrast, smaller details (i.e., higher spatial frequency) and color of visual stimulus. [110, 112]

While recent evidence suggests that subcortical projections are not completely segregated or functionally independent[111, 113], the magnocellular pathway primarily projects dorsally to the parietal-occipital region, where information about motion and spatial location is processed (i.e. the “where” or dorsal stream). The parvocellular pathway projects ventrally to the tempero-occipital cortex, which is critical for object identification (i.e., the “what” or ventral stream)[110]. Because of its rapid speed of conductance and projections to higher-order cortical regions[114], the magnocellular pathway is also thought to play a critical role in overall stimulus organization [54, 115-119] and attention capture[120, 121]. Rapid transfer of information by the magnocellular pathway and dorsal stream provides a low resolution information template that is filled in by input from the slower-to-arrive parvocellular ventral stream[115, 122].

Evidence from behavioral, electrophysiological and imaging studies consistently demonstrates a selective magnocellular impairment in schizophrenia (for reviews, please refer to [4, 5]). Patients require higher contrast levels to successfully detect targets, particularly with dynamic and low spatial frequency stimuli[123-126]. Individuals with schizophrenia also have higher thresholds for discriminating velocity differences[127-129] and increased inhibition of surround perception on center-surround assessments[130]. Evidence from steady state visual evoke potential studies suggests that early visual processing activity is reduced during target detection[36] and patients’ response to magnocellular biased stimuli is attenuated compared to controls, whereas response to parvocellular biased stimuli is comparable[125].

Visual event related potential studies also demonstrate reductions in components thought to reflect early visual processing in response to magnocellular, but not parvocellular biased stimuli [54, 126], which is independent of illness duration and medication status[131]. For example, in one ERP study comparing response to magnocellular and parvocellular biased stimuli, reductions were found for the C1, P1 and N1 components in response to magnocellular biased stimuli, while components were intact in response to parvocellular biased stimuli. Such reductions appear to correlate with symptom severity[131] and predict contrast sensitivity impairments and deficits in complex visual processing[54, 126]. Results from fMRI studies also suggest that activity in regions involved in early visual processing is reduced in patients in response to magnocellular, but not parvocellular biased stimuli[132]. Further, electrophysiological and imagining evidence suggest that early impairments in magnocellular processing likely contribute to impairments in later, attention modulated processes in both the dorsal and ventral streams[54, 126, 133-135].

Endogenous Visual Attention

Endogenous, or top-down modulated attention, refers to attention that is under voluntary control. Assessments of endogenous attention in schizophrenia have been well established in visual processing. As indicated the Sensory Perspective of Attention section (page 7), endogenous visual attention is divided into **spatial**- and **feature**- based, depending on the relevant characteristics of the visual field used to direct focus. In **spatial-based** attention, focus is directed toward a specific location within the visual field and in **feature-based** attention focus is directed toward a specific physical characteristic (i.e., color, shape, spatial frequency, motion, etc.).

Spatial-based Visual Attention

Tasks requiring subjects to direct their attention to one part of the visual scene while suppressing attention to others are commonly used to assess spatial attention. The "Posner paradigm" is a classic spatial attention assessment, in which a cue is presented at a central location to indicate where a subsequent target is most likely to appear. Targets are presented in the absence of a preceding cue (null cue), preceded by cues indicating the location of the target (valid cues) or preceded by cues indicating a location opposite to where the target is displayed (invalid cues). Differences in reaction time between the cue conditions are thought to index spatial attention. In ERP studies, the Posner paradigm enhances P1 and N1 early visual components, suggesting top-down modulation of early sensory regions may be required for target detection.

A primary basis for the recent re-assessment of attentional impairment as a core feature of the disorder comes from studies of visual spatial attention. Studies evaluating spatial attention in schizophrenia consistently find a relative lack of attention deficit [26, 27, 136, 137]. Despite the lack of differential attention effects, patients show consistently prolonged reaction time to both cued and uncued conditions [14]. In a recent ERP study comparing the N2Pc in patients with schizophrenia and controls using the spatial cuing task, response times were significantly slower in patients compared to controls; however, accuracy was comparable between the groups. The N2pc latency and amplitude were also comparable between groups; whereas P1 amplitude was reduced. This suggests that performance may be impacted by impaired early visual processing. A revised version of the spatial cuing task was also included to determine whether speed of spatial attention may be attributed to the slowed reaction times. Negligible time differences were observed between groups, suggesting that slowed reaction times are unlikely attributed to endogenous mechanisms involved in spatial attention [137].

Feature-based Visual Attention

In feature-based attention tasks, subjects are instructed to attend to pre-designated target stimuli, while ignoring all other stimuli, which are designated as distracters. Stimuli are typically presented at central fixation so that spatial attention is not required. Accuracy requires maintenance of vigilance, encoding of visual input for target detection and response selection. Because targets can vary on more than one physical characteristic, feature-based attention can be used to assess both single-channel and multiple-channel sensory processing.

Single-Channel Assessments:

In single channel assessments, targets vary from distracters by one physical characteristic (i.e., color, shape, letter identity, etc.) and attention is measured by comparing accuracy and reaction time between stimuli of varying degrees of difficulty. Feature-based attention is most commonly assessed using versions of the Continuous Performance Task (CPT). In this task, subjects are asked to identify predefined targets among a series of visual stimuli consisting a targets and distracters presented on a computer screen. Patients don’t typically show performance impairments on easy versions of the CPT, such as the “no-back” task [138, 139], in which only simple detection of a pre-designated target is required. The CPT has been modified in several different versions to increase difficulty in order to establish between group differences. Although these modifications lead to differential performance in patients vs. controls, the tests are no longer pure attention tests in that modifications increase difficulty of non-attentional components as well.

For example, in the AX-CPT, subjects are asked to respond only when a target (e.g. “X”) is preceded by a valid cue (“A”). Task difficulty is manipulated by requiring detection of specific predetermined sequences while ignoring other letter sequences. The task requires encoding of contextual information to ensure proper response bias, which places demands on working memory. The valid cue must be translated or “decoded” into a representation that either facilitates response to a valid probe or inhibits response to an invalid probe [139]; thereby requiring intact executive control for accurate response. In traditional versions of the AX-CPT, patients are impaired in the ability to inhibit response to incorrectly cued targets (i.e., targets following a non-A), referred to as “false alarms” but not impaired in ignoring incorrect targets (i.e., letters other than A)[140-142]. In an ERP study, increased false alarms on the AX-CPT was associated with decreased frontocentral activation of later, endogenously modulated neural activity thought to reflect failure to utilize transient memory traces to guide behavior[141].

Modified versions of the AX-CPT have been used to assess the contributions of early visual processing and working memory by manipulating saliency of cues and the interstimulus interval between cues and targets. Detection of targets with more salient cues is likely accomplished through bottom-up pre-attentive processes involved in simple feature search; whereas, less salient cues likely require top-down modulation to conjoin features and discriminate between relevant and irrelevant stimulus characteristics. Using modified AX-CPT assessments, patient performance is comparable to controls for salient cues and disproportionately impaired for conjunctive cues. However, differences between interstimulus interval conditions suggest the initial encoding of contextual information is impaired in schizophrenia[143, 144]. The relative contribution of exogenous processing impairments could not be ascertained from these studies because salient color cues were used, likely biasing processing toward the parvocellular pathway, where functioning is relatively intact in patients (discussed in Exogenous Visual Processing , page 14). Results from a recent ERP study suggest that selective magnocellular processing impairments likely contribute to impaired encoding of contextual information required for accurate target detection on the AX-CPT [145].

The Degraded Stimulus Continuous Performance Test (DS-CPT) is a form of the CPT used to assess sustained attention and vigilance. In the DS-CPT, task difficulty is manipulated by degrading (i.e., blurring) visual stimuli. Assessments of performance are based on sensitivity (i.e., accuracy) and degradation in sensitivity over time (i.e., sensitivity degradations). Sensitivity degradations are thought to reflect vigilance because they measure the capacity to sustain attention at efficient levels. In healthy subjects, sensitivity degradations are accelerated for greater visually degraded stimuli[146] because they likely require a higher processing load. While studies have found more rapid sensitivity degradations in patients compared to controls[147], others failed to find significant differences[148]. Inconsistencies are likely attributed to the length of the assessment and the nature of the visual stimulus manipulation. To examine whether sensory processing impairments impact sensitivity degradations in patients, Mass et al [149] compared performance across trials between visual stimuli degraded to enhance low relative to high spatial frequencies. In patients, vigilance decreased over time, whereas in controls it increased. Overall accuracy differences between patients and controls were found for visual stimuli at the lowest degradation level only, which is likely caused by a selective impairment in visual processing. The findings suggest that schizophrenia is characterized by a differential decrement in vigilance over time and early sensory processing deficits likely contribute to performance impairments, which increases the processing load of visual input.

The Identical Pair CPT (IP-CPT) is another CPT task designed to assess sustained attention[150]. In this task, subjects are required to identify stimuli repetitions, rather than predesignated targets. Visual stimuli either consist of shapes or digits[151]. In the digit version, difficulty is manipulated by including 2, 3 and 4 digit stimuli. Successful target detection requires early exogenous processing to identify relevant visual stimulus as well as working memory to encode visual information[151, 152]. This version of the CPT is more difficult than others because more complicated stimuli are used and the targets are constantly shifting, requiring greater reliance on intact visual processing and processing speed. Overall accuracy and reaction time is consistently reduced in patients on both shape and digit versions of the task[153-156]. However, the pattern of performance across digit types is comparable between patients and controls[154], suggesting that endogenous processes required for target detection of more complex stimuli cannot account for performance differences. Early visual processing and working memory impairments likely contribute to overall performance differences.

Patients reliably demonstrate impaired performance across a wide variety of CPT tasks; however, there is little to suggest that performance differences are caused by attention impairments. Rather, voluntary attentional allocation seems to be among the few processes that are preserved, against a background of impairment in a range of functions, including working memory, executive control and sensory processing.

Multi-channel Assessments:

The idea of a global cognitive impairment in schizophrenia is also inconsistent with findings from multi-channel assessments. In these tasks, subjects must attend simultaneously to multiple stimulus aspects and select the appropriate target from the attending channel. In task switching paradigms, subjects are given at least two tasks (e.g., color task and a letter task) and are cued to switch between tasks either in repetitive sequence (single tasks) or are cued to switch from one task to another (mixed tasks) [157] (Figure 1.2 provides a schematic representation). Switching from one task to the other requires dynamic allocation of attention from one stimulus attribute to another, which places high demands on both rule selection (to select the appropriate precept) and input selection (to identify the appropriate stimulus characteristic) (discussed in Cognitive Model of Attention, page 3).

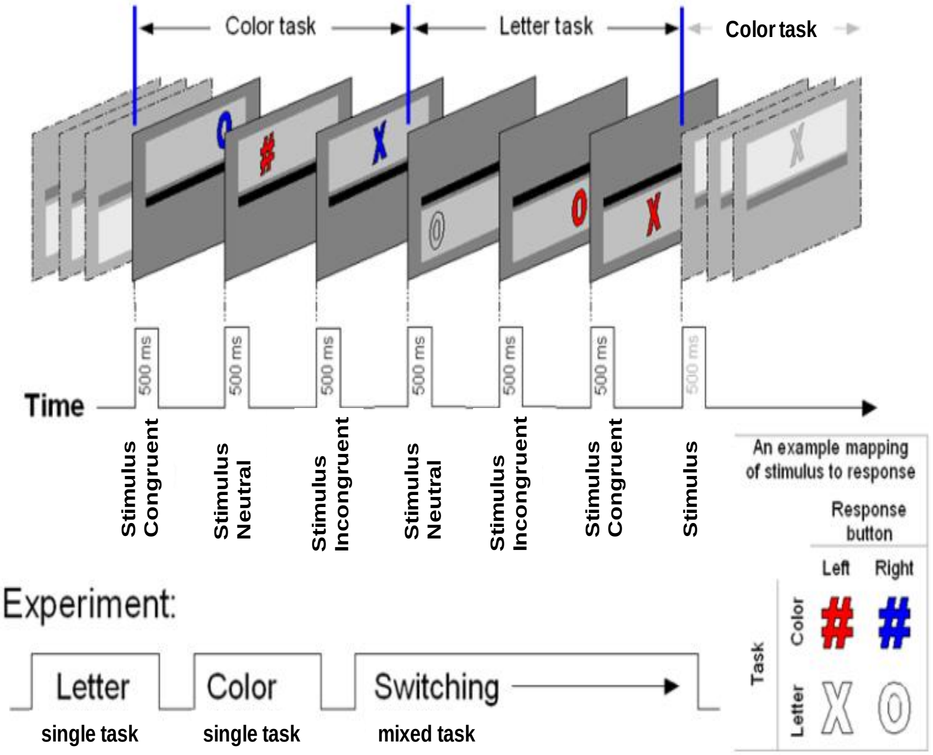


Figure 1.2. Task Switching Paradigm.

Subjects are either asked to perform the same task repeatedly (single tasks) or switch between two or more tasks (mixed tasks). Attention and processing load can be assessed by comparing reaction between single and switching task. (Reprinted from Wylie et al, 2000 with permission from Springer)

Switch costs reflect the difference in reaction time and accuracy to the first stimulus after a switch relative to the accuracy for subsequent stimuli. People are generally slower and less accurate to the first stimulus after a switch than to subsequent stimuli, reflecting time required to disengage and reengage attention. Decreased ability to select stimuli for further analysis would be expected to lead to substantial increases in switch costs. Most studies, however, found no differences between patients and controls on switch costs [158-160], suggesting intact attentional processes.

Mixing costs reflect performance differences when subjects are performing dual vs. single tasks, and represent costs of attending to multiple vs. single task factors. Mixed trials are also associated with greater working memory load because participants are required to retain information about two tasks rather than just one. Differential neural activity associated with varying the response-stimulus intervals [158] provides evidence for the confounding effects of additional cognitive processes, suggesting that comparisons between single and mixed tasks are not necessarily direct assessments of control processes involved in set-switching[157].

Manipulation of stimulus characteristics is used to control for the relative contribution of other cognitive processes. Reaction time differences between single and mixed tasks are observed when both tasks rely on the same stimulus set (i.e, congruent or univalent trials) [161]. **Congruency** costs reflect difference in performance in responding to stimuli when response contingencies are congruent for the two stimulus attributes vs. incongruent[161]. When tasks are congruent, they both elicit similar neural activity; therefore, performing them consecutively increases processing load and requires endogenous attention to select the task appropriate for input selection. When mixed tasks involve incongruent tasks (e.g., letter vs. color identification tasks), there is no increase in processing load because both are performed through serial exogenous mechanisms. Therefore, comparisons between congruent and incongruent tasks (congruency costs) can be used to discriminate between endogenous and exogenous processing, while controlling for the confounding effects associated with working memory. Unlike switching costs, both mixing and congruency costs are increased in schizophrenia[158-160], suggesting impaired performance is due to mechanisms other than endogenous attention impairments.

Like most attention assessments, in task switching paradigms stimuli are typically not chosen based upon psychophysical characteristics, but based upon experimental convenience. In a recent study[162], however, the attributes chosen consisted of color, which would be expected to preferentially activate parvocellular neurons, vs. form (letter identity), which would activate both magnocellular and parvocellular systems, enabling isolation of sensory impairments established in schizophrenia[54, 116, 118, 125, 127, 129, 130, 132-134, 163, 164]. Consistent with previous research, no differences were found for switch costs, whereas patients had increased mixing and congruency costs. Patients also showed preferential deficits for letter vs. color performance, despite similar psychometric properties of the two tests in controls, suggesting that the nature of the stimulus attribute to be attended might dictate, at least in part, the nature of the behavioral outcome.

Auditory Attention in Schizophrenia

Exogenous Auditory Processing

Impairments in basic auditory processing associated with schizophrenia are demonstrated by behavioral studies and ERP assessments of exogenous components. Patients are less accurate at discriminating pitch differences[165] and matching tones [166-168]. As indicated in the Auditory Event Related Potentials (page 10), exogenous attention capture associated with auditory processing is characterized by the N1 and the MMN ERP components. N1 reflects activity in response to isolated auditory events and MMN indexes a specialized mechanism for detecting change in auditory stimulus characteristics [70]. Reductions in N1 are observed in passive listening paradigms[169, 170] and in discrimination tasks for both target detection and distracters [171-173], suggesting that impairments cannot be attributed to attention deficits alone.

Impaired early sensory processing likely reflects an inability to efficiently filter irrelevant auditory input. When the same auditory stimulus is presented repetitively, the N1 amplitude is reduced due to sensory gating, a normal inhibitory response to selectively filtering redundant auditory input (discussed in Auditory Event Related Potentials, page 10). In an ERP study in which subjects participated in a visual distraction paradigm while passively listening to high frequency, short duration tone pairs, N1 amplitude elicited for the first tone was reduced in patients compared to controls. No significant amplitude differences between the tone pairs were observed for patients, whereas amplitude in response to the second tone was significantly reduced in controls[174]. Similar results were produced in a study using identical paired clicks [175]. The results from both studies suggest that exogenous processes involved in inhibiting responses to irrelevant input are impaired in individuals with schizophrenia.

Evidence for impaired early auditory processing is also provided by assessments of the MMN component. Deficits in MMN were first demonstrated by Shelley et al using an oddball paradigm with duration deviants. Patient’s MMN amplitude for deviants was reduced compared to controls whereas no difference was found for MMN amplitudes for standards[176]. Several studies have since replicated these results using deviants for duration [141, 177-179], pitch [141, 180] and frequency [181-183]. Results from a recent meta-analysis of 36 studies found that the effect size of the difference between MMN amplitude in patients and controls was 0.99, providing evidence that MMN reductions are a robust characteristic of schizophrenia [6]. Paradigm comparisons reveal that the degree of amplitude reduction depends on deviant stimulus probability, inter-stimulus interval, and the degree of discrepancy between standards and deviants [177, 184] . Results from a passive listening study comparing MMN amplitude in response to conditions with longer or shorter interstimulus intervals and different deviant-stimulus probabilities suggest that the pattern of impairment in patients reflects a deficit in initial encoding of sensory representation rather retrieval of information required for comparison of deviant characteristics[182].

Assessments of MMN temporal and frontal subcomponents suggest impairments associated with pre-attentive processing of deviant stimuli are attributed to dysfunctional auditory cortex activity involved in initial encoding of the auditory sensory memory. Although studies have found selective impairments in the frontal component[185, 186], failure to detect impaired temporal activity may be due to methodological differences. In these studies, a modified version of the oddball paradigm was used in which a different standard is presented immediately following the presentation of the deviant (referred to as the “roving paradigm”) [185, 186]. The authors concluded that an inability to detect differences in the temporal component may have been due to habituation to the standards caused by the roving technique. Other studies using traditional oddball paradigms have found MMN attenuation in the temporal subcomponent[187, 188].

Impairments in MMN have been demonstrated with such consistency it has been suggested as a potential endophenotype for the disorder [189]. Comparisons with other clinical populations suggest that impaired MMN is specific to schizophrenia[190]. While typically not observed in first episode patients[179, 180, 191, 192], the degree of impairment appears to be correlated with illness duration [191, 193, 194], symptom severity (reviewed by [6]), Global Assessment of Functioning[195], social cognition[196] and presence of hallucinations [197].

Exogenous auditory processing associated with feature-based attention is well characterized in patients with schizophrenia; however, relatively few studies assessing early exogenous processing associated with spatial attention have been published[81, 198]. Behavioral assessments of spatial discrimination abilities have demonstrated that patients with schizophrenia are less accurate than controls at determining the location of a sound relative to the midline[198].

Event related potential studies of early exogenous processing associated with spatial discrimination are limited and the findings are inconsistent. A recent ERP study using inter-aural cue manipulation to simulate location differences found reduced amplitude for inter-aural time but not loudness differences. Patients were also less accurate at detecting sound location changes in a behavioral discrimination task [81]. A second study employing inter-aural time differences failed to find differences in MMN amplitude between patients and controls[197]. Alain et al [199] found reductions in MMN in response binaural location deviants (i.e., sound presented in either the left or right ear); however, the auditory stimuli were comprised of both feature and spatial deviants. In general, these studies are limited in their generalizability to real-world situations because they relied on manipulation of inter-aural cues using headphones to simulate location differences rather than free field sound.

Spatial localization impairments are of particular importance because it has been hypothesized that hallucinations may result from an inability to distinguish between internal and external sources of sound (referred to as the “Mislocation Hypothesis” [11, 12]). Evidence from functional [7, 200-202] and structural [8, 203] imaging studies suggests that hallucinations are associated with abnormalities in supratemporal gyrus, where early exogenous processing is also localized. Further, reductions in MMN amplitude may be specific to individuals with schizophrenia who experience hallucinations[197].

Endogenous Auditory Attention

Previous studies suggest that impairments in exogenous processing associated with schizophrenia may reflect an inability to efficiently process sensory input, leading to increased processing load. Increased processing load places greater demands on networks involved in selectively filtering relevant characteristics, which may lead to impairments in later endogenously modulated processes [204].

Discrimination studies can be used to measure the impact that impairments on early exogenous sensory processing have on later endogenously modulated components by comparing response to targets and distracters.   In dichotic listening discrimination tasks, subjects are presented a series of auditory stimuli simultaneously in each ear and are instructed to identify deviants in one ear while ignoring input from the other. Comparisons of attended and unattended conditions of exogenous and endogenous components can be used to examine the mechanisms underlying attention impairments. ERP assessments of the P300 and PN components provide evidence that exogenous impairments likely impact later endogenous networks involved in attention.

As indicated in the Auditory Event Related Potentials section, (page 10), the N1 and MMN components are followed by the endogenous P300 (P3), which reflects working memory and allocation of attention associated with stimulus processing. The earliest and most well studied cognitive abnormality in schizophrenia is a reduction in the P3 amplitude [104, 205-209] and it’s subcomponents[209-211]. In a dichotic listening discrimination auditory oddball target detection task, using complex tones and consonant vowel sounds as auditory stimuli, both the N1 and N2 components were significantly reduced in patients compared to controls; however, the P3 amplitude was comparable between the groups. Patient accuracy was strongly correlated with P3 amplitude[212]. Increased activity of endogenous components may reflect upregulation of later endogenous mechanisms to compensate for impaired early sensory processing. Other discrimination studies using simple auditory stimuli have found that reductions in N1 are accompanied by reduced P3 amplitude in patients for both targets and distracters[171-173]. In ERP studies employing passive listening and distraction paradigms, reductions in MMN amplitude are accompanied by reduced P3a amplitude in patients with schizophrenia as well [199, 213, 214].

Processing negativity (PN) is an endogenous component evoked by deviant stimulus in the attended channel during dichotic listening tasks. It reflects discrimination of deviants from standards through selective attention of deviating physical characteristics (discussed in the Auditory Event Related Potentials section, page 10). Although not as well studied, later onset and reduced PN amplitude has also been observed in schizophrenia [215, 216], suggesting that endogenous mechanisms involved in processing physical characteristics are likely impaired. In a recent dichotic listening study using short and long ISIs, reduced N1 amplitude for standards and PN amplitude for deviants was observed for patients. In the long ISI conditions, a reduction in slow positive potentials for unattended stimuli was also observed, suggesting impairments are likely attributed to an inability to selectively filter irrelevant auditory input[217].

In summary, ERP studies of auditory attention provide substantial evidence that schizophrenia is associated with impairments in both exogenous and endogenous networks involved in auditory attention. Impairments in early exogenous processing leads to deficits in initial encoding of auditory input.   Poor initial encoding likely impacts later endogenous modulated networks.

Conclusion

Taken together, the findings from both auditory and visual studies suggest that dysfunction associated with both exogenous and endogenous networks likely contributes to observed performance impairments characteristic of schizophrenia on traditional measures of attention. Early pre-attentive sensory processing deficits likely impede encoding of sensory input, which impacts later endogenously modulated processes involved in target detection. Such impairments adversely impact daily functioning and symptom severity.

Dissertation Studies: Assessments of Early Exogenous Processing

There is emerging evidence to suggest that early sensory processing abnormalities are characteristic of schizophrenia. Such abnormalities likely contribute to severity of cognitive and positive symptoms. Attention impairments are consistently demonstrated in schizophrenia; however, the underlying mechanisms contributing to such impairments are poorly understood. The purpose of the present dissertation was to: 1. further characterize early sensory processing impairments associated schizophrenia, 2. examine their contribution to impaired performance on traditional measures of attention and 3. explore their impact on symptom severity.

In subsequent chapters, three studies assessing early exogenous processing in visual and auditory modalities in patients with schizophrenia will be discussed. The first study examined the role of early visual processing impairments on observed performance differences on visual attention assessments (Chapter 2). The remaining two studies used behavioral and electrophysiological investigations to assess auditory spatial localization in schizophrenia (Chapters 3 and 4).

Chapter 2: Early Exogenous Visual Processing and Visual Attention

As indicated in the Endogenous Visual Attention section (page 16), performance differences on traditional versions of the CPT may be caused by deficits in attention and other aspects of cognitive functioning required for accurate target detection. The DS-CPT places high demands on perceptual processing, whereas as the IP-CPT places high demands on working memory. Manipulating both conditions in the same paradigm enables isolation of the contributions of early sensory impairments and higher-order cognitive processing to impaired performance. The study described in Chapter 2 examined the contribution of early visual processing to performance differences between patients and controls on traditional assessments of visual attention.

The first experiment compared performance between patients diagnosed with schizophrenia and healthy controls on the traditional Identical Pairs Continuous Performance Task, digits (IP-CPT). To assess the role of early visual processing on accuracy, a modified version of the IP-CPT (mIP-CPT) was also used. In this task, the spatial frequencies of visual stimuli were manipulated to selectively bias processing towards the magnocellular/parvocellular pathway. The second experiment compared performance between patients and controls on the Attention Network Task (ANT). Performance from the three attention tasks was compared to assessments of early visual processing. In the third experiment, assessments of cognitive functioning and early visual processing were used to predict between group performance differences on the traditional IP-CPT in a larger cohort. To identify predictors of observed performance differences between patients and controls, the impact of early visual processing and cognitive functioning on performance was explored.

Chapter 3: Auditory Spatial Localization

As indicated in the Exogenous Auditory Processing section (page 24), impairments in early auditory processing associated with discrimination of feature characteristics are well documented; however, few studies have assessed spatial localization abilities in schizophrenia. The study described in Chapter 3 assessed spatial localization in patients and controls using two behavioral paradigms. The first paradigm examined the ability to determine the location of sound in space (i.e., sound localization). The second paradigm examined the ability to discriminate between different locations of sound sources (spatial discrimination). For both paradigms, stimuli were presented from seven speakers concavely arranged with 30 degrees spatial separation in the horizontal plane. Auditory stimuli consisted of simple 1000 Hz 10ms rise/fall tones 300 ms in duration. The relationship between performance on both tasks and severity of hallucinations and cognitive symptoms was also assessed.

Chapter 4: Early Exogenous Auditory Processing and Spatial Localization

The study described in Chapter 4 further elucidates the underlying mechanisms responsible for spatial localization impairments by comparing performance between patients diagnosed with schizophrenia and controls on a behavioral discrimination task and a passive listening ERP investigation of MMN response to location, duration and frequency deviants. In both studies, simple tones were presented from eleven speakers concavely arranged with 15° spatial separation from 0°to 60° and at 90° with respect to the midline in both hemifields. The relationship between severity of hallucinations and positive thought disorder and spatial discrimination performance and MMN response was also examined.

Summary

There is growing evidence that sensory processing impairments are a characteristic of schizophrenia. In the present dissertation, assessments of early visual and auditory processing extend upon previous research. The results provide evidence confirming the existence of such impairments and explore their contribution to attention impairments and positive symptom severity.

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Chapter 2: Early Visual Processing and Visual Attention

The Contribution of Early Visual Processing Deficits to Performance Impairments on Traditional Measures of Attention in Schizophrenia

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Abstract

Background: Attention impairments are considered a hallmark of cognitive dysfunction in schizophrenia. However, performance on traditional attention assessments relies on intact processing of other aspects of cognitive functioning known to be disrupted in schizophrenia, such as visual processing. Previous studies consistently demonstrate a selective impairment in magnocellular visual processing in schizophrenia. Such impairments may contribute to the performance differences on traditional assessments of attention.

Methods: Three experiments were conducted on patients diagnosed with schizophrenia spectrum disorders and controls using: the Identical Pairs Continuous Performance Task (IP-CPT), digits version, a modified version of the IP-CPT using the same stimuli with spatial frequency (SF) manipulations to either bias processing towards the magnocellular\parvocellular pathway (mIP-CPT), and the Attention Network Task (ANT). Early visual processing was assessed by measuring contrast sensitivity (CS) with varying degrees of SF. Standardized assessments of working memory and processing speed were used to index cognitive functioning. Structural equation modeling (SEM) was performed to assess the relationships between visual processing, cognitive functioning and IP-CPT performance.

Results: In both the traditional and modified IP-CPT, overall accuracy was reduced in patients compared to controls and the pattern of performance across digits was comparable between the groups. On the mIP-CPT, accuracy was improved in low SF conditions for controls, whereas performance remained unaffected in patients. Performance on the mIP-CPT was correlated with

CS, particularly at low SF levels. On the ANT, accuracy and reaction time were significantly reduced in patients compared to controls; however, no between group differences were found for individual attention networks. ANT performance was also correlated with CS. The results from the SEM revealed that early visual processing likely impacts cognitive functioning, which leads to IP-CPT performance differences.

Conclusion: Selective magnocellular processing impairments characteristic of schizophrenia likely contribute to performance differences on traditional assessments of visual attention.

Introduction

Schizophrenia is a neuropsychiatric illness associated with widespread deficits in neurocognition, including attention[1-3], working memory[4] and visual perception[5]. Attention impairments are considered one of the key components of neurocognitive dysfunction and likely contribute to impaired daily functioning[6-8]. Conventional assessments of attention often have high sensory processing demands and require employment of additional components of cognitive functioning[4], leaving unresolved the degree to which observed performance impairments are truly due attention dysfunction.

While there are conflicting theories about attention, the consensus is that it does not constitute a unitary phenomenon, but instead represents concerted and competitive activity of multiple overlapping networks. In schizophrenia, many forms of attention that appear extremely effortful seem paradoxically intact, while some that require little conscious effort appear substantially impaired. This paradox has been discussed by Luck and Gold [2] who proposed a dichotomy between **control** and **implementation selection**, suggesting that attention impairments characteristic of the disorder arise from an inability to identify relevant input for processing. Similarly, Wang and Fan [1, 3] stress the potential role of executive dysfunction in apparent attention deficits associated with schizophrenia, while suggesting that other aspects of attentional networks, such as orienting and alerting, remain intact. The present study further considers this paradox from a sensory framework and points to the potential contributions of early visual processing deficits to impaired performance on traditional attention assessments.

Sensory Framework of Attention

From a sensory perspective, attention networks can be divided into endogenous and exogenous depending upon whether attention is volitional or stimulus driven. [9-11].

Endogenous networks involve top-down modulation to process attended information by directing neuronal competition. Exogenous networks involve automatic, pre-attentive processing of rudimentary physical features of visual stimulus, such as color, orientation, size, and shape.

Endogenous Visual Attention in Schizophrenia

Endogenous visual attention is divided into **spatial**- and **feature**- based, depending on the relevant characteristics of the visual field used to direct focus. In **spatial-based** attention, focus is directed toward a specific location within the visual field and in **feature-based** attention focus is directed toward a specific physical characteristic (i.e., color, shape, spatial frequency, motion, etc.).

The Continuous Performance Task (CPT) is target identification task used to measure feature-based visual attention[12]. While comparisons are limited by ceiling effects, patients don't typically show performance impairments on easy versions of the CPT, such as the "no-back" task[13, 14], in which only simple detection of a pre-designated target is required. Modified versions increase difficulty and establish between group differences [15]; however, the tasks are no longer pure attention assessments because modifications increase difficulty of non-attentional components as well.

In the Identical Pair CPT (IP-CPT),subjects are required to identify stimuli repetitions, rather than pre-designated targets [16]. Performance is consistently impaired in patients with schizophrenia [17-19], regardless of medication status [19] and disease chronicity [18]. However, performance relies on intact sensory processing and working memory for accurate detection and encoding of contextual information[20]. It is difficult to ascertain how much of the observed patient performance impairments are attributed to attention or other aspects of cognitive functioning.

The Attention Network task (ANT) is target detection task designed to isolate functioning from the three attention networks proposed by the Connectionist Model[21]. Studies of schizophrenia using the ANT generally yield impairments in the executive control network, whereas the alerting and orienting networks appear to be intact [3, 22-25]. Other paradigms assessing the orienting network have, however, identified impairments [26-33]. Inconsistencies may be attributed to the relative lack of sensitivity of the ANT to identify subtle early sensory impairments associated with selecting relevant input for further processing [34-38]. Further, it is possible that within networks dysfunction cannot be identified because assessments are based on reaction time comparisons and reduced processing speed is characteristic of the disorder[39, 40].

Exogenous Processing and Attention

Evidence from early visual processing research suggests that dysfunction of the exogenous, bottom-up processing network may contribute to impairments in visual attention. The visual system is divided into the **magnocellular** and **parvocellular** pathways. The magnocellular pathway processes transient, achromatic, low luminance-contrast, larger details (i.e., low spatial frequency) of visual information and the parvocellular pathway selectively responds to static, color, high contrast, and smaller details (i.e., higher spatial frequency) [41, 42]. Results from behavioral, electrophysiological and imaging studies suggest schizophrenia is associated with a selective magnocellular impairment (for reviews, please refer to [5, 43]). Patients require higher contrast levels to successfully detect targets, particularly with dynamic and low spatial frequency stimuli[44-47]. Electrophysiological studies reveal reductions in early visual processing in patients during target detection[37], with selective attenuation in processing of magnocellular biased stimuli [46] [47, 48].

The present study assesses whether additional cognitive functioning deficits contribute to impaired performance on conventional assessments of visual attention in schizophrenia using data derived from three experiments. In Experiment 1, we compared performance between patients diagnosed schizophrenia spectrum disorders (patients) and controls on the IP-CPT with stimuli containing either 2, 3 or 4 digits. To assess the potential role of early visual processing, we included a modified version of the IP-CPT containing the same digit stimuli with spatial frequency (SF) manipulations to selectively bias processing either towards the magnocellular (i.e., low spatial frequency (LSF)) or parvocellular (i.e., high spatial frequency (HSF)) pathway. Performance was correlated with contrast sensitivity (CS) measures of early visual processing using magnocellular\parvocellular bias visual stimuli. In Experiment 2, we used the ANT to examine whether differences existed between groups on overall attention performance and within attention networks. To determine if early visual processing is associated with performance, correlations with CS measures were also calculated. In experiment 3, we used linear regression analysis and structural equation modeling to assess the relationships between visual processing, standardized assessments of cognitive functioning and traditional IP-CPT performance.

In Experiment 1, we predicted that overall accuracy on both versions of IP-CPT would be reduced in patients compared to controls and the overall pattern of performance across digit types would be comparable between the groups. On the mIP-CPT, we predicted that patient performance would be differentially impaired for LSF and performance would be correlated with CS. In experiment 2, we predicted that overall ANT accuracy and reaction time would be reduced in patients compared to controls. However, because within network performance is measured based on reaction time comparisons and reduced processing speed is a characteristic of the disorder, performance within networks would likely be comparable between the groups. Overall accuracy and RT were predicted to be correlated with CS. In experiment 3, we predicted that IP-CPT group performance differences would be mediated by visual processing and cognitive functioning.

Methods

Participants

Sample sizes varied by experiment and significant differences were found for gender distribution in Experiments 2 and 3 (Table 2.1). Parental socioeconomic status was assessed using the Hollingshead Scale for Socioeconomic Status[49]. No significant differences were found for age at interview or parental socioeconomic status in any of the experiments.

Table 2.1. Demographic Characteristics

	Experiment 1 (Modified IP-CPT)				**Experiment 2 (ANT)**				**Experiment 3 (Traditional IP-CPT)**			
	Patients (n = 32)	**Controls (n=27)**	**X^2**	**p-value[a]**	**Patients (n = 28)**	**Controls (n=45)**	**X^2**	**p-value[a]**	**Patients (n = 92)**	**Controls (n=113)**	**X^2**	**p-value[a]**
Gender												
Male(n(%))	26(81)	18 (67)	1.64	0.200	25 (89)	25 (58)	8.13	**0.004**	77 (84)	75 (66)	7.94	**0.005**
Female (n (%))	6(19)	9 (33)			3 (11)	19 (42)			15 (16)	38 (34)		
	X(SE)	**X(SE)**	**p-value[a]**		**X(SE)**	**X(SE)**	**p-value[a]**		**X(SE)**	**X(SE)**	**p-value[a]**	
Age (years)[b]	41.2(9.9)	39.4(12.3)	0.129		38.0(9.4)	35.2 (11.7)	0.062		37.9 (10.7)	39.6 (16.4)	0.073	
Parental SES[c, d]	41.1(15.3)	38.2(14.8)	0.678		36.7(12.1)	44.2(12.2)	0.304		35.0 (11.6)	43.7 (14.0)	0.077	

[a] two-tailed; [b] $N_{Missing}$: Experiment 1: Controls = 2, Experiment 2: Controls= 2, Experiment 3: Controls = 5, [c] $N_{missing}$: Experiment 1: Patients = 6, Controls = 2, Experiment 2: Patients = 10, Controls= 1, Experiment 3: Patients =26 , Controls = 3; [d] Parental SES calculated based on the Hollingshead scale for Socioeconomic Status

For all three experiments, patients were recruited from an inpatient unit and residential care facilities associated with Nathan Kline Institute for Psychiatric Research. Diagnosis was made based on review of clinical records and the Structured Clinical Interview for DSM-IV (SCID)[50]. The SCID is a semi-structured clinical interview for major Axis-I psychiatric disorders using DSM-IV diagnostic criteria[51]. The Clinical Research Division of the Nathan Kline Institute maintains a pool of graduate-level certified SCID raters who have completed a training program based on the 11-hour SCID-101 recorded training series and have demonstrated interview and rating skills. In addition to interviewing the patient, SCID raters review all available records. Diagnostic challenges are resolved by case conferences involving at least two psychiatrists and the rater.

Patient sample characteristics are presented in Table 2.2. The majority of the patients for all three experiments were diagnosed with schizophrenia, undifferentiated subtype. At the time of the experiment, the majority of the patients were taking atypical antipsychotics and approximately half of the patients resided in the inpatient unit and half in residential care facilities. For all three experiments average age at first hospitalization was in the early- to mid-20's and duration of illness was 15 years.

Table 2.2. Patient Sample Characteristics

	Experiment 1: mIP-CPT **n (%)**	**Experiment 2: ANT** **n (%)**	**Experiment 3: IP-CPT** **n (%)**
Diagnosis			
Schizophrenia, undifferentiated	15 (47)	9 (32)	34 (37)
Schizophrenia, paranoid	7 (22)	8 (29)	28 (30)
Schizophrenia, disorganized	0 (0)	0 (0)	1 (1)
Schizophrenia, residual	4 (13)	2 (7)	8 (9)
Schizoaffective	4 (12)	4 (14)	8 (9)
Schizoaffective, bipolar	1 (3)	5 (18)	9 (10)
Schizoaffective, depression	1 (3)	0 (0)	4 (4)
Medication Status[a]			
Atypical antipsychotics only	24 (80)	21 (75)	55 (60)
Typical antipsychotics only	1 (3)	1 (4)	11 (12)
Combination	5 (17)	6 (21)	23 (25)
Patient Status			
Inpatient	15 (47)	11 (40)	47 (51)
Residential Care Facilities	17 (53)	17 (60)	45 (49)
	X (SE)	**X (SE)**	**X(SE)**
Age of first hospitalization (years)[b]	25.8 (8.9)	23.5 (7.4)	22.9 (8.7)
Illness duration (years)[c]	15.3 (9.3)	15.0 (9.2)	15.0 (10.1)

[a] $N_{missing}$: Experiment 1: 2, Experiment 3= 3; [b] $N_{missing}$: Experiment 2= 2, Experiment 3= 10 [c] $N_{missing}$: Experiment 2= 2, Experiment 3=9

In both groups, individuals were excluded if they had a history of organic brain disorder, mental retardation, past drug or alcohol dependence or current drug or alcohol abuse. All participants underwent an opthamological examination and an assessment of color vision.

Individuals were excluded if they had an ocular disease or were found to have a deficit in color vision. Deficits in red-green vision were assessed using the Ishihara Test [52] and deficits in blue-yellow were assessed using The Farmsworth Panel D-5 test [53] and the Lanthony Desaturated Panel D-15 test[54]. All participants had color vision 20/30 corrected. Controls were excluded if they met criteria for an Axis I psychiatric disorder. Participants provided informed consent prior to participation and the protocol was approved by the Institutional Review Boards at the Nathan Kline Institute for Psychiatric Research and the City University of New York, Graduate Center.

Experiments 1 and 3

Traditional IP-CPT The traditional IP-CPT is a feature-based visual attention task[16]. In this paradigm, visual stimuli consisted of digit pairs and difficulty was manipulated by increasing the number of digits (i.e., 2, 3, or 4). Stimuli were presented on a computer monitor at a viewing distance of 100cm. Subjects were instructed to button press when identical stimuli were presented sequentially.

Modified IP-CPT (mIP-CPT) To assess the role of visual processing on performance, a modified version of the IP-CPT was used in which the same 2,3, and 4 digit stimuli were presented and SF was manipulated to either be neutral (same as IP-CPT), low (biasing the magnocellular pathway), or high (biasing the parvocellular pathway). Stimuli pairs were either presented with the same (congruent) or different (incongruent) SF levels. For both tasks, performance was measured by calculating dprime (d’) for each condition[55]. Larger values of d’ indicate greater accuracy.

Experiment 2

Attention Network Task (ANT). The ANT combines the Posner paradigm and Flanker task to assess the alerting, orienting, and conflict (executive control) networks [21]. Targets were arrows presented on a computer screen and subjects were instructed to indicate whether the arrow pointed to the left or right (Figure 2.1 provides a schematic representation of the task). The target location varied by trial. Targets were either preceded by: 1. center cues, 2. spatial cues, 3. no cue, or 4. double cues to inform the location of the impeding target. The alerting network was calculated by subtracting the mean reaction time (RT) of the double cue and no cue conditions. The orienting network was calculated by subtracting the mean RT of the spatial cue and center cue conditions. Targets also contained flankers with 1. lines (neutral), 2. arrows consistent with the target (congruent) or 3.arrows inconsistent with the target (incongruent). The executive control network was measured by calculating the difference in reaction time between congruent and incongruent target conditions.

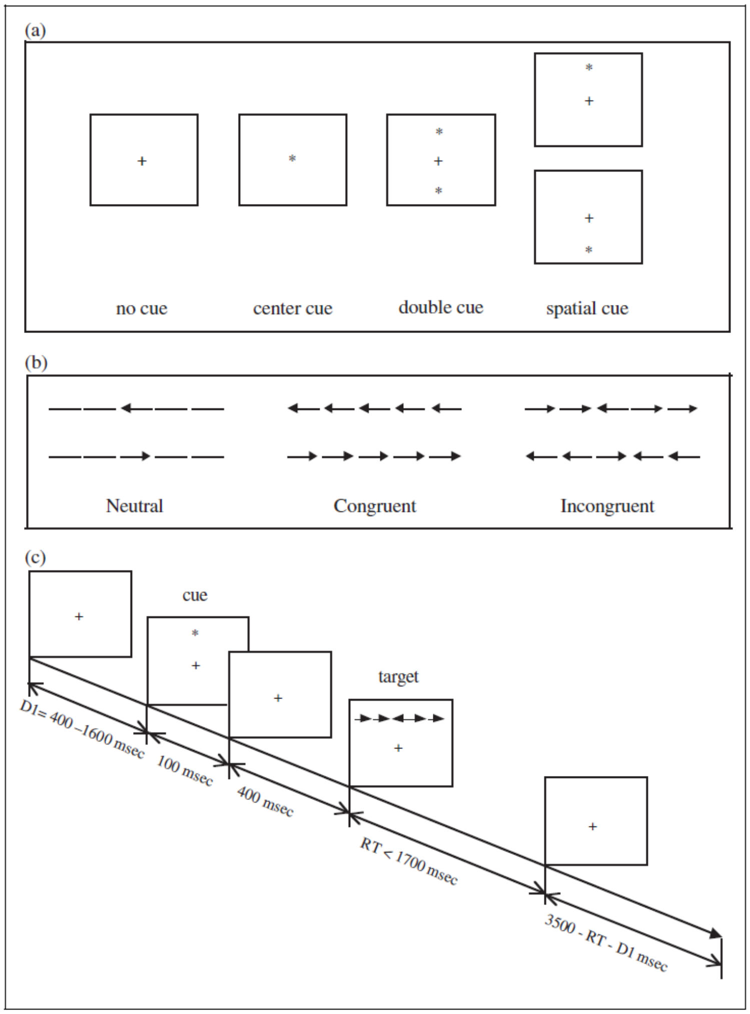


Figure 2.1. Attention Network Task.

(a). The four cue conditions (b) The six stimuli used in the present experiment (c) An example of the procedure (Reprinted from Fan et al, 2002 with permission from MIT Press)

Visual Processing Assessment

Contrast Sensitivity. Assessments of CS relative to varying degrees of SF were used to measure magnocellular\parvocellular visual processing[5]. Visual stimuli were presented at a 160cm viewing distance and the grating at a viewing field subtended 5.7° X 5.7° of visual angle. Horizontal sine-wave gratings were presented for 500 milliseconds at SF of 0.5, 1, 7 and 21 cycles per degree. Spatial frequency refers to the number of cycles of light and dark bars in 1 degree of visual angle[56]. Spatial frequencies were presented randomly on either the right or left half of the visual display. Simultaneously displayed on the other half was a uniform field of equal space average luminance to the pattern of field. Participants verbally indicated which side of the display contained the grating and an experimenter recorded responses with a mouse-button press. An up-and-down transformed response rule was used to determine the contrast thresholds associated with 70.7% correct responses for each SF. Within each SF, contrast was changed in 3dB increments for each correct and incorrect response until 2 errors were made. Subsequently, the up-and-down transform response rule began and contrast was changed in 1.5dB increments. Contrast threshold was calculated based on the mean of 10 reversals and contrast sensitivity (CS) was calculated by taking the reciprocal of contrast threshold. Performance comparisons across stimuli types were used to identify differences in processing between the visual pathways.

Neuropsychological Assessments

Neuropsychological Functioning. Working memory and processing speed were measured based on composite t-scores from The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) subscales[57]. Working memory consisted of Letter Number Sequencing and Spatial Span subscales. Processing Speed included Category Fluency, Symbol Coding, and Trail Making A subscales.

Statistical Analysis

<u>Experiment 1</u>

Repeated measures analyses of variance (RM ANOVA) using SPSS version 17.0 were used to compare performance between patients and controls on both versions of the IP-CPT. Pearson correlation coefficients were calculated to assess whether the performance was consistent between the IP-CPT and mIP-CPT and to assess the relationship between mIP-CPT and CS.

Experiment 2

Independent samples t-tests were performed to identify group differences on overall ANT performance and within attention networks. Pearson correlation coefficients were calculated to assess the relationships between ANT, IP-CPT and CS.

Experiment 3

The relationships between cognitive functioning, visual processing and IP-CPT were examined using two statistical methods: regression analysis and structural equation modeling (SEM). Univariate and stepwise multivariate linear regression analyses were performed to assess the strength of the associations. To determine which variables significantly predicted performance, backward selection was used in the multivariate linear regression analysis. Variables that increased the amount of variance explained in the model (r^2) were retained, using alpha <0.1 as inclusion criteria.

Structural Equation Modeling using a combination of observed variables and latent constructs was performed to further elucidate the nature of the relationships between visual processing, cognitive functioning and IP-CPT performance. Two latent constructs were calculated based on observed measures: visual processing and cognitive functioning. The visual processing construct consisted of CS measures for 4 SF conditions thought to reflect magnocellular\parvocellular processing: 0.5cpd, 1cpd, 7 cpd, and 21 cpd. The cognitive functioning construct was comprised of standardized assessments of working memory and processing speed.

Maximum Likelihood parameter estimation, using AMOS 18, was used to assess *a priori* hypothesized models. Model fit was examined using Chi-square (X^2) and conventional fit indices less sensitive to sample size including: Comparative Fit Index (CFI), Normed Fit index (NFI), Root Mean Square Error of Approximation (RMSEA) and Akaike Information Criterion (AIC). The X^2 statistic measures absolute model fit by comparing the observed covariance matrix with the proposed covariance matrix. Good model fit is indicated by lower, non-significant values. The CFI and NFI compare the fit of the hypothesized model to the baseline model of complete independence. Values greater than 0.95 are indicative of good model fit[58]. The RMSEA assesses how well the given model approximates the true model; values below 0.06 are considered good model fit[58]. The AIC estimates the deviation of the predicted distribution to the true distribution; providing an assessment of how well the model will cross-validate to future observations. Lower values are indicative of better model fit.

Results

Demographic Covariates

As indicated in Table 2.1, there were significantly more females in the control groups in Experiments 1 and 2. Greater neural activity associated with exogenous orienting was recently observed in females during a spatial visual attention task[59]. Further, gender differences have been found for top-down mechanisms involved in selective visual attention[60]. To determine whether gender should be included as a covariate in the adjusted analyses, independent samples t-tests were performed comparing ANT and IP-CPT performance between males and females. Average ANT accuracy was significantly greater in females (X(SE)= 0.97(0.03)) compared to males (X(SE) = 0.94(0.07), $p<0.010$, two-tailed). Average IP-CPT t-score was also significantly higher in females (X(SE) = 44.2(1.7)) compared to males (X(SE) = 36.8(1.2), $p<0.001$, two-tailed). As such, both unadjusted and models controlling for gender will be presented for these tasks.

Experiment 1

IP-CPT Performance Comparisons

To examine performance patterns on the traditional IP-CPT, a 2x3 RM ANOVA was performed with group (patient vs. controls) as the between subject factor and number of digits (2, 3 vs. 4 digits) as the repeated factor(Table 2.3). Average accuracy was significantly lower in patients (X(SE)=1.95(0.14)) compared to controls (X(SE) = 2.93(0.16)) and accuracy significantly decreased with increasing digits in both groups (X(SE)=2 digits:3.17(0.14), 3 digits:2.59(0.11), 4 digits:1.55(0.12), p<0.001 for all pairwise comparisons) (Figure 2.2). The group x digit interaction failed to reach significance, suggesting the pattern of performance was comparable between groups.

Table 2.3.IP-CPT Performance Comparisons

IP-CPT	**F**	**df**	**p-value**
Case	21.69	1, 50	**<0.001**
Digits	117.72	2, 49	**<0.001**
Case x digits	1.84	2, 49	0.170

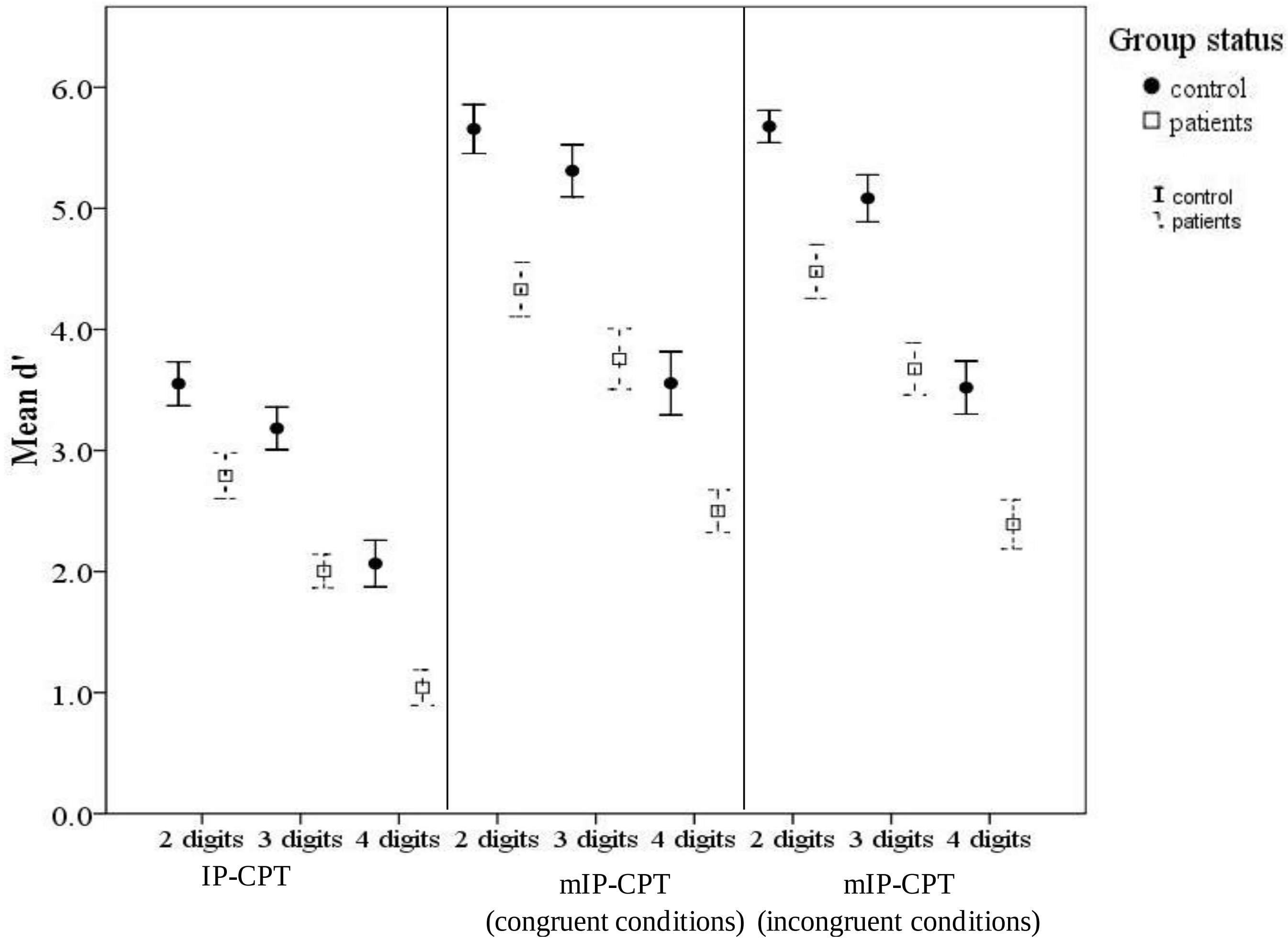


Figure 2.2: IP-CPT and mIP-CPT Performance Comparisons

Accuracy is measured for each condition using dprime. Error bars correspond to 1 +/- SE. Controls are represented by shaded circles and patients are represented by open squares. On both tasks, patient accuracy was significantly reduced compared to controls and the pattern of performance between groups was consistent across all conditions.

<u>Spatial Frequency Manipulation – Congruent Stimuli</u>

To examine whether performance differed between groups on the mIP-CPT for congruent stimuli, we performed a 2x3x3 RM ANOVA with group as the between subject factor and digits and SF (HSF, LSF vs NSF) as repeated measures factors (Table 2.4). Patients were less accurate than controls (X(SE) d’ patients = 3.59 (0.18); controls = 4.89 (0.20), $p<0.001$, two-tailed) and accuracy in both groups significantly decreased with increasing number of digits (Figure 2.3). The digit x group interaction failed to reach significance, suggesting the pattern of performance across digits was comparable between groups. While overall performance was comparable between the SF conditions, a significant interaction was found for group x SF. Controls were more accurate on LSF stimuli (X(SE) d' = 5.15(0.20)) than HSF (X(SE) d'= 4.79(0.20), p=0.059) and NSF (X(SE) d' = 4.74(0.22), p = 0.045, two-tailed), whereas patient performance was comparable across SF (X(SE) d' LSF: 3.41(0.21), HSF: 3.66 (0.24), NSF; 3.72(0.23))(Figure 2.2). The group X digit X SF interaction failed to reach significance.

Table 2.4.mIP-CPT Performance Comparisons (Congruent Conditions)

mIP-CPT (congruent)	**F**	**df**	**p-value**
All digits			
Case	23.63	1, 57	**<0.001**
Digits	100.35	2,56	**<0.001**
Spatial frequency (SF)^a	0.11	2, 56	0.898
Case x digits	1.34	2, 56	0.271
Case x SF^a	4.54	2, 56	**0.015**
Digits x SF^a	0.57	4, 54	0.687
Case x digits x SF^a	0.53	4,54	0.716

^{a} SF: high, low, vs. neutral

Spatial Frequency Manipulation – Incongruent Stimuli

To examine performance differences for incongruent stimuli, a 2x3x3 RM ANOVA was performed with group as the between subject factor and digits and SF (high/low, high/neutral, low/neutral) as the repeated measures factors (Table 2.5). Average accuracy was significantly lower in patients (X(SE) d' = 3.43(0.18)) compared to controls (X(SE) d'= 4.64(0.19)) and accuracy significantly decreased with increasing number of digits (X(SE) d' = 4.93(0.16), 4.33(0.16) and 2.85(0.15) for 2, 3 and 4 digits respectively). Both groups were more accurate at low/neutral (X(SE) = 4.33(0.14)) combinations than high/neutral (X(SE) d' = 3.93(0.16); p

=0.002) and high/low (X(SE) = 3.86(0.16)) (p=0.002)). Performance was comparable between high/low and high/neutral combinations (p = 0.657). The group x digit and group x stimuli type interactions failed to reach significance, suggesting that performance patterns were comparable across groups.

Table 2.5. mIP-CPT Performance Comparisons (Incongruent Conditions)

mIP-CPT (incongruent)	**F**	**df**	**p-value**
Case	21.32	1, 57	**<0.001**
Digits	97.71	2, 56	**<0.001**
Spatial frequency (SF) [a]	8.02	2, 56	**0.001**
Case x digits	0.26	2, 56	0.769
Case x SF[a]	1.71	2, 56	0.190
Digits x SF[a]	1.03	4, 54	0.401
Case x digits x SF[a]	0.40	4, 54	0.809

[a] SF (incongruent): high/low, high/neutral vs. low/neutral

Spatial Frequency Manipulation- Congruent vs. Incongruent Stimuli

To examine whether performance differences existed for congruent vs. incongruent stimuli, separate 2x3x2 RM ANOVAs were performed for each SF with group as the between subject factor and digit and congruency (congruent vs. incongruent) as the repeated measures factors(Table 2.6). For all SF conditions, overall accuracy was significantly reduced in patients compared to controls and accuracy was significantly reduced by increasing number of digits. Both groups were more accurate at congruent than incongruent pairs for HSF stimuli and less accurate at congruent than incongruent pairs for NSF stimuli. While overall accuracy was comparable between congruent and incongruent stimuli on LSF, a significant group x congruency interaction was found. Controls were more accurate at congruent (X(SE) d' = 5.15(0.20)) than incongruent pairs (X(SE) d'=4.81(0.16), p=0.019, two-tailed). In patients, accuracy was comparable between congruent (X(SE) d' = 3.41(0.21)) and incongruent pairs (X(SE) d' =3.50(0.20), p=0.454, two-tailed) (Figure 2.3). The group x congruency interaction was not significant for HSF or NSF conditions, suggesting that the pattern of performance across congruency conditions was comparable between the groups.

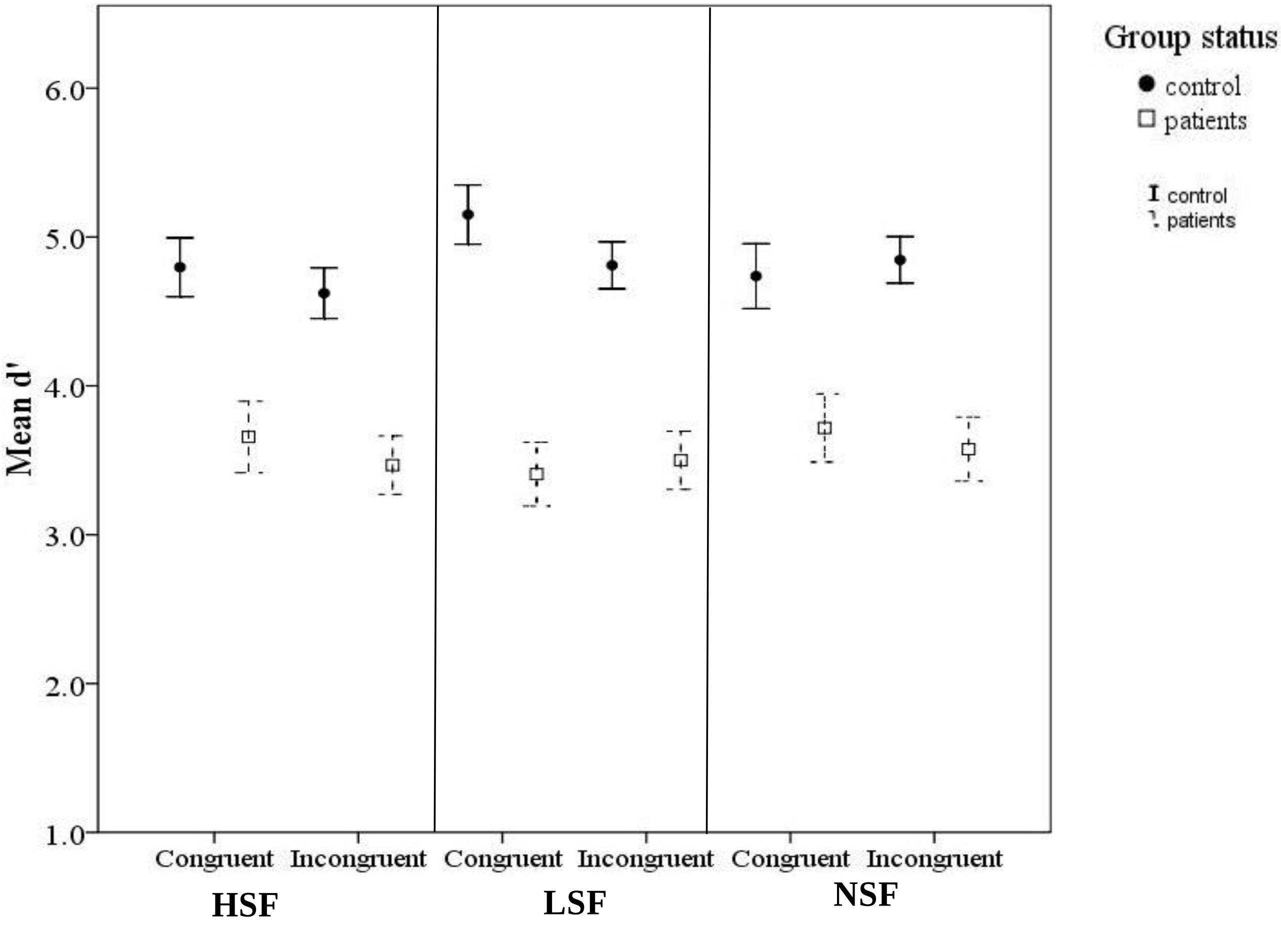


Figure 2.3.mIP-CPT Performance Comparisons (Congruent and Incongruent Conditions)

Accuracy is measured for each condition using dprime. Error bars correspond to 1 +/- SE. Controls are represented by shaded circles and patients are represented by open squares. In HSF and NSF, accuracy was comparable between congruent and incongruent conditions in both patients and controls. On LSF, controls were more accurate congruent than incongruent stimuli whereas accuracy did not improve in the congruent condition in patients.

Table 2.6. mIP-CPT Performance Comparisons (Congruent vs. Incongruent)

mIP-CPT congruent vs. incongruent	**F**	**df**	**p-value**
Hi SF			
Case	17.51	1, 57	**< 0.001**
Digits	90.52	2, 56	**< 0.001**
Congruency[a]	6.07	1, 57	**0.017**
Case x digits	1.46	2, 56	0.240
Case x Congruency[a]	0.03	1, 57	0.854
Digits x Congruency[a]	0.91	2, 56	0.409
Case x digits x Congruency[a]	0.59	2, 56	0.556
Low SF			
Case	33.08	1,57	**<0.001**
Digits	104.31	2, 56	**<0.001**
Congruency[a]	0.35	1, 57	0.558
Case x digits	1.18	2, 56	0.314
Case x Congruency[a]	5.02	1, 57	**0.029**
Digits x Congruency[a]	0.44	2, 56	0.649
Case x digits x Congruency[a]	0.14	2, 56	0.870
Neutral			
Case	17.68	1,57	**<0.001**
Digits	64.81	2, 56	**<0.001**
Congruency[c]	8.93	1,57	0.335
Case x digits	0.29	2,56	0.745
Case x Congruency[a]	0.95	1,57	0.335
Digits x Congruency[a]	11.36	2,56	**<0.001**
Case x digits x Congruency[a]	0.17	2, 56	0.844

[a] Congruency: congruent vs. incongruent

Performance comparisons between Modified and Traditional IP-CPT

Pearson correlations were calculated to examine the associations between the modified and traditional IP-CPT. Significant positive correlations were observed for all three digit types, even after adjusting for group status (Table 2.7). For 3 and 4 digits, the strongest correlations were observed for the respective digit type (adjusted $r^2 = 0.80$, $p<0.001$ and adjusted $r^2 = 0.85$, $p<0.001$ for 3 and 4 digits, respectively).

Table 2.7.mIP-CPT/tIP-CPT and Visual Processing Correlations

	Traditional IP-CPT											
	Unadjusted						**Adjusted[a]**					
Modified IP-CPT	2 digits		3 digits		4 digits		2 digits		3 digits		4 digits	
2 digits	0.58	***	0.76	***	0.75	***	0.49	***	0.65	***	0.66	***
3 digits	0.57	***	0.80	***	0.75	***	0.47	***	0.69	***	0.64	***
4 digits	0.60	***	0.70	***	0.85	***	0.52	***	0.58	***	0.80	***

[a] Adjusted by group status; *** $p<0.001$, two tailed

Association between Modified IP-CPT and Visual Processing

Pearson correlations were calculated to determine whether accuracy on the mIP-CPT was associated with CS (Table 2.8). Contrast sensitivity for 0.5 cpd and 1.0 cpd was significantly associated with mIP-CPT accuracy for all SF conditions, in both congruent and incongruent pairs. After controlling for group status, all associations remained significant for 1.0 cpd. Both 7 cpd and 21 cpd were positively correlated with mIP-CPT accuracy on all incongruent conditions and modest correlations were observed for congruent conditions. After adjusting for group status, the strength of the correlations significantly decreased for all SF levels.

Table 2.8.mIP-CPT and Visual Processing Correlations

	Contrast Sensitivity 500 ms					
	Unadjusted			**Adjusted**[a]		
	0.5 cpd	**7 cpd**	**21 cpd**	**0.5 cpd**	**7 cpd**	**21 cpd**
Congruent						
High SF[b]	0.40 **	0.12	0.26	0.33 *	-0.04	0.09
Low SF	0.36 *	0.29 *	0.38 **	0.26	0.11	0.19
Neutral	0.29 *	0.22	0.30 *	0.21	0.10	0.18
Incongruent						
High SF	0.41 **	0.29 *	0.43 **	0.33 *	0.15	0.29 *
Low SF	0.42 **	0.31 *	0.41 **	0.34 *	0.15	0.24
Neutral	0.36 *	0.36 **	0.43 **	0.26	0.22	0.28 *

[a] Adjusted by group status; [b] SF: spatial frequency; *$p<0.05$; **$p<0.01$, two tailed

Experiment 2

ANT Performance Differences

To examine whether ANT performance differences existed between patients and controls, independent sample t-tests were performed(Table 2.9). To control for gender, ANOVAs with group as the between subject factor and gender as the covariate were performed. Patients were less accurate (X(SD) patients = 0.92(0.1); controls= 0.98(0.0), $p=0.002$, two-tailed) and slower to respond than controls (X(SD) patients= 828.2(162.9); controls=607.6(86.6), $p<0.001$, two-tailed). Group differences remained after controlling for gender(Table 2.9). No differences between groups were observed on assessments of attention networks in either the unadjusted or adjusted analyses.

Table 2.9. ANT Performance Comparisons

	Independent Samples t-tests			Adjusted Analysis (ANOVA)[b]		
	Patients (n=28) X(SD)	Controls (n=45) X(SD)	p-value[a]	F	df	p-value[a]
ANT						
Alerting	23.5 (45.0)	31.2 (32.6)	0.401	0.841	1, 70	0.362
Conflict	122.9(106.9)	109.3(35.3)	0.519	0.45	1, 70	0.507
Orienting	36.0(38.3)	42.8(26.2)	0.415	0.85	1, 70	0.361
Mean Accuracy	0.92 (0.1)	0.98(0.0)	**0.002**	14.39	1, 70	**<0.001**
Mean Reaction Time	828.2(162.9)	607.6(86.3)	**<0.001**	50.30	1, 70	**<0.001**

[a] two-tailed [b] Between group comparisons adjusted for gender

Associations between ANT and IP-CPT

Pearson correlations were calculated to examine the associations between ANT and IP-CPT performance. IP-CPT accuracy was positively correlated with ANT accuracy ($r^2 = 0.44$, $p<0.001$, two-tailed) and inversely correlated with ANT reaction time ($r^2 = -0.56$, $p<0.001$, two-tailed). There were no significant correlations between attention networks and IP-CPT performance(Table 2.10).

Associations between ANT and Contrast Sensitivity

Pearson correlations were calculated to examine the associations between ANT and visual processing measures. Mean ANT accuracy was positively correlated with all CS measures except 1.0 cpd. Slower reaction time was significantly associated with increased CS at all SF levels. No significant associations were found for assessments of attention networks (Table 2.10).

Table 2.10. ANT tIP-CPT and Visual Processing Correlations

			Contrast Sensitivity (500ms)					
	IP-CPT		**0.5 cpd**		**7 cpd**		**21 cpd**	
Alerting	0.00		0.12		0.08		0.07	
Conflict	-0.07		-0.14		-0.10		-0.05	
Orienting	-0.00		0.09		0.06		0.03	
Mean Accuracy	0.44	***	0.34	**	0.32	**	0.28	*
Mean Reaction Time	-0.56	***	-0.45	***	-0.31	*	-0.41	**

*p<0.05; **p<0.01;***p<0.001, two-tailed

Experiment 3

Regression analyses were performed to assess the relationships between cognitive functioning, visual processing and IP-CPT performance (Table 2.11). Because the pattern of performance across digits types was comparable between groups, the IP-CPT t-score was used as an index of performance. Average t-score was approximately 7 points higher in females compared to males (B = 7.35; 95% CI: 2.99-11.70, p= 0.001); however, gender did not significantly improve model fit and was not retained in the adjusted analysis. Average t-score was nearly 18 ½ points lower in patients compared to controls (B= -18.43, 95% CI: - 21.4- -15.4, p<0.001) and performance differences remained significant even after controlling for cognitive functioning and visual processing (B=-5.89, 95%CI: -9.29- -1.86, p=0.004). Working memory and processing speed were significant predictors of IP-CPT performance even after controlling for other factors. Significant independent associations were observed for CS at all SF levels. In the adjusted analyses, CS at 0.5 cpd and 21 cpd were significantly associated with performance. All other assessments of visual processing did not significantly improve model fit and were excluded from the final model. Due to the highly correlated nature of the visual processing variables, it is difficult to ascertain from the regression analysis whether additional measures of visual processing contribute to performance differences.

Table 2.11. Relationship between tIP-CPT, Visual processing and Cognitive functioning

	Unadjusted				**Adjusted[c]**			
	B	**SE**	**95% CI**	**p-value**	**B**	**SE**	**95% CI**	**p-value**
Gender[a]	7.35	2.21	2.99 – 11.70	**0.001**	excluded			
Group[b]	-18.43	1.52	-21.4 - -15.4	**<0.001**	-5.89	2.04	-9.92—1.86	**0.004**
Working Memory	0.46	0.04	0.37 – 0.54	**<0.001**	0.11	0.06	-0.00 – 0.21	0.058
Processing Speed	0.54	0.04	0.46 – 0.61	**<0.001**	0.27	0.07	0.14 – 0.41	**<0.001**
CS 0.5 cpd (500ms)	0.12	0.02	0.08 – 0.16	**<0.001**	0.04	0.02	0.00 – 0.07	**0.044**
CS 1.0 cpd (500ms)	0.08	0.02	0.05 – 0.12	**<0.001**	excluded			
CS 7 cpd (500ms)	0.05	0.01	0.03 – 0.06	**<0.001**	excluded			
CS 21 cpd (500ms)	0.28	0.06	0.16 – 0.39	**<0.001**	0.09	0.05	-0.00 – 0.18	0.070

[a] 1 = female, 0 = male; [b] 1= case, 0 = control; [c] Multivariate Stepwise Regression analysis using Backward selection. Variables were retained if inclusion they significantly increased the amount of variance (r^2). explained by the model Alpha <0.1 was used as inclusion criteria.

Structural equation modeling was performed to further elucidate the nature of the associations between visual processing, cognitive functioning and IP-CPT performance. Latent constructs were created for visual processing and cognitive functioning. Model fit was compared across models specifying mediation and moderation effects of visual and cognitive measures. The most relevant models are presented in Figure 2.4 and additional models considered are presented in Figure 2.5 (Supplemental). The results suggest that the relationship between group and IP-CPT is completely mediated by visual processing and cognitive functioning (Figure 2.4, Model 1). Adding a direct association between group and IP-CPT did not significantly improve model fit (Model 2 X^2=23.0(df=14); Model 1 X^2 = 23.3(df= 15)). Cognitive functioning mediated the relationship between group and IP-CPT both directly and indirectly through visual processing. The association between visual processing and IP-CPT appeared to be mediated through cognitive functioning (Model 1 X^2 = 23.3(df= 15) vs Model 3 X^2=22.7(df=14)). Specifically, visual processing was significantly reduced in patients compared to controls (B=-0.065, p<0.001). Decreased visual processing was associated with decreased cognitive functioning (B=0.47, p<0.001), which lead to reduced accuracy on the IP-CPT (B=0.81, p<0.001). Hence, the results suggested that early visual processing impairments likely contribute to the reduced cognitive functioning which caused observed IP-CPT performance differences between patients and controls.

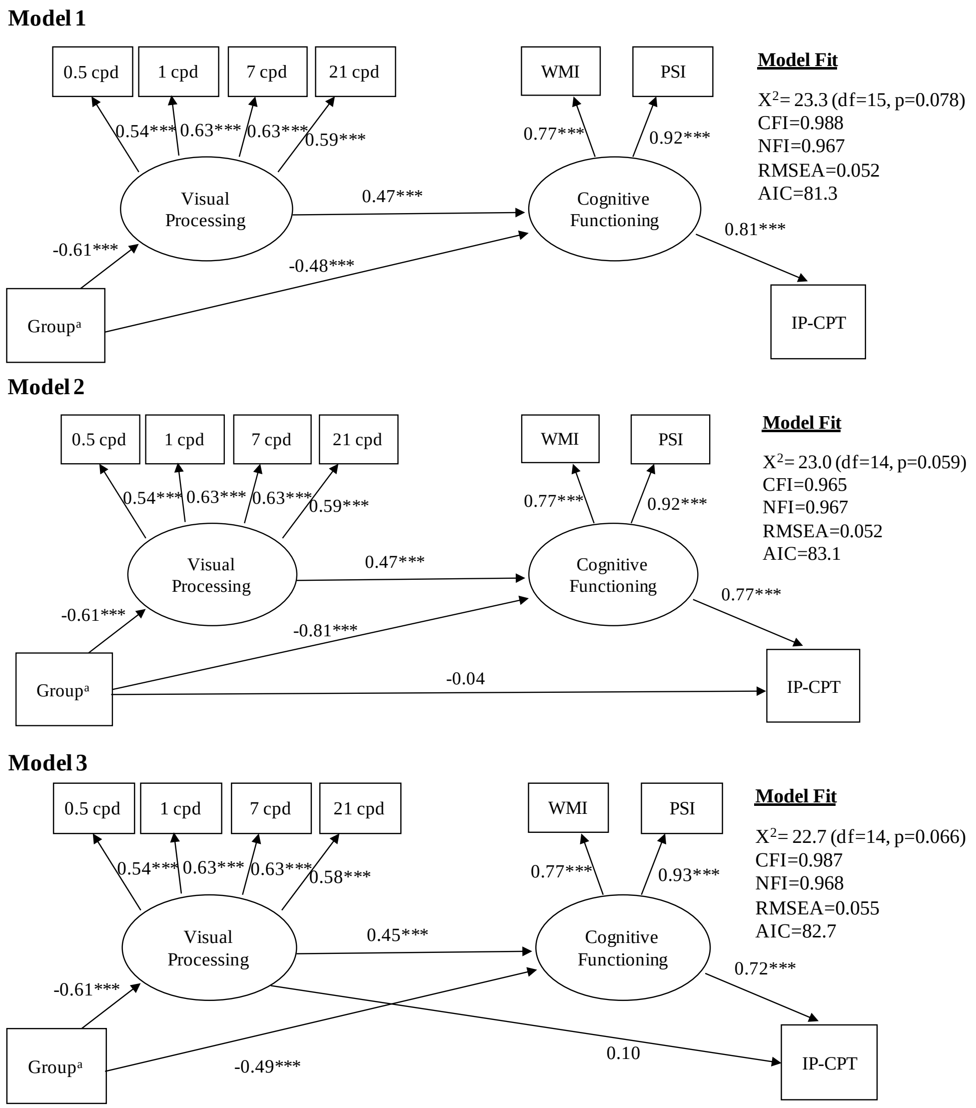


Figure 2.4. SEM Examining the Associations between Visual processing, Cognitive Functioning, and tIP-CPT

Circles represent latent construct variables and squares represent observed variables. Standardized regression weights are provided for the associations with each path. Model fit indices are provided to the right of the model. Comparisons of the three models suggest that Model 1 provides the best model fit. Group differences in IP-CPT performance are completely mediated through visual processing and cognitive functioning. ***p<0.001

Discussion

The present study examined the contribution of early sensory processing dysfunction on attention impairments in individuals with schizophrenia. The results provide evidence for a global performance impairment likely caused by both early sensory processing and higher order cognitive dysfunction. Examination of the relationship between exogenous and endogenous processes also suggests that pre-attentive visual impairments likely impede endogenously modulated networks to adversely impact performance on traditional assessments of attention.

While overall accuracy on both the traditional and modified IP-CPT was reduced in patients compared to controls, the pattern of performance across digits was comparable between groups. This suggests that endogenously modulated processes necessary for accurate detection of complex targets are likely intact and performance impairments are likely caused by a global cognitive deficit, rather than specific endogenously modulated network impairments.

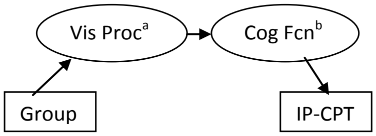
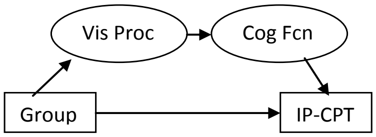
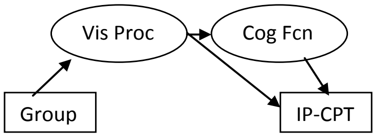
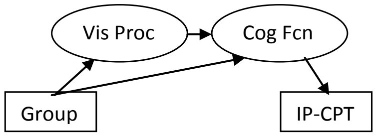
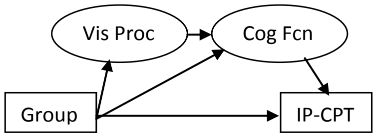
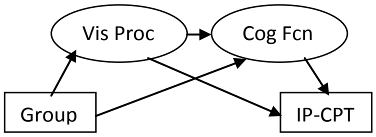
On the mIP-CPT, the overall pattern of performance was similar to that observed on the IP-CPT; however, patient performance was differentially impacted by SF manipulation. While controls were most accurate at LSF, patient accuracy was comparable across all SF conditions. Notably, when the task difficulty was increased by using incongruent stimuli, controls were less accurate for incongruent pairs. Patients were also less accurate on incongruent pairs for HSF and NSF. However, for LSF, where reliance on magnocellular processing is required for accurate target detection, accuracy was comparable between congruent and incongruent conditions. This suggests that early sensory processing deficits likely contribute to performance differences by impeding top-down processes required for filtering relevant stimulus characteristics. Performance in both groups was correlated with CS, with the strongest correlations observed for conditions biasing magnocellular processing.

On the ANT, overall accuracy and reaction time were reduced in patients compared to controls; however, no differences within the attention networks were found between groups. In both groups, overall accuracy and reaction time were also correlated with visual processing; whereas within network performance was not. The results suggest that performance differences are indicative of a global, rather than network specific impairment. Furthermore, reduced processing speed and early visual deficits, rather than network specific impairments, appear to be significant contributors to performance differences.

Results from the SEM analysis revealed that visual processing and cognitive functioning likely account for performance differences on the traditional IP-CPT. Visual processing deficits lead to reduced higher-order cognitive processing of visual information, which impacts the ability to accurately detect targets. Magnocellular processing deficits characteristic of the disorder likely contribute to impairments in encoding contextual information by impeding patients' ability to perceive relevant aspects of visual stimuli.

Because of its rapid speed of conductance and projections to higher-order cortical regions[61], the magnocellular pathway is thought to play a critical role in overall stimulus organization [48, 62-66] and attention capture[67, 68]. Rapid transfer of information by the magnocellular pathway and dorsal stream provides a low resolution information template that is filled in by input from the slower-to-arrive parvocellular ventral stream[62, 69]. Electrophysiological and imagining evidence suggest that early pre-attentive deficits in the magnocellular pathway likely contribute to impairments in later, attention modulated processes in both the dorsal and ventral streams[47, 48, 70-72].

In summary, the results from the present study suggest that impaired performance on traditional measures of attention in schizophrenia is likely indicative of global cognitive dysfunction, rather than a specific impairment in attention. Reduced accuracy is likely caused by early visual processing deficits that impact encoding of relevant visual information. Such deficits impede later endogenously modulated processes involved in accurate target detection.

Model	Description	Model Fit					
		X^2	df	CFI	NFI	RMSEA	AIC
Model 1		33.11	16 (p=0.007)	0.974	0.953	0.072	89.11
Model 2		32.73	15 (p=0.005)	0.973	0.954	0.076	90.73
Model 3		32.34	15 (p=0.006)	0.974	0.954	0.075	90.34
Model 4		23.28	15 (p=0.078)	0.988	0.967	0.052	81.28
Model 5		23.01	14 (p=0.059)	0.965	0.967	0.056	83.08
Model 6		22.66	14 (p=0.066)	0.987	0.968	0.055	82.66

[a] Visual processing construct: Contrast sensitivity 500ms: 0.5, 1, 7, and 21 cpd; [b] Cognitive functioning construct: Working Memory and Processing Speed Indices (Matrix)

Figure 2.5.(Supplemental) SEM Models Examining the Relationships between Visual Processing, Cognitive Functioning and tIP-CPT Performance

Circles represent latent construct variables and squares represent observed variables. Model Fit Indices are provided to the right of each model

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Chapter 3 Auditory Spatial Localization and Schizophrenia

Reprinted from Schizophrenia Research, 124 (1-3). Megan A. Perrin, MPH, Pamela D. Butler, PhD, Joanna DiCostanzo, Gina Forchelli, Gail Silipo, Daniel C. Javitt, MD, PhD Spatial Localization Deficits and Auditory Cortical Dysfunction in Schizophrenia. 161-168, Copyright. 2010. with permission from Elsevier

Abstract

Background: Schizophrenia is associated with deficits in the ability to discriminate auditory features such as pitch and duration that localize to primary cortical regions. Lesions of primary vs. secondary auditory cortex also produce differentiable effects on ability to localize and discriminate free-field sound, with primary cortical lesions affecting variability as well as accuracy of response. Variability of sound localization has not previously been studied in schizophrenia.

Methods: The study compared performance between patients with schizophrenia (n=21) and healthy controls (n=20) on spatial localization and discrimination tasks using low frequency tones generated from seven speakers concavely arranged with 30 degrees separation.

Results: For the localization task, patients showed reduced accuracy (p=0.004) and greater overall response variability (p=0.032), particularly in the right hemifield. Performance was also impaired on the discrimination task (p=0.001). On both tasks, poorer accuracy in the right hemifield was associated with greater cognitive symptom severity. Better accuracy in the left hemifield was associated with greater hallucination severity on the localization task (p=0.026), but no significant association was found for the discrimination task.

Conclusion: Patients show impairments in both localization and discrimination of sounds presented free-field, with a pattern comparable to that of individuals with right superior temporal lobe lesions that include primary auditory cortex (Heschl’s gyrus). Right primary auditory cortex dysfunction may protect against hallucinations by influencing laterality of functioning.

Introduction

Schizophrenia is a severe neuropsychiatric illness associated with widespread deficits in neurocognition. Although deficits have been studied primarily in relationship to higher cognitive function, increasing evidence implicates dysfunction within primary sensory cortex. In the auditory system, deficits in functioning of primary sensory cortex are supported by the observation that patients show significant impairment in ability to match tones following brief delay [1-5] with no increased susceptibility to within-modal [1] or cross-modal [6] distraction.

Although less well studied, sound localization also appears to be impaired in schizophrenia. Balogh et al (1979) found that individuals with schizophrenia were less accurate at determining the location of sound relative to the midline. Behavioral and electrophysiological findings from a recent event-related potential (ERP) study using manipulation of intra-aural cues to simulate location differences also provide evidence for impairments [7]. Individuals with schizophrenia were less accurate at detecting location deviants than controls and mismatch negativity (MMN) amplitude was attenuated in the schizophrenia group, suggesting that deficits in early auditory processing may account for performance impairments [7].

In humans, auditory regions are located within superior temporal gyrus (STG), with primary auditory cortex located on the transverse gyri of Heschl (HG) [8]. Recently, effects of temporal lobe lesions on auditory localization have been detailed [9]. In both cats and monkeys, both hemispheres participate primarily in contralateral spatial localization and primary cortical lesions impair localization within but not across midlines [10]. Humans, however, show a different pattern in which right hemisphere lesions affect localization and discrimination in both hemifields [9, 11, 12]. Furthermore, lesions affecting the primary auditory cortex are distinguished from other lesions based upon increased variability of localization, rather than just decreased accuracy. The present study assessed localization and discrimination in schizophrenia using free-field stimuli in order to compare patterns of dysfunction in schizophrenia to published patterns in individuals with known auditory cortical lesions. We hypothesized that patients should show patterns consistent with bilateral primary auditory cortical dysfunction, including decreased accuracy and increased variability.

A secondary aim of the study was to evaluate the relationship between performance in schizophrenia and symptom severity. Left STG abnormalities are implicated in cognitive symptoms such as thought disorder based upon both structural [13], [14] and functional [15] investigations. In addition, hallucinations may represent “mislocalization” of thoughts generated within the head to external locations [2, 3], and have also been associated with auditory cortical dysfunction based upon electrophysiological [16, 17], functional [15, 18-20] and structural [13, 21] brain imaging. To date no studies have evaluated symptom severity relative to localization and discrimination abilities in schizophrenia. An exploratory analysis in the present study thus assessed the relationship between impaired spatial localization ability particularly within right hemifield and severity of thought disorder, hallucinations, and other potential symptom correlates.

Experimental/Materials and Methods

Participants

Participants included 21 patients with schizophrenia diagnosed based upon the Structured Clinical Interview for DSM-IV [22] and 20 healthy controls.   Patients were recruited from an inpatient unit and outpatient facilities associated with Nathan Kline Institute. Controls who met diagnostic criteria for a psychiatric disorder or reported a history of substance abuse during the initial screening were excluded.   Individuals with hearing problems were also excluded.

Socioeconomic status was calculated based on the Hollingshead scale [23]. In patients, symptom severity was assessed using the Positive and Negative Syndrome Scale [24]. Participants provided informed consent prior to participation and the protocol was approved by the appropriate institutional review boards.

Sound Localization and Discrimination Paradigm

Stimuli were projected from seven speakers concavely arranged with 30 degrees separation to enable assessments across 180° in the horizontal plane with positions as illustrated in Figure 3.1. Two paradigms were presented in two blocks each in counterbalanced order. In the localization paradigm, 20 tones were generated randomly from each of the seven speakers (140 total) and participants pointed to the speaker they thought the sound came from. In the discrimination paradigm, 16 trials per speaker pair (700 trials total) were presented in random order. In each trial, two tones were sequentially presented 150 ms apart from either the same or different speakers. The participant was asked to indicate whether the tones came from the same or different speakers, ignoring relative position of the tones.

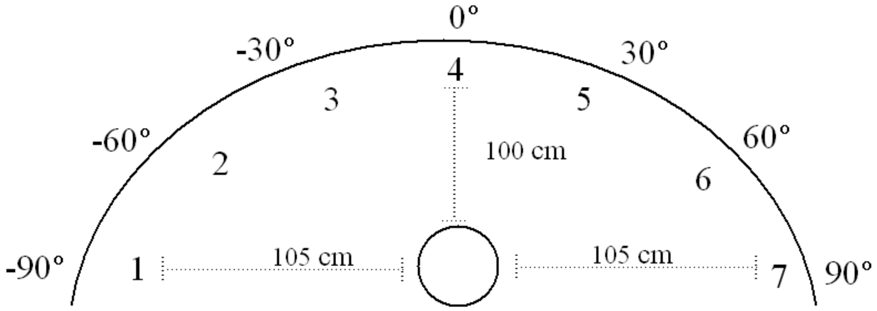


Figure 3.1 Speaker Arrangement

Seven speakers were concavely arranged with 30° spatial separation enabling assessments across 180° in the horizontal plane. Subjects were seated 100cm from the front and sides of the structure and the speakers were adjusted to be approximately at the level of the subject’s pinnae.

For both paradigms, stimuli consisted of 300ms 10ms rise/fall, 1000Hz tones presented at 60dB . Prior to each stimulus presentation, participants were instructed to fixate on a light presented at the midline. Subsequent stimuli were presented only after a response was provided. Participants completed approximately 35 practice trials for the localization task and 70 for the discrimination task. Feedback was not provided for either task.

Statistical Analysis

Mixed Model Analysis of Variance (RM ANOVA) using SPSS version 17.0 were performed to compare performance between patients and controls for both tasks. Comparable analyses were used to examine performance differences between patients and controls in the monaural cue conditions.

Localization Paradigm

In the localization paradigm, accuracy and precision were measured on three indices: percent correct, error difference and response variability. Accuracy reflects whether a given response was correct or incorrect, irrespective of degree of error. Error difference corresponds to the average degree of absolute difference between the reported and the actual location for each speaker location. Response variability represents the standard deviation of the error difference across trials for each individual at each location. In order to examine the effect of speaker location on performance, 2 (group status: patients vs controls) x 7 (speaker location: -90°, -60°, -30°, 0°, 30°, 60°, 90°) RM ANOVAs were completed for each accuracy assessment with group status as the between subjects factor and speaker location as the repeated factor. Preplanned follow-up analyses assessed performance within each hemifield using separate 2 (group status:

patients vs. controls) X 3 (speaker location: 30°, 60°, 90° relative to the midline) RM ANOVAs for each hemifield.

Discrimination Paradigm

For the discrimination paradigm, performance was assessed by calculating the d prime (d') for each speaker combination [25]. Larger d' values are indicative of greater accuracy. Assessments of normality revealed that the data were negatively skewed and moderately kurtotic. Reciprocal and log linear transformations were employed to correct for normality violations. Separate analyses were conducted within hemifield and across the midline.

For within hemifield comparisons, a 2 (group status: patients vs. controls) x 12 (speaker combination position: -90°/-60°, -60°/-30°, -90°/-30°, -90°/-0°, -60°/-0°, -30°/0°, 90°/60°, 60°/30°, 90°/30°, 90°/0°, 60°/0°, and 30°/0°) RM ANOVA was conducted with group status as the between subjects factor and position as the repeated factor.

For across midline analyses, a 2 (group status) x 3 (degree of separation between speakers: 60 degrees, 120 degrees and 180 degrees) RM ANOVA was performed.

Performance and Symptom Severity

Symptom severity was assessed for total, positive, negative, and cognitive symptoms on the PANSS [26]. Severity of hallucinations was assessed using the single item from the PANSS. Stepwise multiple regression analyses were performed to assess potential associations, with symptom severity as the dependent variable and location specific performance as the independent variables. For the localization task, individual performance was averaged within each hemifield and at the midline. For the discrimination task, individual performance was averaged for eccentric and central combinations in each hemifield and across the midline. Data in text represent mean±sem.

Results

Sample Characteristics

Table 3.1 presents relevant sample characteristics. No significant between group differences were observed for any of the demographic characteristics.

Table 3.1. Sample Characteristics

	Patients **n (%)**	**Controls** **n (%)**	X^2	**p-value**
Gender			1.78	0.238
Male	19 (90.5)	15 (75.0)		
Female	2 (9.5)	5 (25.0)		
Ethnicity			2.99	0.489
White/Caucasian	11 (52.4)	13 (65.0)		
Black	9 (42.9)	4 (20.0)		
Hispanic/Latino	1 (4.8)	1 (5.0)		
Asian/Other	0 (0.0)	2 (10.0)		

	Mean (SD)	**Mean (SD)**	**p-value**
Age at Interview (years)	39.2 (10.1)	38.1 (13.0)	0.783
Parental Socioeconomic Status[a]	40 (14.9)	44 (15.2)	0.465

[a] N missing: cases = 5, controls = 2

Localization Analysis

Localization analyses focused on three measures: overall percent correct at each location, degree of difference between actual and indicated position at each location and the degree of response variability at each location. For each measure, primary analysis consisted of a group X location RM ANOVA. Separate analyses were conducted across and within hemifields.

Across Hemifield Comparisons

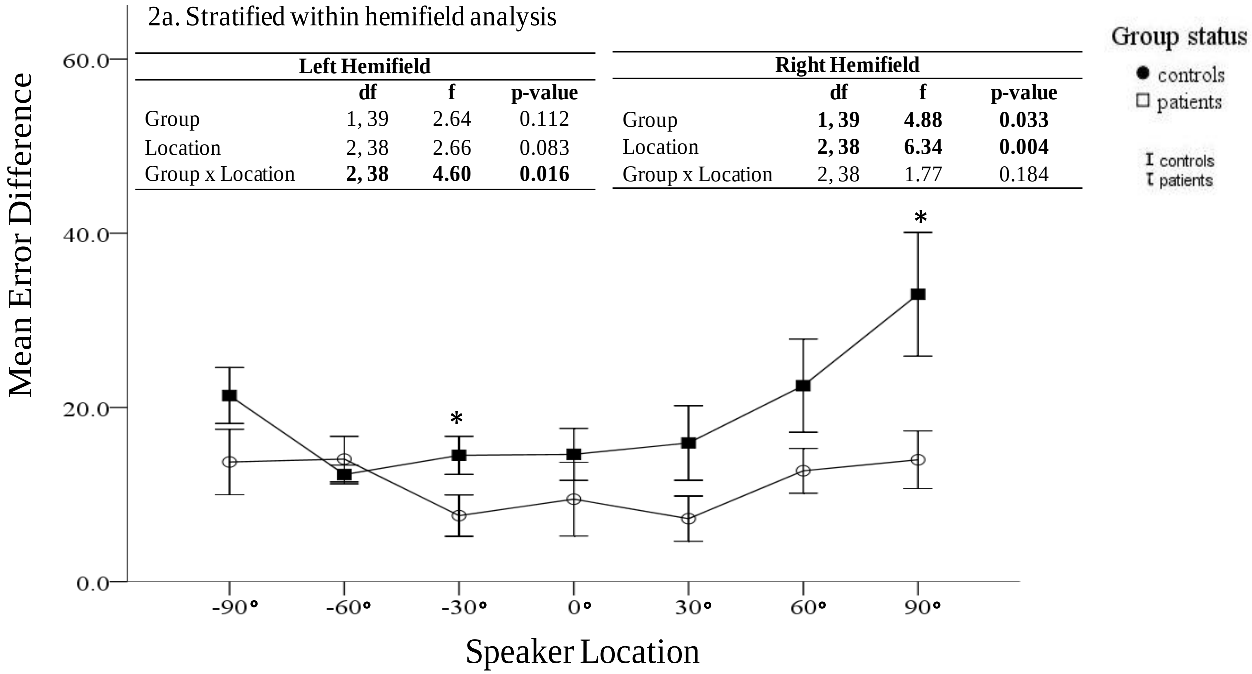
For the percent correct performance analysis, there was a highly significant main effect of group [*F*(1, 39) = 9.65, p =0.004)] reflecting significantly lower performance in patients (56.3±3.4%) compared to controls (71.3±3.5%). Both groups were more accurate at central compared to peripheral locations as shown by a significant main effect of location [*F*(6, 34) = 3.55, p =0.008]. However, the groups did not differ significantly in performance distribution across locations, as shown by non-significant group X location interaction [*F*(6, 34) = 1.52, p = 0.2].

In the absolute error difference comparison, a significant main effect of group was also observed [*F*(1, 39) = 5.21, p =0.028], reflecting greater error difference for patients (19.2±2.4º) than controls (11.3±2.5º). Both the main effect of location [*F*(6, 34) = 2.11, p = 0.077] and the group X location interaction [*F*(6,34) = 2.24, p = 0.068] tended toward significance.

With respect to response variability, a significant main effect for group [F(1, 39) = 4.94 p= 0.028] and location [*F*(6, 34) = 2.74, p = 0.028] was again observed with no significant group X location interaction [*F*(6, 34) = 0.96, p = 0.5].

Within Hemifield Comparisons

Performance comparisons for absolute error difference and response variability are provided in Figure 3.2 and Figure 3.3**.** In both assessments, significant main effects were found for group and location in the right hemifield only. In the right hemifield, patients were less accurate and more variable in their responses than controls and both groups were more accurate at locations closer to the midline than eccentric locations. The greatest differences in accuracy between patients and controls were found for more eccentric locations (i.e., 60° and 90).



2a. Stratified within hemifield analysis

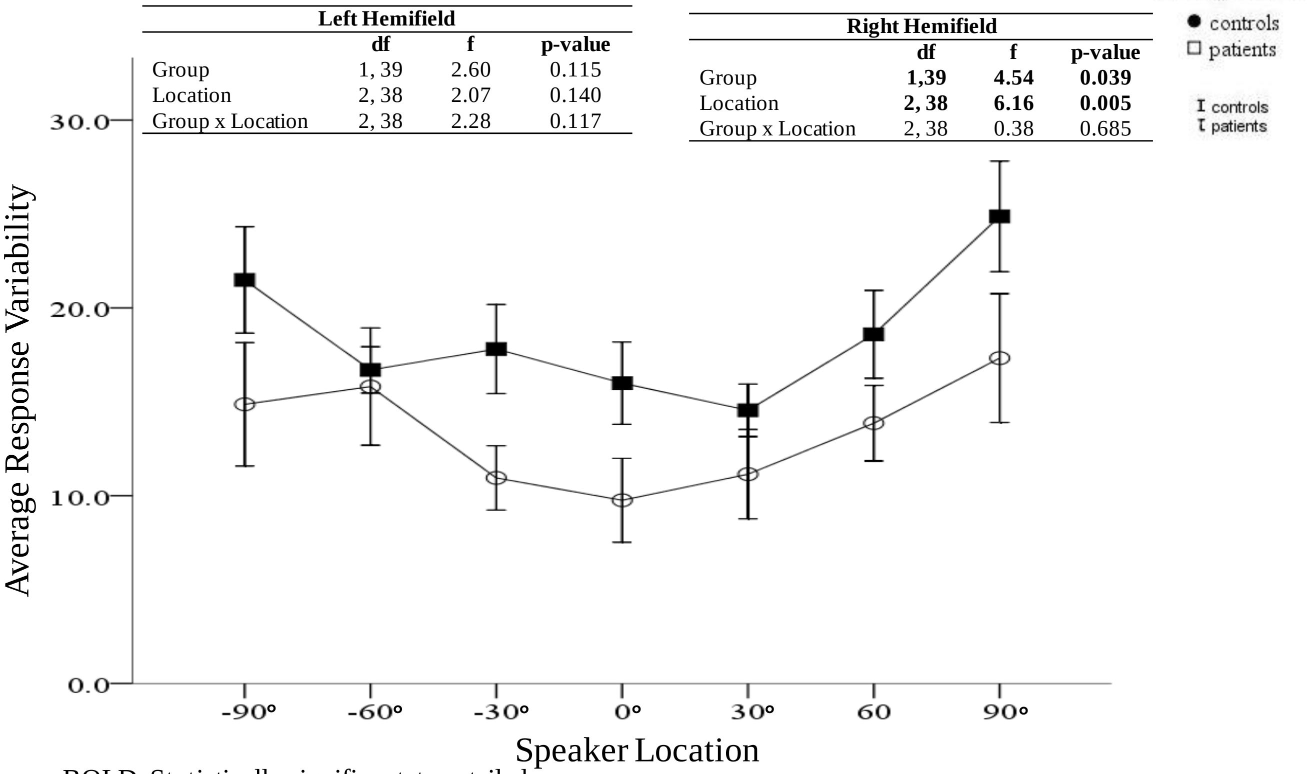
	Left Hemifield			Right Hemifield		
	df	**f**	**p-value**	**df**	**f**	**p-value**
Group	1, 39	2.64	0.112	**1, 39**	**4.88**	**0.033**
Location	2, 38	2.66	0.083	**2, 38**	**6.34**	**0.004**
Group x Location	**2, 38**	**4.60**	**0.016**	2, 38	1.77	0.184

BOLD: Statistically significant, $^{*}p < 0.05$

Figure 3.2. Error difference between patients and controls (localization task)

Accuracy was measured at each speaker location using error difference (the absolute difference between the actual and reported speaker location); greater error differences are indicative of poorer accuracy. Patients are represented by the dark squares and controls by the open circles. Error bars correspond to +/- 1SE. Significantly greater error differences were found in patients compared to controls, particularly in the right hemifield. Within hemifield analysis confirm significant differences in the right but not left hemifield (Figure 2a).

3a. Stratified within hemifield analyses



Left Hemifield	df	f	p-value
Group	1, 39	2.60	0.115
Location	2, 38	2.07	0.140
Group x Location	2, 38	2.28	0.117

Right Hemifield	df	f	p-value
Group	**1,39**	**4.54**	**0.039**
Location	**2, 38**	**6.16**	**0.005**
Group x Location	2, 38	0.38	0.685

BOLD: Statistically significant, two-tailed

Figure 3.3. Response variability comparisons between patients and controls (localization task).

Performance was measured at each speaker location using response variability (the standard deviation of the error difference). Patients are represented by dark squares and controls by open circles. Error bars correspond to +/- 1SE. Across locations, response variability was significantly greater among patients compared to controls. Within hemifield analysis revealed significant group differences in the right but not left hemifield (Figure 3a).

Discrimination Analysis

For the discrimination analysis, performance was measured using d'. Separate RM ANOVAs were performed for comparisons across the midline, within hemifield and within hemifield vs. across the midline.

Across Midline Comparisons

Overall accuracy was significantly worse in patients than controls for across midline comparisons [$F(1, 39) = 7.40$, p = 0.01]. Both groups were more accurate at combinations with 120 degrees separation (i.e, -60°/60°) than either 60 (i.e., -30°/30°) or 180 (i.e, -90°/90°) degrees separation. The group X location interaction was not significant [*F*(2, 38) = 0.39, p = 0.7]. (Figure 3.4)

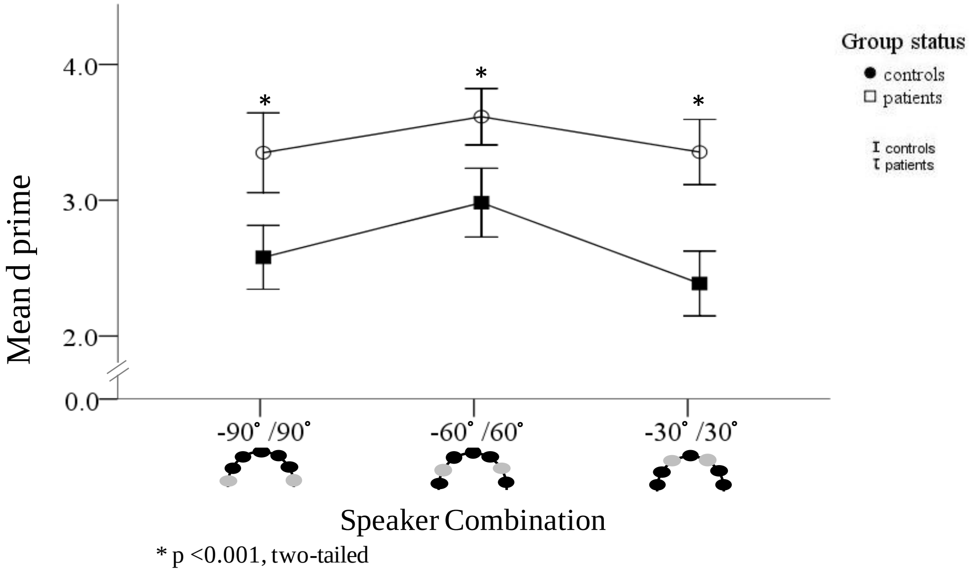
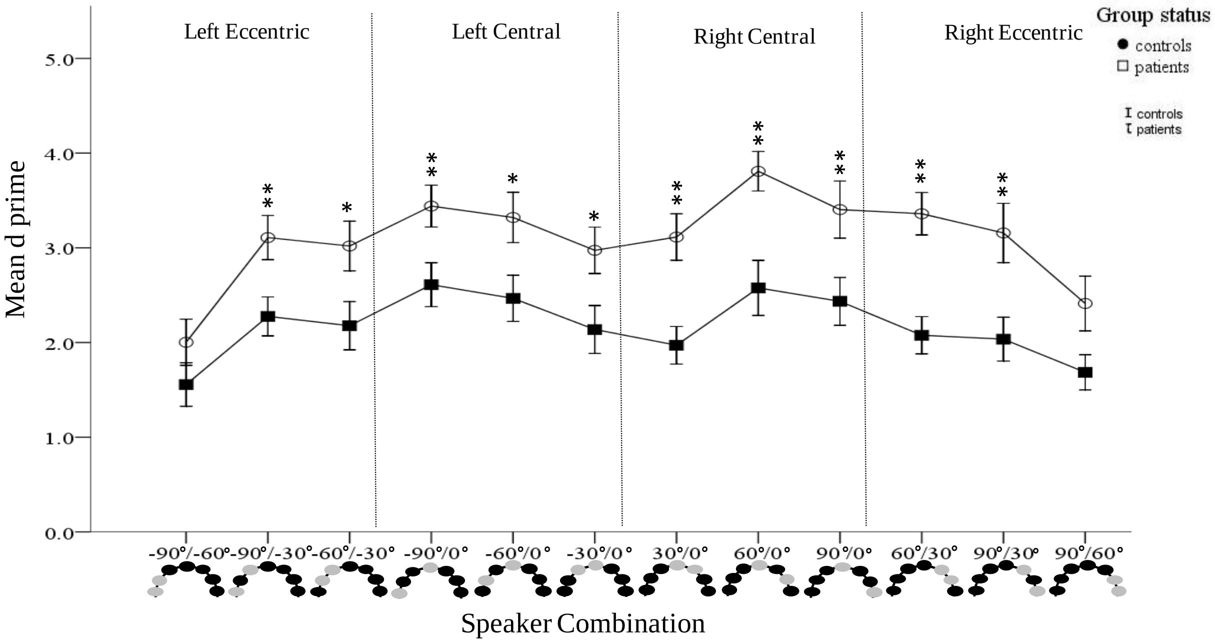


Figure 3.4. Accuracy comparisons between patients and controls (discrimination task).

D prime was calculated for each speaker combination. Higher d' values are indicative of better accuracy. Combinations crossing the midline are presented. Schematic representations of the speakers are provided at the bottom of the figure with light colored circles representing the sound locations. Patients are represented by dark squares and controls by open circles. Error bars correspond to +/- 1SE. Poorer accuracy was found in patients compared to controls at all three speaker combinations

Within Hemifield Comparisons

For the discrimination task, within hemifield comparisons yielded significant main effects for group [*F*(1, 39) = 1.17, p = 0.001], and location [*F*(11, 29) = 42.24, p <0.001] and a significant group X location interaction [*F*(11, 29) = 2.45, p = 0.026]. Across speaker combinations, average d' prime was significantly lower in patients (3.09±2.0) than controls (2.17±.20). With the exception of the most eccentric combinations in both hemifields (−90°/−60° and 90°/60°), patients were less accurate than controls for all speaker combinations (Figure 3.5)



*p<0.05; **p<0.01

Figure 3.5. Accuracy comparisons between patients and controls (discrimination task).

D prime was calculated for each speaker combination. Higher d' values are indicative of better accuracy. Within hemifield speaker combinations are presented. Schematic representations of the speakers are provided at the bottom of the figure with the light colored circles representing the sound locations. Patients are represented by dark squares and controls by open circles. Error bars correspond to +/- 1SE. With the exception of the most eccentric combinations, poorer accuracy was found in patients compared to controls at all speaker combinations.

Within Hemifield vs. Across Midline Comparison

For within hemifield versus across midline comparisons, overall accuracy was significantly worse in patients than controls [$F(1, 39) = 9.27$, $p = 0.004$] and both groups were more accurate for combinations across the midline than within either hemifield [$F(2, 38) = 10.66$, $p < 0.001$]. A significant group X hemifield interaction was also found [$F(2,38) = 3.69$, p 0.034], reflecting greater differences in the right, then left hemifield.

Symptom Correlations

For cognitive symptoms, poorer performance in the right hemifield predicted greater severity of cognitive symptoms in both the localilzation ($\beta = -0.51$, $p = 0.043$) and discrimination (β = -0.59, p = 0.013) tasks. At all three speaker combinations, severity of cognitive symptoms was inversely correlated with performance (Table 3.2). Significant correlations were also observed for disorganization and difficulty in abstract thinking symptoms considered independently (Table 3.2). No other cognitive symptoms significantly correlated with performance.

Table 3.2.Correlations between performance and symptom severity

Localization	**30°**	**60°**	**90°**
Cognitive Symptoms	-0.33	-0.38	-0.50[a]
Conceptual disorganization	-0.40	-0.58[b]	-0.07
Poor attention	-0.20	-0.14	-0.21
Mannerisms and posturing	0.18	0.22	-0.38
Difficulty in abstract thinking	-0.22	-0.31	-0.60[b]
	-30°	**-60°**	**-90°**
Hallucinations	-0.37	-0.13	-0.46[a]

Discrimination	**0°/30°**	**0°/60°**	**0°/90°**
Cognitive Symptoms	-0.53[a]	-0.53[a]	-0.58[b]
Conceptual disorganization	-0.34	-0.26	-0.37
Poor attention	-0.22	-0.13	-0.17
Mannerisms and posturing	-0.07	-0.10	-0.17
Difficulty in abstract thinking	-0.51[a]	-0.72[b]	-0.67[b]

[a] $p<0.05$; [b] $p < 0.01$, two tailed

Greater accuracy (i.e., lower average absolute difference) in the left hemifield was associated with greater severity of hallucinations (β = -0.54, 95% CI: -0.03 to -0.02, p =0.026). Post hoc exploratory correlation analyses were performed to identify whether specific locations accounted for the significant associations (Table 3.2). Significant correlations were found for the most eccentric location for both symptom types. Correlations at other locations were moderate, but failed to reach significance.

Discussion

Deficits in auditory processing are now well documented in schizophrenia, primarily using measures such as pitch or duration discrimination that localize to primary auditory cortex (Heschl's gyrus, HG) [1, 4-6]. Spatial localization, an additional HG-dependent process, has been studied in schizophrenia to only a limited degree. This is the first study to evaluate localization using free-field sound within and across hemifields and to assess not only correct performance, but also absolute and relative localization disparities, which are known to be specifically sensitive to HG dysfunction.

The primary finding of the present study is that schizophrenia patients, as predicted, showed reduced accuracy and increased variability of localization relative to controls. Although reduced localization accuracy is seen following lesions of either primary or secondary auditory cortex, increased variability is reported as a hallmark of primary auditory cortical dysfunction. Patients had the greatest difficulty with the discrimination task in which reduced accuracy was found at nearly every location. In contrast, impairments on the localization task were seen throughout the right hemifield, but only at specific locations (-30 & -90) on the left. Increased variability of localization was also observed in the right-, but not left-, hemifield.

In imaging studies, spatial discrimination is associated with bilateral activation of posterior auditory association regions [27, 28]. Lesion studies, however, provide evidence that hemispheric involvement depends on the hemisphere and region of damage [29-31]. For example, in one study of post-stroke individuals, localization ability in both hemifields was affected primarily by lesions in the right hemisphere, whereas left hemisphere lesions affected primarily discrimination abilities. Furthermore, lesions that affected HG were distinguished from those that spared HG based upon pattern of deficit. Discrimination abilities were impaired in individuals with HG lesions in either hemisphere; whereas localization abilities were only affected if the lesion was in the right hemisphere[9].

Similar findings were obtained in other studies of post-stroke individuals [30, 32]. These studies thus provide a neuroanatomical basis for interpretation of deficit patterns in schizophrenia. In the present study, deficits were seen in patients across both left and right hemifields, with greater within- hemifield discrimination impairments found in the right hemifield compared to the left hemifield and across the midline. This pattern closely resembles the pattern observed for patients with brain lesions affecting right temporal lobe including primary auditory cortex (HG) [9] but differs from patterns seen following HG sparing [9]. Subtle findings in the present study, however, support a bilateral, rather than purely right unilateral lesion. First, patients showed preserved function at the left mid-hemifield location (-60º). At this site, left temporal lesions lead to somewhat improved accuracy relative to controls[9], suggesting that lack of deficit in patients may reflect combined effects of left and right auditory dysfunction.

Second, the greater deficit in right vs. left hemifield may reflect additive effects of left and right hemispheric dysfunction. However, isolated bilateral brain damage is rare, so there is relatively little information regarding effects of bilateral vs. unilateral auditory lesions. As a result, it is difficult to determine whether present findings reflect solely right temporal dysfunction or combined left and right dysfunction. In one study of MMN to intraaural time, phase and intensity delay cues, MMN deficits were seen bilaterally [7], suggestive of bilateral dysfunction. In a second study, however, no deficits in location MMN were observed (Fisher et al., 2008). However, MMN has yet to be evaluated for sounds presented free-field as in the present study.

Symptom Severity and Spatial Localization

In the present study, we also observed significant correlations of cognitive symptoms and hallucinations, but not other symptoms, with spatial localization ability. Within the localization paradigm, significant associations were only found for left hemifield performance, which is indicative of right hemisphere involvement. Paradoxically, however, better performance on the task (greater accuracy) was associated with greater hallucination severity. Given the inverse correlation, results might best be understood in terms of interhemispheric balance, with bilateral dysfunction producing the types of auditory deficits typically seen in schizophrenia, but relatively preserved right vs. left hemisphere dysfunction leading to overstimulation of external localization percepts. This theory is supported by electrophysiological evidence suggesting that schizophrenia is characterized by altered functional hemispheric asymmetry of the STG (Youn et al. 2003).

In contrast to the left hemifield correlations with hallucinations, cognitive symptoms correlated most strongly with right hemifield dysfunction, suggesting preferential association with left hemisphere dysfunction. In our study, performance was associated with conceptual disorganization and abstract thinking difficulties, cognitive symptoms which are heavily dependent on language function. As language dysfunction is known to be localized to left hemisphere and correlated with left STG dysfunction [14], right hemifield spatial localization deficits may provide a selective index of left auditory cortical dysfunction in schizophrenia.

Conclusion

Overall, sensory deficits have been increasingly documented in schizophrenia, along with histopathological changes in primary sensory cortices. The present study demonstrates impaired spatial localization ability in schizophrenia in a pattern consistent with right or bilateral primary cortex dysfunction. These findings support generalized models of cognitive dysfunction in schizophrenia, and suggest need for further studies investigating the relationship of sensory cortical dysfunction to symptoms and deficits of schizophrenia.

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Chapter 4. Early Sensory Processing and Spatial Localization

Differential Spatial Localization Impairments Associated with Hallucinations in Patients with Schizophrenia

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Abstract

Background: Previous studies demonstrating that patients with schizophrenia are impaired in their ability to discriminate auditory differences in pitch and duration provide evidence for primary auditory cortex abnormalities. However, few studies have examined the contribution of primary auditory dysfunction to spatial discrimination abilities. Results from lesion and imagining investigations suggest that the superior temporal gyrus is also involved in processing auditory spatial information. Impaired perception of sound sources and superior temporal gyrus abnormalities have been proposed as causes for hallucinations in schizophrenia.

Methods: The present study examined spatial discrimination abilities between patients diagnosed with schizophrenia (n=20) and controls (n=20) using low frequency simple tones generated from 11 speakers concavely arranged with 15 degrees spatial separation from 0° to 60° and 90° relative to the midline in both hemifields. Event related potentials were collected during a passive listening task to compare MMN response to frequency, duration and location deviants. Spatial discrimination accuracy and MMN peak amplitude were correlated with severity of hallucinations and positive thought disorder. Post-hoc exploratory analysis was performed to compare MMN peak between hemifields in controls and patients with and without a history of hallucinations.

Results: Overall spatial discrimination accuracy was significantly reduced in patients compared to controls ($p<0.001$). In patients, MMN peak amplitude was reduced in the left, but not the

right hemifield. Significant reductions in peak amplitude were observed for frequency (p= 0.013) but not duration deviants (p=0.340). Positive thought disorder severity was significantly correlated with spatial discrimination for the most eccentric locations in both hemifields. Hallucination severity was significantly correlated with MMN peak amplitude in the right hemifield. In patients without hallucinations, attenuations in MMN peak amplitude were observed for all locations in both hemifields. In patients with hallucinations, attenuations in MMN peak were only found in the left hemifield.

Conclusion: The results suggest that spatial discrimination is impaired in individuals with schizophrenia, which are likely attributed to primary auditory cortex abnormalities. Correlations between hallucination severity and MMN peak in the right hemifield and differential hemifield specific attenuations between patients with and without a history of hallucinations suggests that primary auditory cortex abnormalities associated with spatial localization may be causally related to hallucinations.

Introduction

Schizophrenia is a neuropsychiatric illness characterized by widespread cognitive impairments; symptoms thought to have the greatest impact on daily functioning[1, 2]. There is increasing evidence suggesting that dysfunction in the primary sensory cortices likely contributes to impairments in higher-order cognitive functioning[3]. Widespread deficits in auditory information processing are consistently demonstrated[4]; however, relatively few studies have focused on spatial localization. The present study examined whether early auditory processing impairments adversely impact spatial discrimination abilities in individuals diagnosed with schizophrenia using behavioral and electrophysiological investigations.

Behavioral assessments of auditory processing suggest that patients with schizophrenia are less accurate at discriminating pitch differences[5] and matching tones [6-8] following a brief delay [7-9]. While less studied, evidence for impairments in spatial localization has also been established. Patients were less accurate at discriminating the source of sound relative to the midline on a free-field sound study [10] and a study using interaural cue manipulations to simulate location differences [11]. Both provide evidence that sound localization is impaired in schizophrenia; however, limited information can be ascertained about the degree of impairment because assessments were restricted to 15°[10] and 90° [11] relative to the midline.

To further characterized localization impairments, we recently conducted a discrimination study using free-field tones presented from 7 speakers concavely arranged with 30° spatial separation in the horizontal plane [12]. Assessments of the ability to identify the location of a sound source (i.e., sound localization) and to discriminate between different locations (i.e., spatial discrimination) were conducted in patients and controls. On the sound localization task, overall accuracy was reduced in patients and responses were more variable, particularly in the right hemifield. Overall accuracy was also reduced on the spatial discrimination task[12]. The pattern of performance within conditions across both tasks was comparable to that observed in a study of patients with temporal lobe lesions encroaching upon the Heschyl's gyrus [13], suggesting that impaired spatial localization abilities may reflect impairments in early auditory processing.

Human auditory regions are located within superior temporal gyrus (STG), with primary auditory cortex located on the transverse gyri of Heschl (HG) [14]. Event related potential (ERP) studies are frequently employed to assess early auditory processing by examining neural activity generated in the primary auditory cortex in response to auditory stimuli. The auditory mismatch negativity (MMN) component is often studied because it is generated even in the absence of attention. The MMN is a negative deflecting component generated in the STG in response to a deviant tone presented infrequently among repetitively presented standards. Deviants differ from standards by one physical characteristic, such as duration, frequency or loudness. Onset of the component typically occurs between 100-250 ms, with variations in latency depending on the physical characteristic of deviance. MMN is thought to reflect an "automatic change-detection"[15, 16] mechanism for processing the discordance between a pre-attentive sensory-memory representation of the preceding repetitively presented stimuli and the deviant stimuli[17]. As such, it is thought to elicit an automatic attention switch to deviations in the auditory background(reviewed by Naatanen et al)[18, 19]).

ERP studies consistently demonstrate an attenuation in MMN peak amplitude in patients with schizophrenia in response to duration [20-24], pitch [22, 25] and frequency [26-28] deviants. Results from a meta-analysis of 36 studies found that the effect size of the difference between MMN amplitude in patients and controls was 0.99, providing evidence that MMN reductions are a robust characteristic of schizophrenia [29]. Paradigm comparisons reveal that the degree of amplitude reduction depends on deviant stimulus probability, inter-stimulus interval and the degree of discrepancy between standards and deviants [20, 30].

Evidence from lesion studies suggests that the STG is also involved in spatial localization[13]; however, relatively few studies have examined MMN in response to location deviants in schizophrenia and all have relied on interaural cue manipulations to simulate location differences. In one study, MMN amplitude was reduced in patients in response to inter-aural time but not loudness differences[11]. A second study employing inter-aural time differences failed to find significant group differences for MMN amplitude [31]. Alain et al [32] found reductions in MMN peak in response to binaural location deviants (i.e., sound presented in either the left or right ear); however, the deviants differed from standards based on both location and frequency, making it difficult to ascertain whether differences were attributed to deviances in frequency, location or a combination of the two.

Abnormalities of the STG may also contribute to increased severity of positive symptoms. Results from structural imaging studies suggest that reductions in STG volume[33], particularly in the left hemisphere, is associated with greater severity of hallucinations and thought disorder[34-37]. One theory postulated for hallucinations is that they represent a “mislocalization” of thoughts generated within the head to external locations[38, 39]. This theory is corroborated by evidence from functional imagining and electrophysiological investigations. For example, in an fMRI study, reduced left STG activity during an auditory target detection task was found for patients with schizophrenia with a history of hallucinations compared to patients with no history of hallucinations[40]. In ERP studies, differential reductions in MMN peak amplitude in patients with a history of hallucinations[31] have been observed and MMN generated in the left STG has been found to be correlated with positive symptom severity. To date, no studies have examined the associations between MMN response to location deviants using free-field stimuli and positive symptom severity.

In the present study, we employed a spatial discrimination task and an ERP investigation using free-field sounds presented from eleven speakers concavely arranged with 15° spatial separation.On the behavioral task, we assessed accuracy at discriminating between sound sources relative to the midline at varying degrees of spatial separation in both hemifields. For the ERP paradigm, we employed a passive listening study to assess MMN response to location deviants at varying degrees of spatial separation relative to standards (i.e., midline) in both hemifields. We also included duration and frequency deviants as control measures.

On the behavioral task, we predicted that overall accuracy would be impaired in patients compared to controls. Because MMN peak amplitude is typically inversely proportional to the degree of difference between the standards and deviants, on the ERP task, we predicted that in both groups MMN peak amplitude would increase with increasing spatial separation from standards. We also predicted that overall MMN peak amplitude would be reduced in patients compared to controls. MMN peak amplitude is predicted to be correlated with spatial discrimination performance in both groups. Because previous literature suggests right hemisphere dominance for encoding of spatial localization information[13, 41-43], post hoc exploratory analyses were conducted to examine whether group differences existed between hemifields on MMN peak and the relationship between MMN peak and discrimination abilities.

A secondary aim of the study was to assess whether spatial localization impairments are associated with increased severity of positive symptoms in schizophrenia. As such, post hoc exploratory analyses were conducted to examine the relationships between spatial discrimination performance, MMN peak amplitude and severity of positive thought disorder and hallucinations. Symptom severity was predicted to correlate with discrimination and MMN peak amplitude.

Methods

Participants

Participants included patients diagnosed with schizophrenia spectrum disorders (n=20) and healthy controls (n=20). The groups were matched for age and sex. Parental socioeconomic status was assessed using the Hollingshead Scale for Socioeconomic Status[44]. No significant differences were observed between groups for relevant demographic characteristics (Table 4.1).

Table 4.1.Demographic Characteristics

	Patients n (%)	**Controls n (%)**	**X^2**	**p-value**[a]
Gender				
Male	16 (80)	16 (80)	0.000	0.999
Female	4 (20)	4 (20)		
	X (SD)	**X (SD)**	**p-value**[a]	
Age at Interview (years)	41.6 (8.8)	36.4(10.2)	0.092	
Parental Socioeconomic Status[b,c]	39 (9)	42 (16)	0.495	

[a] two-tailed; [b]Parental SES calculated based on the Hollingshead scale for Socioeconomic Status [c]$N_{missing}$ = Patients = 7, Controls = 6

Patients were recruited from the inpatient unit (n= 9) and residential care facilities (n=11) associated with the Nathan Kline Institute for Psychiatric Research. Diagnoses were made based on review of clinical records and the Structured Clinical Interview for DSM-IV(SCID)[45]. The SCID is a semi-structured clinical interview for major Axis-I psychiatric disorders using DSM-IV diagnostic criteria[46]. The Clinical Research Division of the Nathan Kline Institute maintains a pool of graduate-level certified SCID raters who have completed a training program based on the 11-hour SCID-101 recorded training series and have demonstrated interview and rating skills. In addition to interviewing the patient, SCID raters review all available records. Diagnostic challenges are resolved by case conferences involving at least two psychiatrists and the rater.

Patient sample characteristics are presented in Table 4.2. The majority of patients were diagnosed with schizophrenia, undifferentiated subtype and most were taking atypical antipsychotics at the time of participation. Average age at first hospitalization was 22 years and average illness duration was 15 years.

Table 4.2. Patient Characteristics

	N (%)
Diagnosis	
Schizophrenia-Undifferentiated	10 (50)
Schizophrenia,Paranoid	5 (25)
Schizo-Affective, Bipolar	2 (10)
Schizo-Affective	1 (5)
Schizo-Affective, Depression	2 (10)
Medication Status	
Atypical antipsychotic	15 (75)
Typical antipsychotic	3 (15)
Combination	2 (10)
Patient Status	
Outpatient	11 (55)
Inpatient	9 (45)
	X(SD)
Age at first hospitalization (years)^q	22.5 (7.6)
Illness Duration (years)^b	15.6(7.5)

$^a N_{missing} = 3$; $^b N_{missing} = 5$

Healthy controls were recruited from the surrounding community by local advertisements. Controls were excluded if they meet criteria for an Axis I psychiatric disorder. In both groups, individuals were excluded if they had a history of organic brain disorder, mental retardation, past drug or alcohol dependence, current drug or alcohol abuse, or hearing impairments. Individuals were also excluded if they were left hand dominant because lateralization of auditory processing cannot be assumed in left handed individuals. Patients provided informed consent prior to participation. The study was approved by the Nathan Kline Institute for Psychiatric Research and the City University of New York, Graduate Center Institutional Review Boards.

Speaker Apparatus

Stimuli were projected from eleven speakers concavely arranged with 15 degrees separation for locations from 0-60° and 90°. This enabled assessments across 180° in the horizontal plane at the level of the pinnae with greater sensitivity to identify differences closest to the midline (illustrated in Figure 4.1).

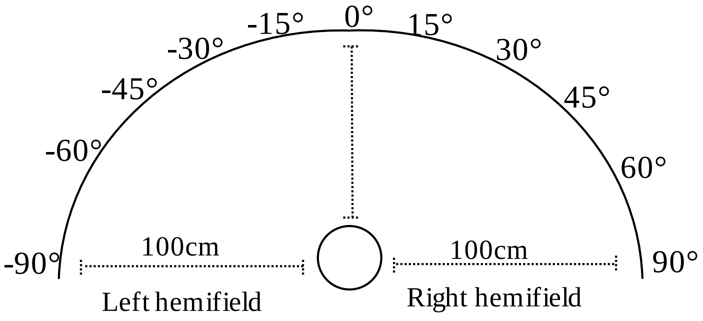


Figure 4.1. Speaker Arrangement

Eleven speakers were concavely arranged with 15° spatial separation from 0°-60° and at 90° enabling assessments across 180° in the horizontal plane. Subjects were seated 100cm from the front and sides of the structure and the speakers were adjusted to be approximately at the level of the subject’s pinnae.

Spatial Discrimination Paradigm

In the discrimination paradigm, 16 trials per speaker pair (700 trials total) were presented in random order. Prior to the presentation of each trial, participants were instructed to fixate on a light presented at the midline. Stimuli consisted of 300ms 10ms rise/fall, 1000Hz tones presented at 60dB. In each trial, two tones were sequentially presented 150 ms apart from either the same or different speakers. The participant indicated whether the tones came from the same or different speakers, ignoring relative position of the tones. Subsequent stimuli were presented only after a response was provided. Participants completed approximately 70 practice trials prior to initiating the task and feedback was not provided.

Oddball Passive Listening Paradigm

During ERP data acquisition, standard (90%) and deviant (10%; 33% duration, 33% frequency and 33% location) tones were presented in pseudo-random order from the speaker apparatus while subjects watched a silent movie. Standard stimuli consisted of 100ms 10ms rise/fall 1000Hz simple tones presented at 60dB at the midline (0°). Deviants differed from standards based on duration, frequency or location. Duration and frequency deviants were also presented at the midline. Duration deviants were 150ms 10ms rise/fall 1000Hz simple tones. Interstimulus interval was 150ms. Because tone matching abilities have been previously demonstrated to be impaired in patients, frequency deviants were collaborated based on individual performance on a tone matching task (described below). Location deviants had the same physical characteristics as standards but were presented at varying degrees of spatial separation with respect to the midline in either the left or right hemifield.

Tone Matching Task

The Tone Matching Task was used to determine the relevant threshold for detecting differences between tones [8]. In this task, a reference tone of 1000Hz and subsequent comparison tones were presented that differ from the reference tone by 1%, 2.5%, 5%, 10%, 15%, 20%, 50%, 75%, and 100%. All tones were presented for 100ms at 75Db. Blocks of 24 tones were presented for each tone pair. Within each block, half of the tones were identical and half were different. Participants indicated whether the two tone pairs were the same or different. Thresholds were calculated based on the percentage correct for each block. The tone closest to the 1000Hz reference tone with at least 95% correct was used as the deviant tone in the MMN paradigm.

ERP Data Acquisition

ERPs were collected during a single session. Continuous electroencelophalogram data and digital auditory stimulus codes were acquired using a 64 channel Neuroscan system (http://www.neuroscan.com/index.cfm). Epochs (-100ms to 400 ms) were created offline and were baseline corrected from 100 pre-stimulus presentation and artifact rejected at 100 uV. Epochs were averaged for each participant for each stimulus type. The average number of accepted sweeps across all conditions was 74% (+/-15) and 79% (+/-13) for patients and controls respectively. The MMN component was calculated by subtracting the standard waveform from the deviant waveform. Data were filtered with a zero-phase shift 40-Hz low pass filter (12 dB/octave) and a forward phase 1.0 high pass filter (6 dB/octave).

ERP Components

The auditory components of interest consisted of the MMN in response to three deviant types: frequency, duration and location. MMN was assessed by measuring latency and peak amplitude. The latency windows for selecting peaks were determined based on visual inspection of the grand average waveforms. For the location deviants, separate waveforms were created for each location within each hemifield and averaged across hemifields. For the waveforms averaging across hemifield, right and left hemisphere electrodes were averaged with respect to the hemifield of the location deviant (i.e., ispi vs. contralateral projections). Latency windows for each deviant type were determined based on inspection of grand averages of within hemifield and across hemifield conditions.

Peaks were identified as the greatest negative deflecting amplitude within the specified timeframe for each participant for each deviant type and latencies correspond to the onset of the peak amplitude. Timeframes for the components differed by deviant type. For location deviants, latency generally increased with increasing spatial separation between standards and deviants. Consistent with previous studies, the peak latency for duration deviants was later than frequency deviants (Table 4.3). Peak amplitudes used for comparisons correspond to frontocentral electrode sites, which were referenced to the average of the mastoids.

Table 4.3. Latency Windows for MMN Peak Selection

Deviant Condition	**Collapsed (ms)**	**Left Hemifield (ms)**	**Right Hemifield (ms)**
15°	80-180	78-182	100-145
30°	84-227	84-217	107-166
45°	84-248	100-248	96-145
60°	154-252	100-237	156-240
90°	131-258	158-238	164-240
Duration	189-342	n/a	n/a
Frequency	70-250	n/a	n/a

Positive Symptom Severity

The Scale for Assessment of Positive Symptoms (SAPS) is a semi-structured interview used to assess the frequency and severity of hallucinations, delusions and thought disorder[47]. Interviews were conducted and rated by a trained, doctoral graduate student. Interviews were performed after the completion of the behavioral and ERP studies.

Statistical Analysis

Mixed Model Analysis of Variance (RM ANOVA) using SPSS version 17.0 were performed to compare spatial discrimination and MMN amplitude differences between patients and controls. Linear regression analyses stratified by group and hemifield were performed to compare group differences in the relationship between spatial discrimination and MMN peak amplitude. Pearson correlation analyses were conducted to examine the associations between positive symptom severity and spatial discrimination performance and MMN peak amplitude at locations within each hemisphere where significant group differences were observed. A RM ANOVA was performed to identify hemifield specific differences in MMN peak amplitude between patients with and without hallucinations.

Results

Tone Matching Thresholds

Between group comparisons for tone matching thresholds are presented in Table 4.4. As demonstrated in previous studies, tone matching thresholds were higher in patients compared to controls ($X^2 = 16.4$, $p = 0.012$).

Table 4.4 Tone Matching Thresholds

Tone Matching Threshold	Patients n (%)	Controls n (%)	X^2	p-value
1020 Hz (2% difference)[a]	0 (0)	5 (25)	16.4	0.012
1025 Hz (2.5% difference) [a]	2 (10)	1 (5)		
1050 (5% difference) [a]	1 (5)	5 (25)		
1100 (10% difference) [a]	4 (20)	5 (25)		
1200 (20% difference) [a]	2 (10)	1 (5)		
1500 (50% difference) [a]	3 (15)	3 (15)		
2000 (100% difference) [a]	8 (40)	0 (0)		

[a] Percent difference from standards used in the ERP study

Spatial Discrimination

Performance on the spatial discrimination task was assessed by calculating the d prime (d') for each speaker combination [48]. Larger d' values are indicative of greater accuracy. To assess performance differences with respect to location, a 2 (group: patients vs controls) x 5 (location: 90°, 60°, 45°, 30°, 15° (averaging across hemifields)) RM ANOVA with group status as the between subjects factor and location as the repeated measures factor was performed. Overall performance was significantly reduced in patients(Mean (Standard Error) (X(SE)) = 1.63 (0.2) compared to controls (X(SE) = 2.76 (0.2)) and both groups were less accurate at locations closer to the midline than those farther away. The group x location interaction failed to reach significance, suggesting that the overall pattern of performance was comparable between the groups (Table 4.5, Figure 4.2)

Table 4.5. Spatial Discrimination Comparisons

Spatial Discrimination	F	df	p-value
Group	18.09	1, 38	**<0.001**
Location	14.74	4, 35	**<0.001**
Group x location	1.24	4, 35	0.311

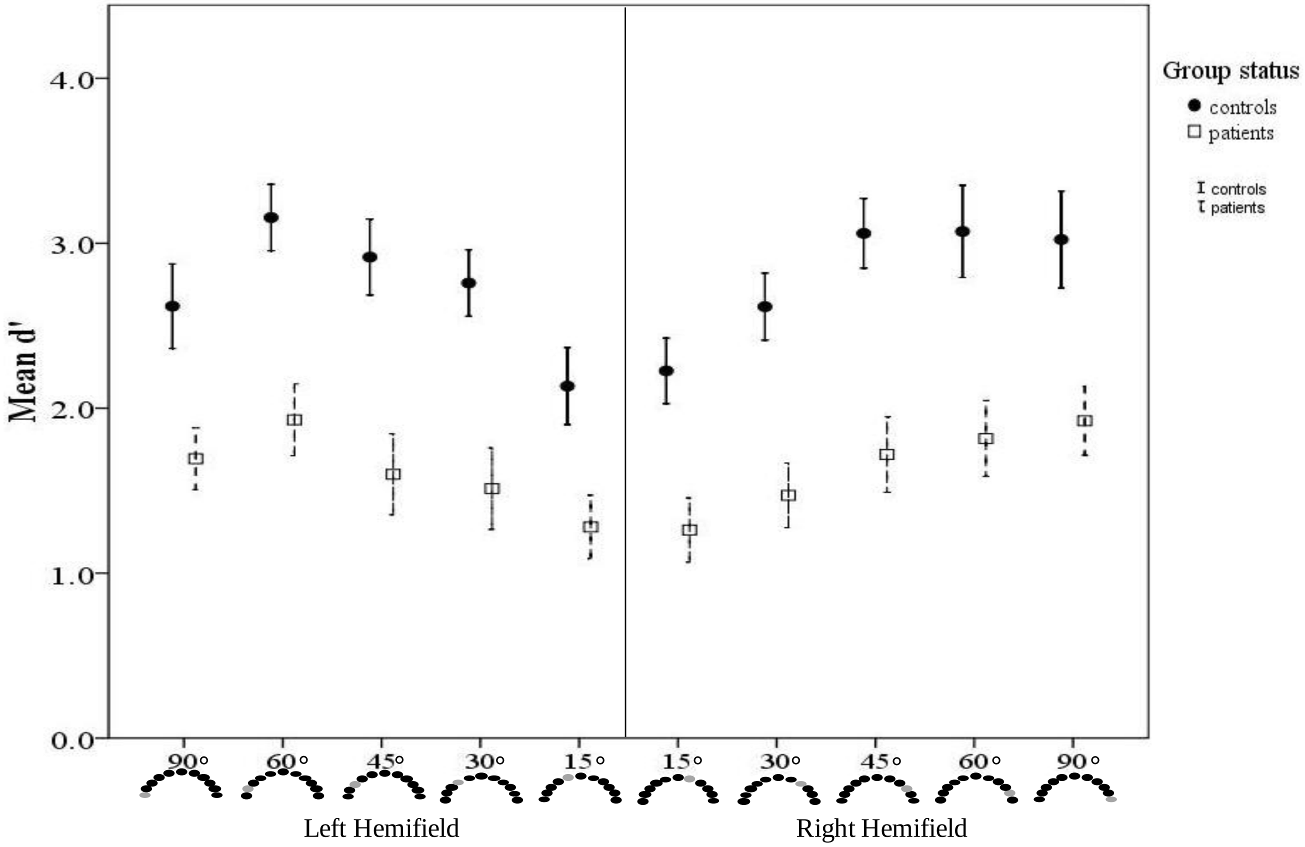


Figure 4.2. Spatial Discrimination Accuracy Differences

Shaded circles represent controls and open squares represent patients. Error bars correspond to+/-1 SE. Performance is assessed using dprime for each speaker location. A graphical representation of the speakers is presented at the bottom of the table. Grey circles represent the location being measured. Overall accuracy was significantly reduced in patients compared to controls, with the greatest differences observed for locations with 45° or greater spatial separation from the midline.

Mismatch Negativity

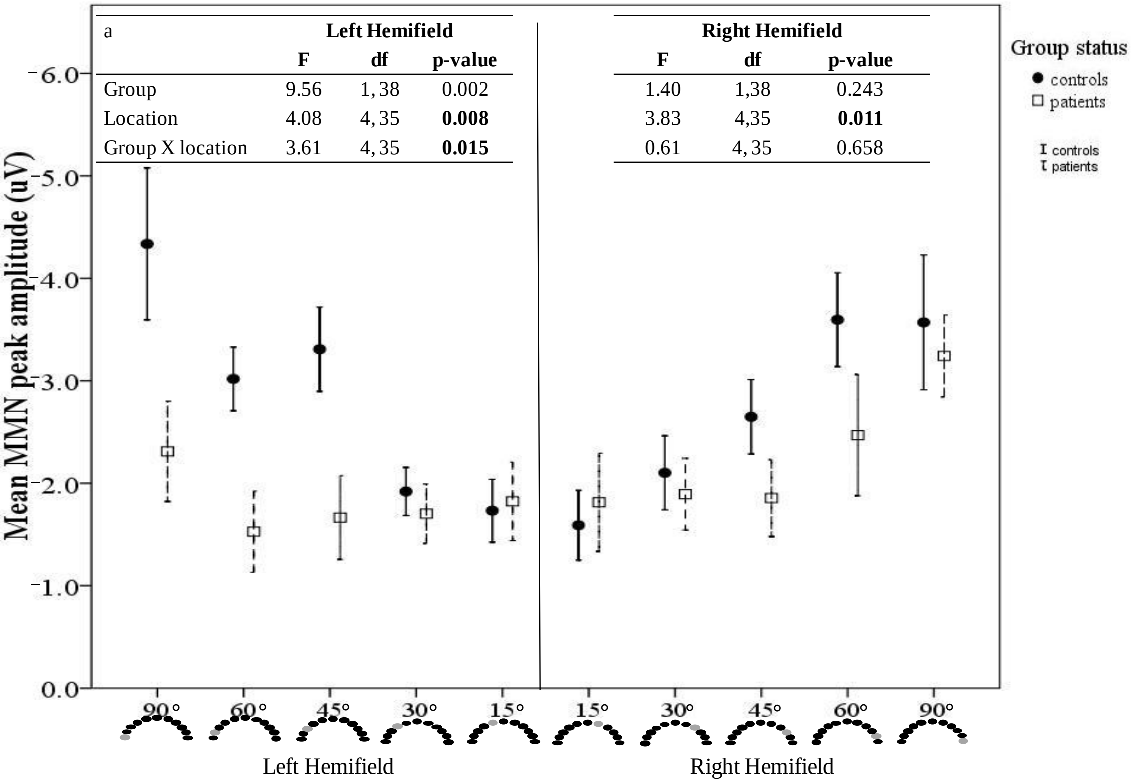
Location Deviants

Mismatch negativity was assessed using measurements of latency and peak amplitude, which were calculated by taking the average of four frontocentral electrodes (i.e, Fz, FCz, F1 and F2). A 2 (group) x 5 (location) RM ANOVA was performed to identify group differences in latency with respect to location (Table 4.6). Average MMN latency was comparable between groups and latency increased with increasing spatial separation between standards and deviants (X (SE) Latency 15°: 127.9 ms (4.6), 30° = 152.9ms (6.5), 45°=157.7ms (6.9), 60°= 194.2ms (4.9), 90°=194.3ms (6.5)). In patients, latency increased with increased spatial separation at all locations. In controls, while longer latencies were observed for the farther locations (i.e., 60° and 90°), there was no clear pattern between spatial separation and peak onset for closer location deviants.

To assess differences in average MMN peak amplitude with respect to location, a 2 (group) x 5 (location) RM ANOVA was performed (Table 4.6). Overall amplitude was reduced in patients (X (SE)= -1.61uV (0.2)) compared to controls (X(SE)=2.14uV (0.2)) and the difference approached significance. Average peak amplitude significantly differed by location, with lower amplitudes at locations closer to the midline than those farther away. The group x location interaction was also significant. In controls, MMN peak amplitude increased with increasing spatial separation. In contrast, in patients, mean amplitude was comparable for locations closest to the midline (i.e., 45° or less) (Figure 4.3). Voltage maps are presented in Figure 4.4 and average waveforms are presented in Figure 4.8(Supplemental).

Table 4.6. MMN Response Comparisons (Location Deviants)

Mismatch Negativity	**F**	**df**	**p-value**
Latency			
Group	0.00	1, 38	0.981
Location	24.26	4, 35	**<0.001**
Group x location	3.06	4, 35	**0.029**
Peak amplitude			
Group	3.72	1, 38	0.061
Location	3.56	4, 35	**0.015**
Group x location	2.76	4, 35	**0.043**



a	**Left Hemifield**			**Right Hemifield**		
	F	**df**	**p-value**	**F**	**df**	**p-value**
Group	9.56	1, 38	0.002	1.40	1,38	0.243
Location	4.08	4, 35	**0.008**	3.83	4,35	**0.011**
Group X location	3.61	4, 35	**0.015**	0.61	4,35	0.658

Figure 4.3. MMN Peak Differences (Location Deviants)

Shaded circles represent controls and open squares represent patients. Error bars correspond to +/- 1SE. Mean MMN peak amplitude corresponds to the average of FC, FCz, FC1, and FC2 frontocentral electrodes. A graphical representation of the speakers is presented at the bottom of the table. Grey circles represent the location being measured. In controls, MMN peak amplitude increased with increasing spatial separation between standards and deviants in both hemifields. (a) Results from RM ANOVA stratified by hemifield. In the left hemifield, overall MMN peak was reduced in patients and with the exception of 90°, MMN peak amplitude was comparable across all spatial deviants. In the right hemifield, overall MMN peak was comparable between patients and controls.

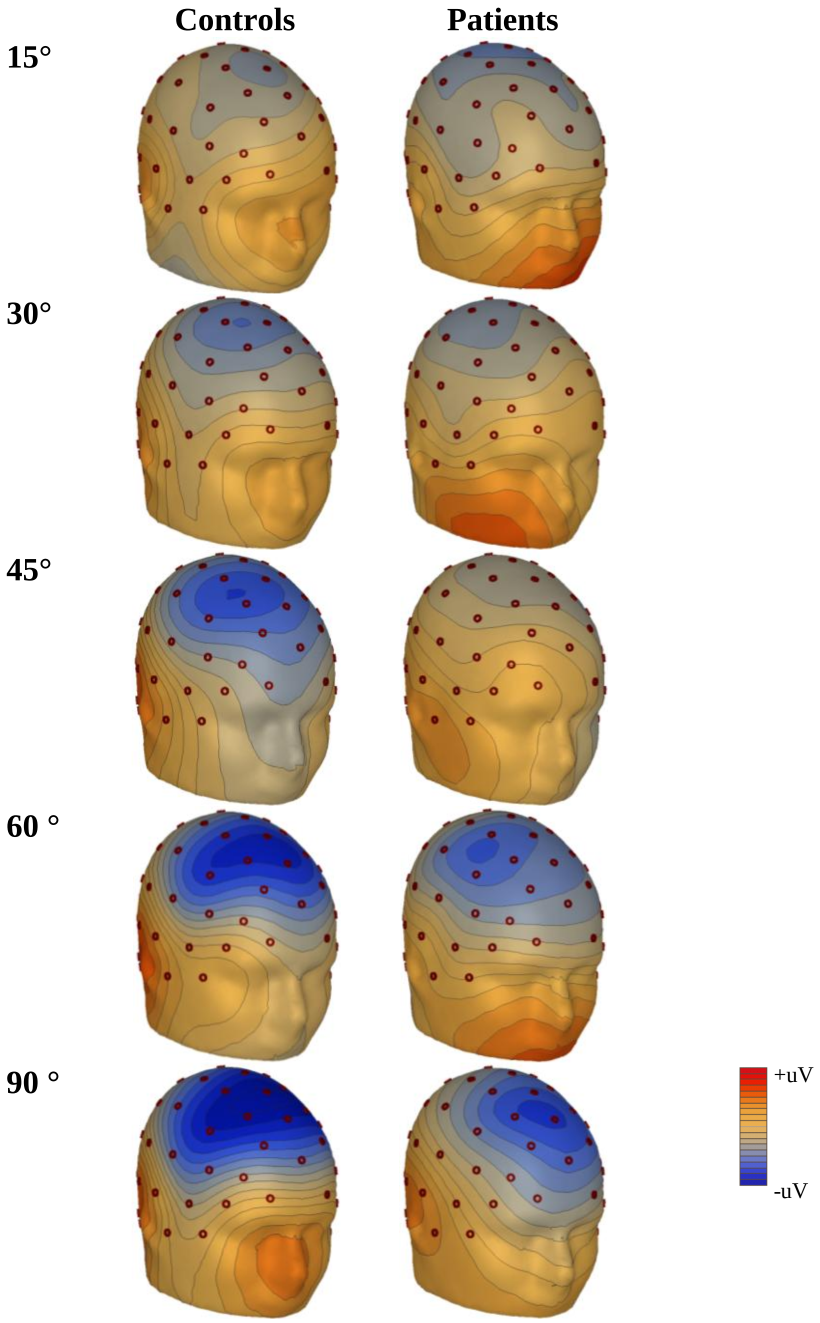


Figure 4.4. Voltage Topography Maps of MMN Peak Response Averaged Across Hemifields (Location Deviants)

High density electrodes were selected from the vicinity of Fz, Cz, and FCz. In both groups, MMN peak increased with increasing spatial separation between standards and deviants. No between differences were observed for location deviants closest to the midline (15°); whereas at larger degrees of separation, patients' response was attenuated and between group differences increased with increasing spatial separation.

Within Hemifield Comparisons

To identify hemifield specific differences in MMN peak amplitude in patients, separate 2 (group) x 5 (location) RM ANOVAs were performed stratifying by hemifield (Figure 4.3). In the left hemifield, overall MMN peak amplitude was significantly reduced in patients (X(SE) = -1.8uV(0.2)) compared to controls (X(SE) = 2.8uV(0.2)) and MMN peak amplitude significantly differed by location deviant. In controls, MMN peak amplitude increased with increasing spatial separation; whereas in patients, with the exception of 90°, MMN peak amplitude was comparable at all location deviants. In contrast, in the right hemifield there were no significant between group differences.

Duration and Frequency Deviants

Independent samples t-tests were performed to compare MMN peak amplitude between patients and controls for duration and frequency deviants. No significant between group differences were observed for average latency for either duration (X (SE) patients= 266.8 ms(9.5), controls= 275.8 (8.2), p=0.480) or frequency (X(SE) patients=152.0(10.3), controls=156.4(8.7), p= 0.751). While the voltage topography maps clearly suggest an attenuation in MMN in response to duration deviants (Figure 4.5), no statistically significant differences for peak amplitude were found (X(SE) patients = -2.09uV(0.3), controls=-2.56(0.4), p = 0.340). Peak amplitude for frequency deviants was significantly reduced in patients compared to controls (X(SE) Patients = -2.8uV(0.4), Controls -4.3uV(0.5), p = 0.034). Average waveforms are presented in Figure 4.9(Supplemental)

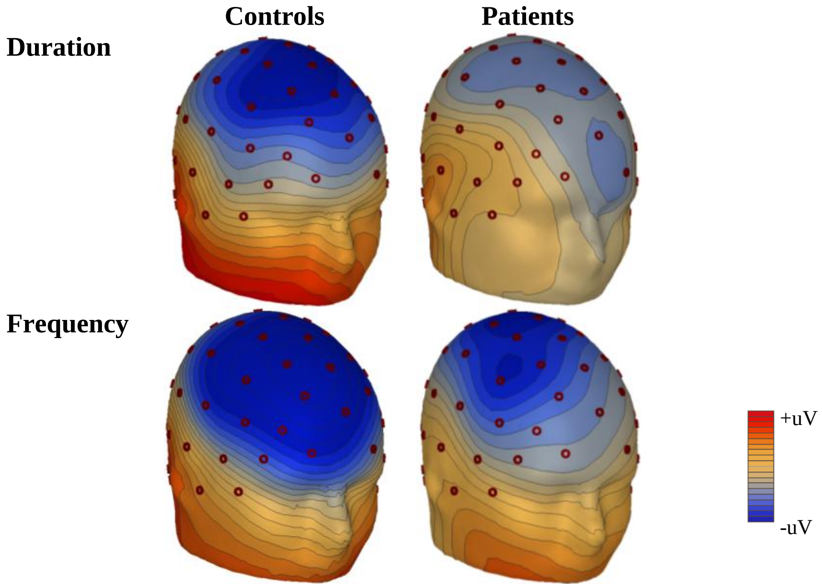


Figure 4.5. Voltage Topography Maps of MMN Response (Duration and Frequency Deviants)

High density electrodes were selected from the vicinity of Fz, Cz, and FCz. Compared to controls, patient's response was attenuated for frequency deviants. While response also appears to be attenuated for duration deviants, differences were not statistically significant.

Relationship between Spatial Discrimination and MMN Peak

To compare the relationship between d' and MMN peak across locations between groups, separate linear regression analyses were performed stratifying by group and hemifield (Figure 4.6). Consistent with the MMN peak analysis, hemifield specific differences existed between patients and controls. In controls, there was a significant linear relationship between spatial discrimination and MMN peak amplitude in both hemifields. As the degree of spatial separation increased, both spatial discrimination accuracy and MMN peak amplitude increased (r^2 left hemifield: 0.41, p= 0.049; r^2 right hemifield: 0.91, p=0.012). In patients, a similar pattern was observed in the right hemifield and the association approached significance (r^2 =0.70, p = 0.078); whereas no association was found in the left hemifield (r^2 =0.012; p =0.326).

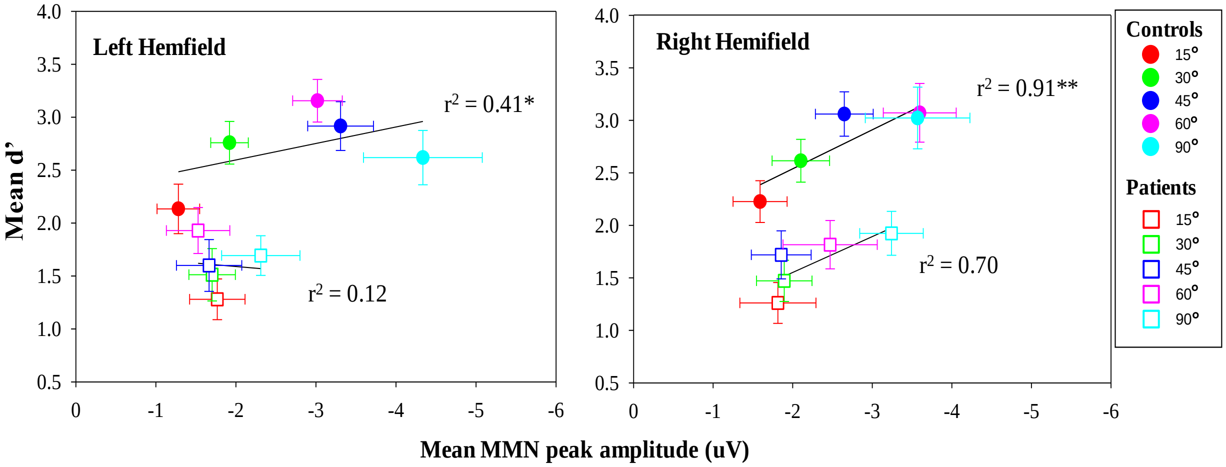


Figure 4.6. Associations between Average Spatial Discrimination and MMN Peak Amplitude

Solid circles represent controls and open square represent patients. In controls, accuracy and MMN peak amplitude increased with increasing spatial separation from the midline in both hemifields. In patients, increases approaching significance (p=0.078) are observed in the right hemifield; whereas no relationship was observed in the left hemifield. ; *p<0.05;**p<0.01, two-tailed

Symptom Severity

Pearson correlation analyses were conducted to assess the relationship between symptoms, performance and MMN peak amplitude for each spatial location associated with the greatest group differences (i.e., 45°, 60° and 90° in each hemifield) (Table 4.7). Correlations were also performed with MMN peak amplitude in response to duration and frequency deviants in order to verify that associations were specific to spatial localization impairments.

Increased severity of positive thought disorder was associated with spatial discrimination accuracy for the most eccentric locations in both the right and left hemifield (r^2 = -0.51 and -0.49 for the 90° left and right hemifield, respectively, p<0.05, two-tailed); whereas no significant associations were observed for MMN peak amplitude at any location. Increased severity of auditory hallucinations was associated with attenuated MMN peak for all right hemifield locations (r^2 45°= -0.50, 60°=-0.61, 90°-0.47, p<0.05, two-tailed). No significant correlations were found for left hemifield locations. In contrast, no significant associations between severity of auditory hallucinations and spatial discrimination performance were observed.

Table 4.7. Relationship between Symptom Severity, Spatial Discrimination and MMN

	Left hemifield			**Right hemifield**			**Duration**	**Frequency**
	90º	**60º**	**45º**	**45º**	**60º**	**90º**		
Spatial Discrimination (dprime)								
Auditory Hallucinations Severity	0.20	-0.20	-0.13	0.13	-0.06	-0.04	Not applicable	
Positive Thought Disorder Severity	**-0.52**	-0.08	-0.19	-0.17	-0.37	**-0.49**		
MMN Peak Amplitude								
Auditory Hallucinations	-0.39	0.00	0.14	**-0.50**	**-0.61**	**-0.47**	-0.32	-0.30
Positive Thought Disorder Severity	0.12	0.32	0.09	-0.22	0.03	0.22	0.15	-0.17

MMN Peak Amplitude Hemifield Differences and Hallucination Status

To assess whether hemifield specific differences in MMN peak amplitude in response to location deviants are characteristic of patients with hallucinations, the patient group was divided into patients with (n=12) and without a history of auditory hallucinations (n=8), based on self report from the SAPS. To compare groups, a 3 (group: controls, patients with hallucinations vs. patients without hallucinations) x 2 (hemifield: left vs. right) x 5 (location: 15°, 30°, 45°, 60° vs. 90) RM ANOVA was performed (Table 4.8). Average MMN peak amplitude was significantly greater in controls (X(SE)= -2.7(0.2)) compared to patients without hallucinations (X(SE) = -1.5 (0.3),p= 0.004, two-tailed) but comparable to patients with hallucinations (X(SE)=-2.3 (0.3), p=0.277, two-tailed). Peak amplitude differences between patients with and without hallucinations approached significance (p=0.058, two-tailed). Average peak amplitude increased with increasing spatial separation [F(4, 34) = 2.67; p= 0.049] and no significant main effect was observed for hemifield [F(1, 37) = 2.39, p = 0.130]. A significant hemifield x group interaction was observed [F(2, 37) = 3.9, p= 0.030]. Overall peak was comparable between hemifields for controls (X(SE): left hemifield: -2.8(0.2), right hemifield: -2.7(0.3); p = 0.696, two-tailed) and patients without hallucinations (X(SE): left: -1.5(0.3) right: -1.5 (0.4); p = 0.912, two-tailed). In patients with hallucinations, MMN peak amplitude was significantly reduced in the left hemifield (X(SE)-2.0(0.2)) compared to the right (X(SE)= -2.8 (0.3); p = 0.035, two-tailed). The location x group interaction was also significant. In patients without hallucinations, with the exception of 60° in the left hemifield, MMN peak was comparable across all location deviants in both hemifields. In patients with hallucinations, with the exception of 90°, MMN peak amplitude was comparable across all locations in the left hemifield. In contrast, in the right hemifield, peak increased with increasing spatial separation; a pattern similar to that observed in controls(Figure 4.7). All other interactions failed to reach significance.

Table 4.8. MMN Peak Comparison between Control and Patients with and without Auditory Hallucinations

MMN Peak amplitude	**F**	**df**	**p-value**
Group[a]	4.80	2, 37	**0.014**
Hemifield	2.39	1, 37	0.130
Location	2.69	4, 34	**0.049**
Group x hemifield	3.87	2, 37	**0.030**
Group x location	3.32	4, 35	**0.021**
Hemifield x location	0.55	4, 34	0.700
Group x hemifield x location	1.74	4, 35	0.163

[a] Group: Controls, patients with hallucinations vs. patients without hallucinations

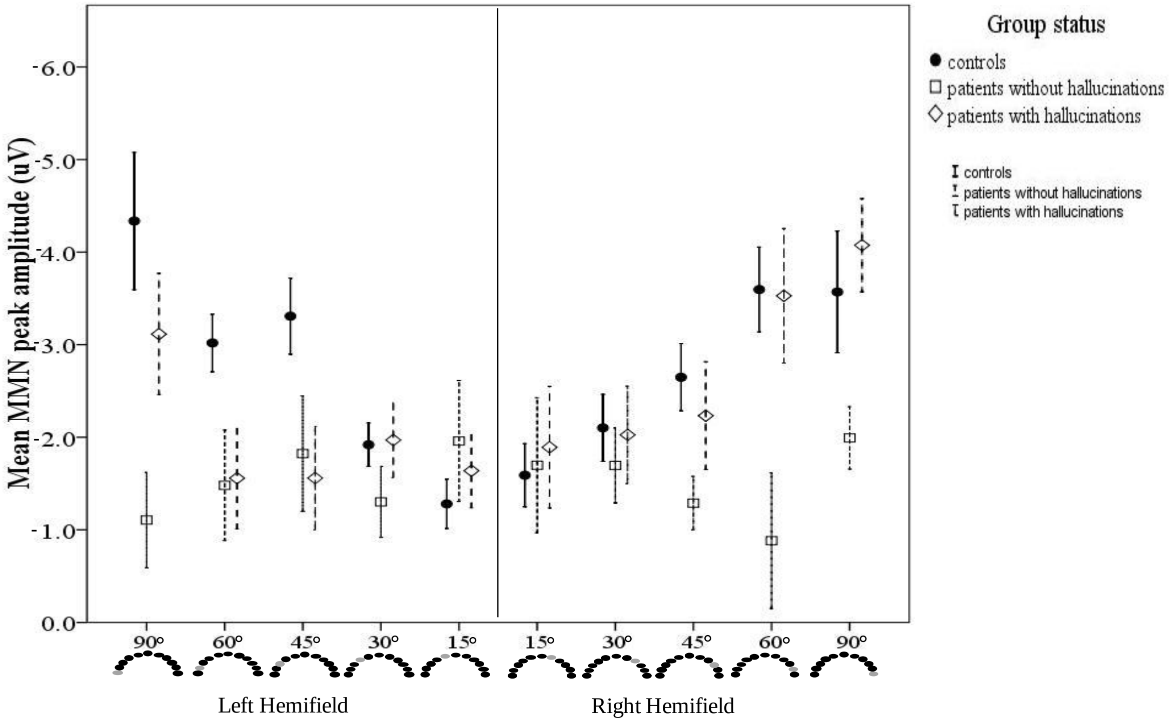


Figure 4.7. MMN Peak Differences in Controls and Patients with and without Auditory Hallucinations

Shaded circles represent controls, open squares represent patients without history of auditory hallucinations and open triangles represent patients with auditory hallucinations. Error bars correspond to +/- 1SE. Mean MMN peak amplitude corresponds to the average of FC, FCz, FC1, and FC2 at frontocentral electrodes. A graphical representation of the speakers is presented at the bottom of the table. Grey circles represent the location being measured. Hemifield specific differences in MMN peak were observed between patients with and without a history of hallucinations. In patients without a history of hallucinations, MMN peak was comparable across all locations in both hemifields. In patients with a history of hallucinations, a similar pattern is observed in the left hemifield. In contrast, in the right hemifield, MMN peak increased with increasing spatial separation; a pattern comparable to controls.

Laterality and Hallucination Status

To examine laterality differences in MMN peak amplitude between controls and patients with and without a history of auditory hallucinations, paired samples t-tests were performed on left and right frontal electrodes (F3) averaged for ispi and contralateral projections with respect to hemifield of location deviants. No significant hemisphere differences were observed for controls (ipsilateral p = 0.736; contralateral p = 0.118) or patients without hallucinations (ipsilateral: p = 0.657, contralateral: p = 0.424). In patients with a history of hallucinations, MMN peak amplitude was significantly reduced in the right hemisphere for contralateral projections (X(SE) Right= -2.0uV(0.2), Left=-2.7(0.3), p =0.017). In contrast, MMN peak amplitude in the left hemisphere was attenuated for ipsilateral projections(X(SE) Right=-2.8uV(0.2), Left=-1.9(0.3), p =0.064).

Discussion

It is well established from behavioral and electrophysiological investigations of duration, loudness and frequency deviants that schizophrenia is associated with early auditory processing impairments, which are attributed to a dysfunction of the STG [29]. However, relatively little is known about the contribution of STG dysfunction on spatial localization. In the present study we used behavioral and electrophysiological investigations of spatial discrimination to determine whether early auditory processing abnormalities impact spatial localization. The findings extend upon previous studies by examining multiple locations in both hemifields. The results provide evidence that spatial discrimination is impaired in schizophrenia and suggest that impairments are attributed to a dysfunction in the primary auditory cortex. Further, evidence is provided that hallucinations may arise due to hemisphere specific abnormalities in early auditory processing associated with spatial localization.

In the present study, spatial discrimination abilities were impaired in patients; however, the pattern of performance across locations and between hemifields was comparable between groups. Unlike spatial discrimination, MMN peak in response to location deviants was differentially impacted by hemifield. In controls, MMN peak amplitude increased with increasing spatial separation between standards and deviants in both hemifields. In patients, although overall MMN peak amplitude was attenuated compared to controls, a similar pattern with respect to spatial separation was observed in the right hemifield; however, in the left hemifield, MMN peak was comparable across all location deviants. Similar hemifield specific differences were observed for the relationship between spatial discrimination performance and MMN peak amplitude. In controls, as the degree of spatial separation increased, significant increases in accuracy and MMN peak amplitude were found in both hemifields. In patients, a linear association was observed in the right hemifield; whereas no relationship was found in the left hemifield.

Taken together, the results suggest that spatial localization impairments characteristic of the disorder are likely attributed to right STG abnormalities. Unlike processing of feature based characteristics of auditory stimuli, such as pitch and duration, early auditory processing of spatial information is thought to be predominately right hemisphere dependent [41]. Patients with temporal lobe lesions are less accurate on discrimination tasks [13] and right hemisphere lesions appear to affect spatial discrimination abilities in both hemifields [13, 49]. Right hemisphere dominance for encoding spatial information is demonstrated by observations of differential MMN peak and amplitude responses between hemifields for location deviants in ERP investigations[42, 43].

Symptom Severity and Superior Temporal Gyrus Dysfunction

In the present study, we found that associations with symptom severity differed between discrimination abilities and MMN peak amplitude. Increased severity of positive thought disorder was associated with reduced accuracy on the spatial discrimination task for the most eccentric locations in both hemifields; whereas no significant associations were found with MMN peak amplitude. Reductions in peak MMN amplitude for all relevant location deviants in the right hemifield were associated with increased hallucination severity. In contrast, no significant associations were found for left hemifield location deviants. Further, hallucination severity was not significantly associated with MMN peak amplitude in response to duration or frequency deviants, suggesting the relationship with early auditory processing is specific to localization impairments.

Right hemifield specific correlations suggest hallucination severity is associated with left STG abnormalities. This is consistent with results from previous studies suggesting that reduced STG volume [33] and abnormal activity[40] is associated with increased hallucination severity in schizophrenia. However, post hoc comparisons of hemifield specific differences in MMN peak amplitude between controls and patients with and without auditory hallucinations provide evidence that early auditory processing abnormalities associated with spatial localization abilities may be differentially impaired by hallucination status. Significant left hemifield attenuations in MMN peak amplitude were observed in patients with hallucinations; whereas peak amplitude was comparable between hemfields in patients without hallucinations. Further, in patients without hallucinations MMN peak amplitude was comparable across all spatial deviants in both hemifields. In contrast, in patients with a history of hallucinations; MMN peak amplitude abnormalities were only observed in the left hemifield. Taken together, the findings suggest that impaired spatial discrimination accuracy is likely caused by a bilateral STG abnormality, which likely differentially affects patients with a history of hallucinations.

Given the paradoxical relationship between left hemifield specific reductions in MMN peak (right hemisphere dysfunction) in patients with hallucinations and significant correlations between hallucination severity in right hemifield locations (left hemisphere) for MMN peak amplitude, the results might best be understood in terms of interhemispheric imbalance, leading to overstimulation of external localization percepts. This theory is supported by electrophysiological evidence suggesting that schizophrenia is characterized by altered functional hemispheric asymmetry of the STG [37] .

This theory is supported in the present study by the results from between groups comparisons for MMN peak with respect to ispilateral and contralateral projections. In patients with a history of hallucinations, reduced amplitude was found in the right hemisphere for contralateral projections and in the left hemisphere for ispilateral projections. No hemisphere differences were found for controls or patients without a history of hallucinations. While hemisphere comparisons between patients with and without hallucinations provide evidence for differential impairment associated with hallucinations, the results must be interpreted with caution due to limitations in sample size. Further investigations are required to confirm the findings.

Conclusion

Sensory deficits and abnormalities associated with primary sensory cortices have been increasingly demonstrated in schizophrenia. Results from the present study suggest impaired spatial localization abilities are among the early auditory processing deficits associated with the disorder. Evidence is also provided that hallucinations may be associated with differential primary auditory cortex abnormalities. Overall, the findings suggest that spatial localization abnormalities characteristic of the disorder may be caused by impairments in the primary auditory cortex and the nature of dysfunction is dependent of hallucination status. The findings support generalized models of cognitive dysfunction in schizophrenia and suggest a need for further investigations of the relationship between spatial localization impairments and symptom severity.

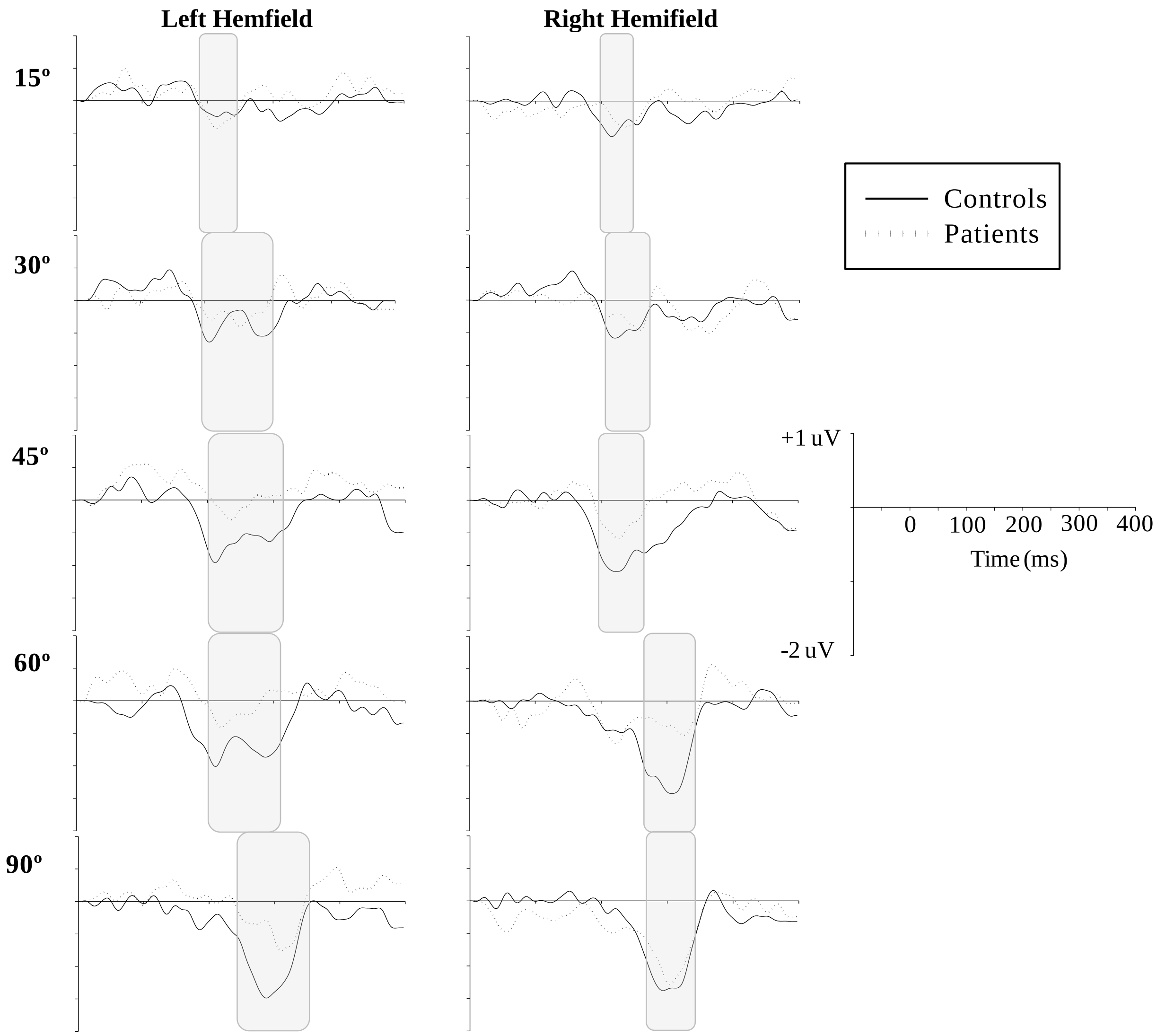


Figure 4.8 (Supplemental) Average Waveforms (Location Deviants)

Controls are represented by solid lines and patients by dotted lines. The shaded area refers to the latency window for MMN. In controls, MMN peak amplitude increased with increasing spatial separation in both hemifields. In patients, peak amplitude increased in the right hemifield. In the left hemifield, with the exception of 90º, MMN peak amplitude was comparable across all location deviants.

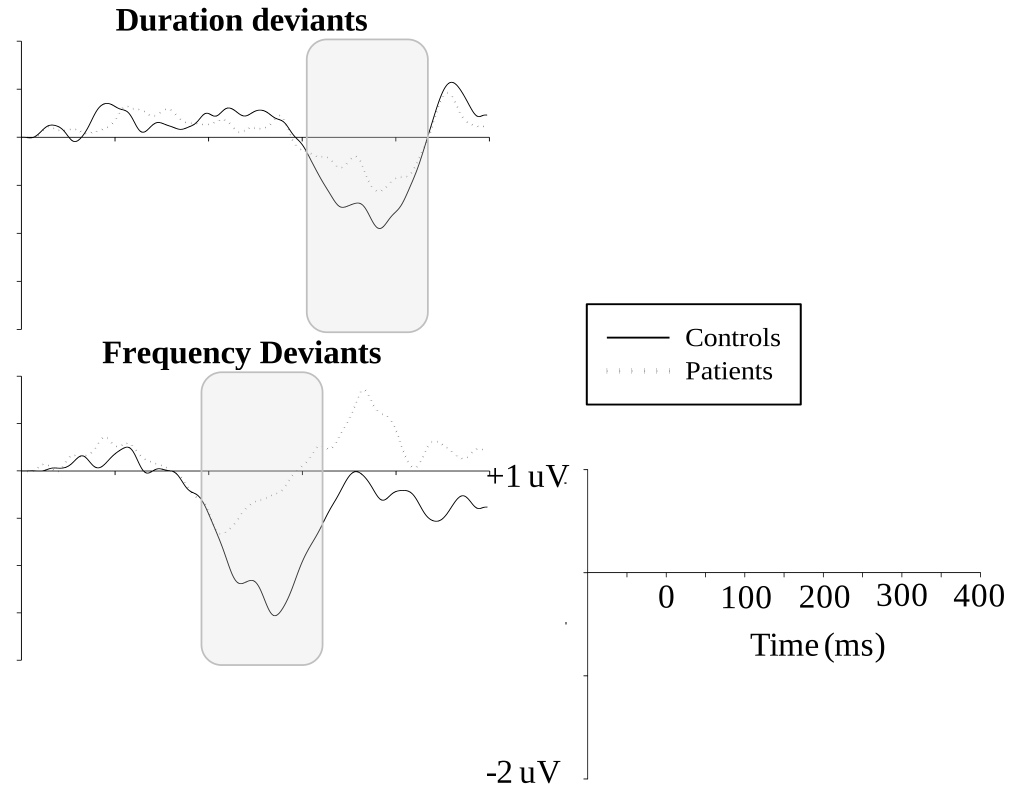


Figure 4.9 (Supplemental). Average Waveforms (Duration and Frequency Deviants)

Controls are represented by solid lines and patients by dotted lines. The shaded area refers to the latency window for MMN peak identification. Average MMN peak amplitude in response to frequency deviants was significantly attenuated in patients compared to controls.

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Chapter 5: Discussion

Schizophrenia is a neuropsychiatric disorder characterized by significant cognitive dysfunction.[1] Increasing evidence suggests early sensory processing impairments may contribute to cognitive dysfunction. Results from three studies in the present dissertation extend upon previous research by further examining early sensory processing impairments in schizophrenia and assessing their contribution to attention impairments and positive symptom severity.

Visual Attention Study

In Chapter 2, early exogenous processing and visual attention were assessed. The results suggest that dysfunction associated with early visual processing contributes to observed visual attention impairments in schizophrenia. Overall accuracy was reduced in patients on traditional assessments attention. In both groups, performance was significantly correlated with assessments of contrast sensitivity, particularly for low spatial frequency conditions. This suggests that magnocellular processing is necessary for accurate target detection. The results from structural equation modeling analyses provide evidence that performance differences on feature-based attention tasks are mediated by visual processing, working memory and processing speed. Reduced early exogenous processing causes reductions in higher-order cognitive processes necessary for accurate target detection.

To further establish the contribution of early visual processing to performance differences, the study also included a modified version of the Identical Pairs Continuous Performance Task, in which visual stimuli were manipulated to bias processing either towards the magnocellular (low spatial frequency) or parvocellular (high spatial frequency) pathway. On this task overall accuracy was reduced in patients. Differential performance was also observed between patients and controls for low spatial frequency conditions.

Exogenous Processing and Visual Attention

Until recently, as influenced by Broadbent's theories of cognitive top-down modulation, it was believed that sensory systems played a passive role in projecting information to higher order cortical regions and input selection was accomplished by cognitive modulation, even at the level of the primary sensory cortices[2]. However, with the advent of more sophisticated imagining techniques, it is becoming increasingly clear that attention allocation is controlled by both top-down endogenous and bottom-up sensory-driven exogenous networks. Input from exogenous and endogenous networks is integrated in higher-cortical regions through feedforward and feedbackward streams to enable perception and awareness of the visual scene[3]. Exogenous bottom-up influences also compete with top-down mechanisms to facilitate and inhibit processing of relevant and irrelevant features, enabling attention modulation.

As demonstrated in the present and previous studies[4, 5], early exogenous processing involving the magnocellular pathway is impaired in individuals with schizophrenia. Because the magnocellular pathway is more rapid than the parvocellular, it may play a role in framing input in the ventral stream for object recognition and perceptual closure [6-9]. Results from imaging studies suggest that exogenous input from the magnocellular pathway is initially projected to the orbitofrontal cortex to enable selection of relevant stimulus characteristics for further processing. The orbitofrontal cortex projects back to higher-order cortical processing areas to facilitate processing of relevant stimulus characteristics and inhibit processing of irrelevant characteristics[6, 9-11]. Hence, selective magnocellular impairments likely impede encoding of visual input necessary for accurate target detection and attention modulation.

Gamma Oscillations and Magnocellular Processing Involved in Perception

It has been postulated that schizophrenia represents abnormal integration since Kraeplin[12] described the disorder as a “loss of inner unity” and “intrapsychic coordination”. More recent theories propose that social and cognitive impairments are likely caused by abnormal integration of sensory input[13] or a failure to integrate the activity of local and distributed neural circuits[14]. The cognitive dysmetria theory of schizophrenia postulates that cognitive impairments are caused by a temporal asynchrony, which leads to abnormal communication between regions responsible for coordination of cognitive processes[15]

Studies of neuronal oscillations provide evidence supporting the cognitive dysmetria theory [16] and further elucidate the contribution of early exogenous dysfunction to selective attention impairments. The primary and extrastriate visual cortex is visuotopically organized. Individual characteristics of a visual scene are processed parallely in separate areas of the visual cortex. Perception of the visual scene is accomplished through “feature integration”. Feature integration is a process by which activation of individual neurons involved in processing each characteristic is bond together to produce a complete precept. Neurons with similar firing rates encode input of similar visual characteristics. Simultaneous action potentials become phase synchronized in domains of field potentials to produce a structured, complete percept of the visual scene[17-19]. Phase synchronization of neural oscillations is thought to represent a mechanism for transient cortical assembly[20], which enables cortical information processing

Oscillations are distinguished by their frequencies. Two types of oscillations are thought to be involved in different aspects visual perception: alpha (α) (8-13 Hz) and gamma (γ) (30-90 Hz) ([19, 21, 22]) (although some research suggests that beta oscillations may also be involved[23]). Perception of an entire visual scene is likely accomplished by an interaction of phase synchronized α -band and γ -band oscillatory neurons[19, 24, 25] While not well studied, there is evidence suggesting that α -band oscillations primarily occur in the parvocellular pathway and γ-band oscillations primarily occur in the magnocellular pathway[19, 26]; although oscillations are not completely segregated and interact to produce a complete visual precept.

Gamma activity in response to sensory stimulus is differentiated into two types: **evoked** (or phase locked) and **induced**, (or steady state) γ activity[25]. Evoked γ activity is early activity time locked to a stimulus (onset around 150ms post stimulus) and is thought to be an index of integrative sensory processing [27]. Evoked γ is also modulated by attention[28]. Induced activity is later (400 ms post stimulus response) and produces phase synchronization[24]. Induced γ oscillatory activity also occurs in pre-frontal cortices and is involved in context processing and integration[29]. Induced activity been demonstrated to contribute to the long term potentiation (LTP) and depression (LTD) mechanisms involved in associative learning[30] and working memory[31]. It has been proposed that evoked γ activity represents perception by synchronizing the sensory cortices and induced γ activity represents global cortical integration[29].

Recent evidence suggests that gamma band activity may play an important role in selective visual attention by modulating processing of attended stimuli [32, 33]. Evoked γ activity is enhanced by discriminating features of visual targets during target detection tasks[34]. This suggests that it may be involved in selecting and identifying relevant information of target stimuli. Attending to certain characteristics of a visual stimulus while ignoring other aspects also enhances induced γ activity in specialized regions responsible for processing these features[35].

Abnormal Gamma Oscillations and Schizophrenia

Studies assessing γ oscillations in schizophrenia have found abnormalities in both evoked [36-41] and induced oscillations[42]. Abnormal evoked γ oscillations have been found in patients during visual perception tasks, such as the visual oddball task[39], the Gestalt perception task[38] and visual backward masking tasks[37]. Reductions in induced γ oscillations in patients have also been observed on tasks requiring cognitive control[43]. Reduced phase synchrony has been demonstrated to be correlated with cognitive impairment[23, 44]. Previous research also suggests that gamma synchrony is reduced in the frontal and left hemisphere in patients with schizophrenia and differential patterns of synchrony abnormalities are observed for different subtypes of the disorder[45].

Gamma Oscillations and Processing Speed

In the present study we found that between group differences on feature-based attention assessments were significantly mediated by processing speed. Further, on the Attention Network Task, while overall accuracy and reaction time were reduced in patients, no significant between network differences were observed. Performance within networks is calculated based on reaction time differences. Since processing speed is reduced in patients, it is unlikely that differences would be detected. Gamma oscillatory activity plays an important role in modulating alertness, arousal and motor response (reviewed by Lee [46]). Dysfunction within these mechanisms would impede processing speed. It has been suggested that slowed reaction times associated with schizophrenia may be attributed to abnormal gamma oscillatory activity, which impedes movement preparation (referred to as “preparatory set dysfunction”[47])[46]. Hence, it is likely that abnormalities in gamma oscillations impact performance on attention tasks by impeding both perception and higher cognitive processes.

Myelination Abnormalities and Processing Speed and Sensory Impairments

As indicated in the Gamma Oscillations and Magnocellular Processing Involved in Perception section (page 134), recent theories propose that social and cognitive impairments underlying the disorder are likely caused by impaired neural connectivity. Increased white matter disorders are common in schizophrenia[48] and functional imagining studies provide evidence for impaired connectivity between temporal and frontal regions[49]. Results from genetic, neuropathological and neuroimagining studies suggest that ogliodendroglial dysfunction and myelin maintenance abnormalities likely contribute to white matter structure abnormalities characteristic of the disorder (reviewed by Davis [50] and Walterfang[51]).

Myelination abnormalities have also been implicated in impairments in neural connectivity and decreased processing speed [51] associated with schizophrenia. Diffusion tensor imagining studies suggest that white matter pathology [52, 53] and myelin impairments [54] may underlie cognitive dysfunction associated with schizophrenia. Previous studies of healthy individuals demonstrate that interindividual variability in processing speed is also associated with mylenation integrity[55]. A recent study employing parallel DTI and magnetic transfer imagining (MTI) (an imagining technique used to assess white matter tissue composition[56-58]) observed significantly reduced myelin integrity (referred to as 'dysmyelination') in regions adjacent to visual processing areas. The degree of dysmyelination also predicted processing speed impairments[59] on a digit-symbol substitution task. While the research examining the contribution of myelin impairments to early, pre-attentive sensory processing is limited, a gene expression study recently revealed that schizophrenia is associated with reduced mRNA expression of proteins involved in myelination in the primary visual cortex[60].

In general, previous research suggests that mylenation impairments likely predict higher-order cognitive dysfunction characteristic of the disorder. Reduced processing speed caused by myelination impairments may have impacted performance in present visual attention study (Chapter 2). Additional DTI and MTI investigations are necessary to determine whether white matter tract abnormalities and myelin impairments underlie pre-attentive sensory processing dysfunction observed in the present studies.

Auditory Spatial Localization Studies

Previous assessments of auditory processing in schizophrenia consistently demonstrate impairments in feature-based discrimination[61]; however, relatively few studies have examined spatial-based discrimination[62, 63]. Investigations of early auditory processing in the present dissertation revealed that in addition to the well-replicated featured-based impairments, spatial-based endogenous auditory processing also appears to be impaired in schizophrenia.

In Chapter 3, two behavioral assessments of auditory spatial localization were conducted. One paradigm examined the ability to determine the location of sound in space (i.e., sound localization) and the other examined the ability to discriminate between locations of sound sources (spatial discrimination). The results from the behavioral investigations confirmed the existence of spatial localization impairments in individuals with schizophrenia and provided evidence that impairments are associated with symptom severity.

On the sound localization task, overall accuracy was reduced in patients compared to controls and responses were more variable, particularly in the right hemifield. On the spatial discrimination task, overall accuracy in patients was reduced in both hemifields. The pattern of performance across both tasks was comparable to that observed in patients with right superior temporal lobe lesions that included the primary auditory cortex in a recent lesion study[64].

Performance was significantly associated with severity of cognitive and hallucination symptoms and the associations differed by hemifield. On both tasks, reduced accuracy in the right hemifield was associated with increased severity of conceptual disorganization and abstract thinking difficulties. As language dysfunction is known to be localized to left hemisphere and correlated with left superior temporal gyrs (STG) dysfunction [65], right hemifield spatial localization deficits may provide a selective index of left auditory cortical dysfunction in schizophrenia.

Interestingly, better accuracy on the localization task in the left hemifield was associated with greater hallucination severity. The paradoxical nature of the findings suggest that the association may be caused by interhemispheric imbalance, with bilateral dysfunction producing the types of auditory deficits typically seen in schizophrenia and right vs. left hemisphere dysfunction leading to overstimulation of external localization percepts. This theory is supported by electrophysiological evidence suggesting that schizophrenia is characterized by altered functional hemispheric asymmetry of the superior temporal gyrus (STG) [66]

Exogenous Auditory Spatial Localization

The focus of the study in Chapter 4 was to identify the underlying mechanisms for spatial localization impairments and to further explore the relationship between impairments and symptom severity. Performance was compared between patients and controls on the spatial discrimination paradigm. To assess the role of early exogenous processing, an event related potential (ERP) investigation was conducted using a passive listening oddball paradigm.

Mismatch negativity in response to location, frequency and duration deviants was measured. Accuracy on the spatial discrimination task was compared to MMN peak amplitude for spatial location deviants. Performance and neural activity were correlated with severity of positive thought disorder and hallucinations.

Exogenous Auditory Processing Dysfunction and Schizophrenia

The results provide evidence that spatial localization impairments are likely attributed to early exogenous processing deficits associated primary auditory cortex dysfunction. Consistent with the findings from the study described in Chapter 3, overall accuracy was reduced n patients in both hemifields on the spatial discrimination task. On the ERP paradigm, significant attenuations were found in MMN peak amplitude in response to frequency deviants, which is consistent with previous research[67-69]. MMN peak amplitude in response to duration deviants was, however, comparable between patients and controls. Previous studies typically identify reduced amplitude in response to duration deviants[70-73]. However, in one ERP study significant reductions in MMN amplitude were observed for patients with a history of hallucinations, whereas amplitude was comparable to controls in patients without a history of hallucinations[74]. The lack of between group differences in the present study may be due to the heterogeneity of the patient sample.

With respect to location deviants, overall MMN peak amplitude was attenuated in patients compared to controls and the pattern of peak amplitude across spatial conditions within hemifields differed between groups. In controls, MMN peak amplitude increased with increasing spatial separation between standards and deviants in both hemifields. In contrast, in patients, MMN peak amplitude increased with increasing spatial separation in the right hemifield, whereas peak amplitude in the left hemifield was comparable across all spatial locations.

Similar hemifield specific differences were observed for the relationship between spatial discrimination performance and MMN peak amplitude. In controls, as the degree of spatial separation increased, significant increases in accuracy and MMN peak amplitude were found in both hemifields. In patients, a linear association was observed in the right hemifield; whereas no relationship was found in the left hemifield. Due to contralateral projections in auditory processing, abnormalities in MMN peak of locations in the left hemifield suggest right STG dysfunction may underlie spatial localization impairments in schizophrenia.

Spatial Localization and Laterality

In humans, auditory regions are located within superior temporal gyrus (STG), with primary auditory cortex located on the transverse gyri of Heschl (HG) [75]. Unlike processing of feature-based characteristics of auditory stimuli, such as pitch and duration, early auditory processing of spatial information is thought to be primarily right hemisphere dominant [76]. Patients with temporal lobe lesions are less accurate on discrimination tasks [64] and right hemisphere lesions appear to affect spatial discrimination abilities in both hemifields [64, 77]. Right hemisphere dominance for encoding spatial localization information is also demonstrated by observations of differential MMN peak and amplitude responses between hemifields for location deviants in ERP investigations [78, 79].

Unilateral right hemisphere dysfunction would produce findings consistent with that observed in the present studies. However, this is inconsistent with the previous literature demonstrating bilateral attenuation in MMN response to feature-based auditory deviants (reviewed by Umbricht[61]) and research identifying bilateral MMN attenuation to location deviants in individuals with schizophrenia[63]. Furthermore, a unilateral impairment cannot account for the reductions in MMN response to frequency deviants in patients in the present study. Further investigation of the relationship between symptom severity and neural activity revealed that the relationship between STG abnormalities and spatial discrimination may be differentially impacted by the presence of hallucinations.

Mismatch Negativity and Hallucination Severity

In the present study, MMN peak amplitude in response to location deviants was significantly correlated with auditory hallucination severity for all location deviants in the right hemifield in which significant differences were observed between patients and controls. In contrast, no significant correlations were observed for left hemifield locations. These findings suggest that hallucination severity is associated with left STG dysfunction attributed to spatial localization impairments.

No significant correlations were observed between hallucination severity and MMN peak for duration of frequency deviants, suggesting that the relationship between hallucination severity and MMN peak is specific to location deviants. Comparisons of MMN peak amplitude for location, duration and frequency deviants suggest that this is unlikely a spurious finding, due to greater sensitivity to detect location deviants. With the exception of 90° in the right hemifield, MMN peak amplitude was comparable or greater for duration than location deviants.   Further, MMN peak amplitude was comparable or greater for frequency than location deviants for all locations. (Table 5.1)

Table 5.1.MMN Peak Amplitude Comparisons for Location, Duration and Frequency deviants

	MMN Peak			**MMN peak**	
	Location	**Duration**	**p-value[a,c]**	**Frequency**	**p-value[b,c]**
Left Hemifield					
15°	-1.52	-2.32	0.018	-3.56	0.000
30°	-1.81		0.069		0.000
45°	-2.49		0.639		0.002
60°	-2.27		0.866		0.001
90°	-3.32		0.044		0.617
Right Hemifield					
15°	-1.70	-2.32	0.099	-3.56	0.000
30°	-2.00		0.255		0.000
45°	-2.25		0.811		0.001
60°	-3.03		0.077		0.249
90°	-3.41		0.014		0.711

[a] paired samples t-test for location vs. duration MMN peak; [b] paired samples t-test for location vs. frequency MMN peak; [c] two-tailed

Perceptual Distortion and Hallucinations

From a sensory perspective, two predominant hypotheses for the cause of hallucinations have been proposed. The "auditory-perceptual" model proposes that hallucinations are caused by an impaired ability to determine the source of an external stimuli [80, 81]. The "verbal self-monitoring" hypothesis proposes that hallucinations result from attributing the source of inner thoughts to an external source[82]. Results from fMRI investigations provide evidence supporting both theories. Reduced activation of the left STG during an auditory discrimination task was observed in patients with a history of hallucinations while activity in patients without hallucinations was comparable to controls[83]. In another fMRI study neural activity was measured while participants determined whether pre-recorded words were from themselves or someone else. Patients with a history of hallucinations made more misattribution errors and altered neural activity was observed in the temporal cortex[84]. While the underlying cognitive mechanisms are slightly divergent, both hypotheses propose that perceptual disturbances and primary auditory dysfunction likely contribute to hallucinations.

Laterality of STG Dysfunction and Hallucinations

While unilateral left STG dysfunction is consistent with many previous studies regarding hallucinations, it is inconsistent with findings demonstrating that spatial localization is right hemisphere dominant (described above). To further explore the relationship between hemisphere differences and hallucination status, MMN peak amplitude response to location deviants was compared between controls and patients with and without a history of hallucinations. Hemifield specific differences in MMN peak amplitude reductions were observed between patients with and without a history of hallucinations. In patients without a history of hallucinations, MMN peak was comparable across all spatial location deviants in both hemifields. This suggests that in patients without a history of hallucinations, early processing dysfunction attributed to spatial localization is caused by a bilateral STG impairment. In patients with a history of hallucinations, MMN peak amplitude was attenuated in response to location deviants in the left hemifield, whereas response to spatial deviants in the right hemifield increased with increasing spatial separation between standards and deviants; a pattern comparable to that observed in controls. Taken together, the findings suggest that the relationship between hallucination severity and spatial localization is associated with left STG dysfunction, whereas right STG dysfunction is associated with spatial localization abnormalities.

While auditory projections are predominantly contralateral, as indicated above, spatial localization is primarily right hemisphere dominant. Hence, it difficult to base conclusions about hemisphere specific activity based comparisons of neural activity measured in central electrodes with respect to hemifield of location deviants. To further explore laterality differences, comparisons were made between controls and patients with and without a history of hallucinations at left and right hemisphere frontocentral electrodes in response to average location deviants in the contralateral and ispilateral hemifields.

In controls and patients without a history of hallucinations, MMN peak response was comparable in both hemispheres for both ispilateral and contralateral stimuli. In contrast, in patients with a history of hallucinations, MMN peak amplitude was significantly attenuated in the right hemisphere for contralateral stimuli; whereas MMN peak amplitude was reduced in the left hemisphere for ispilateral stimuli. Overall, the results suggest early exogenous auditory processing involved in spatial localization in both groups reflects a bilateral STG impairment. Hemispheric differences between patient subgroups may be attributed to additional left STG dysfunction or impaired interhemispheric communications associated with hallucinations.

Laterality and Hallucinations

Results from functional and structural imagining studies provide support for this interpretation. Because language is primarily left hemisphere dominant, the left STG is typically implicated in language-related psychotic symptoms, such as positive thought disorder and hallucinations[85]. Results from PET and fMRI investigations of neural activity during hallucinations in individuals with schizophrenia provide evidence for the involvement of the primary auditory cortex; however, the findings regarding laterality are inconsistent. Many studies observed left lateralized activity (7 out of 13), whereas others observed right lateralized activity (2 out of 13) and still others found bilateral activity (4 out of 13)(reviewed by Allen[86]).

A recent meta-analysis of MRI investigations suggests structural STG abnormalities associated with schizophrenia may be differentiated by the presence of hallucinations and positive thought disorder[65]; however, again, the findings regarding laterality are inconsistent. In this study, 35/46 studies examined observed STG volume reductions. Nearly half of these studies observed unilateral left STG reductions and volume was correlated with severity of positive thought disorder and hallucinations. However, bilateral reductions and right hemisphere reductions were also observed in many of these studies. In contrast, the results from magnetic resonance diffusion tensor imaging (DTI) studies consistently demonstrates reduced integrity of white matter tracts in the temporal cortices in patients with a history of hallucinations (reviewed by Allen [86]). The findings suggest that both dysfunction in structural and functional integrity of perceptual networks may underlie hallucinations in schizophrenia.

Gamma Oscillation Abnormalities and Auditory Dysfunction

Although less studied, previous research also suggests that gamma oscillation abnormalities may underlie early auditory dysfunction associated with schizophrenia. Pre-stimulus gamma activity is increased in patients during auditory paradigms[87, 88]. Greater noise, prior to stimulus presentation likely impedes mechanisms involved in selection of relevant auditory input for further processing. Abnormalities in evoked γ gamma band activity were observed during a passive listening paired-tone auditory paradigm[87] and a steady state investigation using auditory clicks with varying frequency[89]. In an auditory oddball paradigm, evoked γ band abnormalities were observed for both targets and non-targets and abnormalities were correlated with symptom severity[90].

NMDA Receptor Abnormalities in Schizophrenia

The glutamatergic hypothesis of schizophrenia postulates that neurological abnormalities characteristic of the disorder are caused by a glutamate deficiency that results from N-methyl-D-aspartic acid receptor (NMDAR) abnormalities. The hypothesis was initially proposed based on behavioral observations of healthy controls in response to administration of PCP, an NMDAR antagonist, which is found to induce both positive and negative symptoms [91]. Such findings have been consistently replicated in human and animal studies [92]. Chronic exposure to NMDAR antagonists produces dopaminergic transmission abnormalities consistent with schizophrenia and findings from animal studies suggest that early NMDAR dysfunction causes neurodegeneration consistent with that observed in schizophrenia [93]. Furthermore, NMDAR are located throughout cortical and subcortical structures associated with sensory and higher order associative processes disrupted in schizophrenia (reviewed by Javitt [94]).

Gamma Oscillatory Abnormalities and NMDAR Dysfunction

Dysfunctional NMDAR likely contributes to gamma oscillation abnormalities through modulation of receptors involved in gamma synchrony. One proposed theory for γ synchrony is that it is accomplished through short-range interneuron networks and long range synchrony of pyramidal cells[95]. Among the neurotransmitter systems involved in neural synchrony, GABA neurons appear to be crucial for high-frequency short-range interneuron oscillation[96]. Metabotropic glutamate receptors activate GABAergic interneurons to induce synchrony of post-synaptic interneuron potentials at approximately 40Hz[97]. This forms a recurrent feedback loop, which leads to γ synchrony[98]. Long-range γ synchrony occurs when there is simultaneous firing of multiple short-range interneuron networks in-phase with pyramidal cells. Glutamerigic connections control the strength and duration of long-range synchronization[99].

Previous research suggests that NMDAR abnormalities may be responsible for γ synchrony abnormalities observed in schizophrenia. Results from an in vitro study of neocortical slices of the mouse prefrontal cortex demonstrated that ketamine causes gamma oscillation abnormalities[100]. An in vivo study also demonstrated that ketamine administration induced gamma abnormalities in the rat frontal, parietal and occipital cortices [101]. Taken together, the findings suggest NMDAR abnormalities likely lead to abnormal gamma oscillations. This impacts transient cortical assemblies involved in early sensory processing and higher-order cognitive functioning.

NMDAR Abnormalities and Exogenous Auditory Processing

Evidence for role of NMDAR dysfunction in early sensory processing impairments is also provided by assessments of auditory processing. Administration of competitive and non-competitive NMDAR antagonists in the primary auditory cortex in nonhuman primates results in an abolished MMN response to deviant stimuli in the auditory oddball paradigm[102, 103]. Reductions in MMN have also been found in healthy controls after administration of ketamine and other NMDAR antagonists in response to pitch or duration deviants. Figure 5.1 and Figure 5.2 compare the results from two studies using the same methodology to examine MMN response to duration and pitch deviants in a passive auditory oddball paradigm during performance the CPT-AX[71, 104]. The first study examined MMN generation in patients compared to controls[105]; whereas the second study examined generation in pre- and post-ketamine administration in controls[104]. The pattern of MMN in the patient group is comparable to the control group post-ketamine administration. In both groups, reductions in MMN amplitude were observed for both duration and pitch deviants.

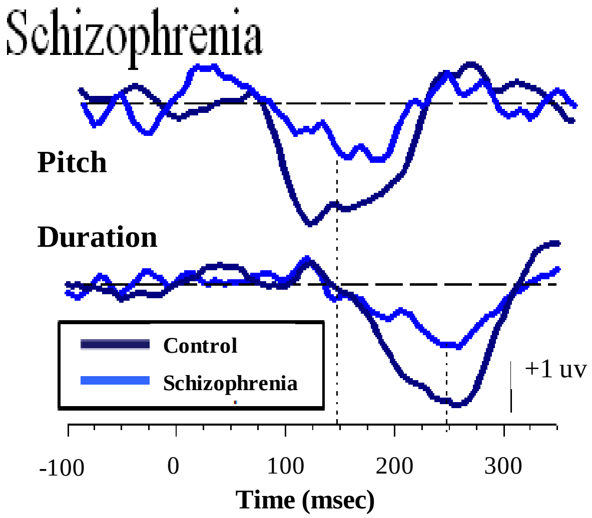

Figure 5.1. MMN for pitch and duration deviants between patients and controls

Controls are represented by the dark blue line and patients by light blue. For both pitch and duration, MMN amplitude is significantly reduced in patients compared to controls (revised reprint from Leitman et al, 2010 [106]with permission from American Psychiatric Association, Inc)

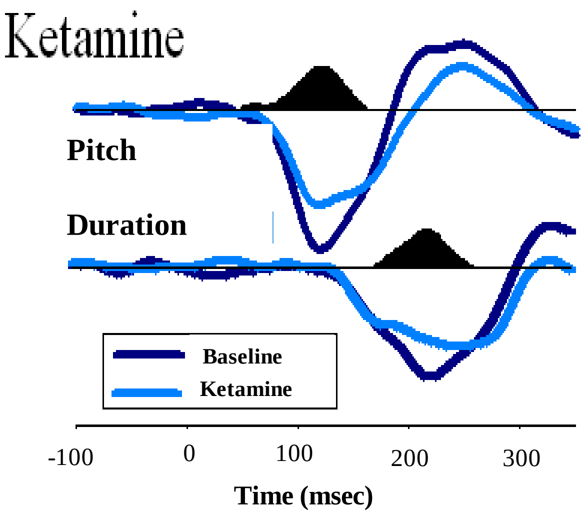

Figure 5.2. MMN for pitch and duration deviants between controls pre and post ketamine administration

Controls at baseline are represented by the dark blue line and controls after ketamine administration are represented by light blue. For both pitch and duration, MMN amplitude is significantly reduced in the ketamine condition. MMN closely resembles that observed in patients. (revised reprint from Umbritch et al, 2000, with permission from American Medical Association)

NMDAR agonists also appear to provide significant relief of all three types of symptoms characteristic of the disorder and negative symptom improvement is significantly correlated with glycine levels [107].

NMDAR Abnormalities and Dopamine and GABA Dysfunction

In addition to the abnormal glutamate, previous theories of schizophrenia have also implicated abnormalities in dopamine and GABA transmission. It has recently been that proposed NMDAR dysfunction may be responsible for abnormalities in these neurotransmitters as well [108].

The “Dopamine Hypothesis” posits that schizophrenia is caused by excessive activation of the dopamine D_2 receptor[109], which results in an imbalance of dopamine, with hyperactivity in the subcortical dopamine pathway and hypoactivity in the cortical pathway[110, 111] (reviewed by Kuepper [112]). A major limitation of the Dopamine Hypothesis is that typical and atypical antipsychotics, which impact dopamine transmission by binding to the D_2 receptor, have negligible effects on negative symptoms and cognitive impairment[113].

Previous research also suggests that reduced GABA neurotransmission is likely associated with the disorder (reviewed by Stan & Lewis [114]). Post-mortem findings provide evidence that GABA synthesis and uptake is decreased in schizophrenia. Further, levels of a glutamic acid decarboxylase (GAD67), the enzyme responsible for GABA synthesis, have been consistently demonstrated to be reduced in neocortical structures involved in cognitive functioning, such as the dorsolateral pre-frontal, anterior cingulate, orbitofrontal, superior temporal and primary motor and visual cortices[114]. While GAD67 is consistently observed to be reduced, there appears to be substantial variability among patients in GAD67 mRNA levels, with some studies finding normal and even elevated levels of GAD67 mRNA [114].

GABA interneurons express calcium binding proteins, including calretin, cladindin and paravalbum[115]. Paravalbum is expressed predominately in chandelier and basket cells, which are regulated by afferent synaptic activity and receive direct input from pyramidal neurons [116]. Synaptic contacts are concentrated on the proximal axon and soma of the pyramidal cell. These interneurons are thought to regulate cortical excitatory output[108]. Reductions in paravalbum, but not other calcium binding proteins are consistently demonstrated in schizophrenia[117], suggesting that paravalbum GABA neurons deficits likely cause impaired synchronization of cortical activity in the postsynaptic pyramidal cells[118].

Based on evidence from genetic, imagining and post-mortem studies, Coyle et al (2010) recently proposed the “pathologic circuit” hypothesis of schizophrenia, which postulates that NMDAR hypofunction likely causes abnormal expression of dopamine and GABA[108, 119]. Disinhibition of glutamergic output from the ventral hippocampus leads to increase activity of dopaminergic neurons in the ventral tegmental area, causing enhanced dopamine release. Hypofunction of corticolimbic NMDAR also causes GABA interneuron alterations by downregulating GAD67 and paravalbum expression. This causes a reduction of inhibitory post synaptic potentials and disinhibition of postsynaptic pyramidal cells, which increases excitatory output and disrupts cortical processing[119, 120] likely producing gamma oscillation abnormalities [121, 122].

Clinical Implications

Neurodevelopmental models of schizophrenia propose that the disorder likely arises from genetic and\or environmental disruptions to normal central nervous system development that occur prior to onset of psychosis; potentially as early as prenatal development[123-125]. A recent review of longitudinal and cross-sectional structural imaging studies, suggests that early pre- and peri-natal neurological abnormalities result in increased vulnerability to anomalous neurodevelopmental processes, such as accelerated gray matter loss and aberrant connectivity at the onset of psychosis[124]. Because neurological dysfunction is known to develop prior to psychosis onset, assessments of sensory processing in individuals at risk for schizophrenia may enable early detection of the disorder.

It has recently been proposed that sensory impairments may represent a biomarker for the disorder[126]. Results from a recent ERP study suggest that reduced MMN amplitude for auditory deviants likely predicts premorbid functioning, onset of illness and educational attainment[127]. As such, noninvasive diagnostic techniques may be created to identify individuals at risk for the disorder prior to the onset of psychosis and to assess sensory impairments at the onset of psychosis to predict functional outcome. Pharmacological and behavioral interventions can be altered to provide the most effective treatment regimen. Furthermore, cognitive remediation therapies aimed at improving early sensory processing will likely lead to cognitive and positive symptom relief.

Limitations

While the studies described in the present dissertation are informative, several limitations are worth mentioning. All three studies included heterogeneous patient samples. As indicated above, studies of early sensory processing and gamma oscillations indicate that differential impairments occur within clinical subtypes. Further investigations are necessary to identify subtype specific differences. In all three studies, the patient samples were comprised of medicated, patients with chronic illness (average duration of illness was 15 years). As such, it is difficult to ascertain whether impairments are generalizable to first episode, unmedicated patient samples. Lastly, the findings from the auditory studies provide evidence that early auditory processing dysfunction contributes to reduced accuracy on spatial discrimination tasks. However, the contribution of early exogenous impairments to endogenous top-down dysfunction involved in spatial localization requires further elucidation.

Conclusion

The present dissertation extends upon the previous literature demonstrating impairments in early sensory processing and provides evidence for the contribution of such impairments to impaired attention and positive symptom severity. Overall, the findings support the cognitive-sensory framework of attention and provide evidence that early sensory processing dysfunction has a significant impact on daily functioning. Further research is necessary to determine whether such impairments are representative of the disorder as a whole or can be differentiated by clinical subtype.

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