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Reduced Multisensory Integration in Individuals with Schizophrenia:

Evidence from Psychophysical Studies

A dissertation submitted in partial satisfaction of the requirements for the degree  
Doctor of Philosophy

in

Psychology

by

Lisa E. Williams

Committee in charge:

Professor Vilayanur S. Ramachandran, Chair  
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Professor Karen Dobkins  
Professor Steven Hillyard  
Professor Donald MacLeod

2009

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University of California, San Diego

2009

## DEDICATION

To Ed, who kept me going, and is always my inspiration.  
I can't wait to begin our new life together.

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Chapter 3, in full, is being prepared for publication, Williams, L.E., Ramachandran, V.S., Braff, D.L., & Light, G.A. The dissertation author was the primary investigator and author of this paper.

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- McGeoch, P.D., **Williams, L.E.**, Lee, R.L., & Ramachandran, V.S. (2008) Behavioural evidence for vestibular stimulation as a treatment for central post-stroke pain. *Journal of Neurology, Neurosurgery, and Psychiatry*. Epub ahead of print June 11 2008.
- Ramachandran, V.S., McGeoch, P.D., & **Williams, L.E.** (2007) Can vestibular caloric stimulation be used to treat Dejerine-Roussy Syndrome? *Medical Hypotheses*, 69, 486-488.
- Ramachandran, V.S., McGeoch, P.D., **Williams, L.E.**, & Arcilla, G. (2007) Rapid relief of thalamic pain syndrome induced by vestibular caloric stimulation. *Neurocase*, 13, 185-188.

### Manuscripts In Revisions

- Light, G.A., **Williams, L.E.**, Sprock, J., Sharp, R., Swerdlow, N.R., & Braff, D.L. (in revisions) Electroencephalography (EEG) and Event-Related Potentials (ERP's) with Human Participants. *Current Protocols in Neuroscience*.

## Manuscripts Under Review

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## Manuscripts in Prep

**Williams, L. E.**, Ramachandran, V.S., Braff, D.L. & Light, G.A., (in preparation) Reduced Multisensory Integration in Patients with Schizophrenia on a Target Detection Task.

Light, G.A., Sprock, J., **Williams, L.E.**, Swerdlow, N.R., & Braff, D.L. (Invited manuscript). Prepulse Inhibition (PPI) in Human Participants. *Current Protocols in Neuroscience*.

Brang, D., **Williams, L.E.**, & Ramachandran, V.S. (in preparation) Synesthetes show enhanced cross-modal interactions in standard cognitive tasks that do not involve their synesthetic associations

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Horvath, M., **Williams, L.E.**, Brang, D., & Ramachandran, V.S. (May 2007) "Filled in" Letters Evoke Synesthetic Colors. Poster presented at the 13<sup>th</sup> Annual Meeting of the Cognitive Neuroscience Society, New York, NY.

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ABSTRACT OF THE DISSERTATION

Reduced Multisensory Integration in Individuals with Schizophrenia:  
Evidence from Psychophysical Studies

by

Lisa E. Williams

Doctor of Philosophy in Psychology

University of California, San Diego, 2009

Professor Vilayanur S. Ramachandran, Chair

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The studies in this dissertation investigate multisensory integration in a sample of patients with schizophrenia using three different paradigms. Chapter 2 evaluates the integrity of visual-tactile integration in this population using the size-weight illusion (SWI), in which the smaller of two objects of identical mass feels substantially

heavier compared to a larger object. The result show a reduced SWI in schizophrenia patients which cannot be explained by observed differences in weight discrimination sensitivity. These results support the idea of reduced multisensory integration, as well as dysfunctional efference copy mechanisms, in this population. These integration deficits are correlated with reduced sensorimotor gating, as assessed by prepulse inhibition (PPI). Chapter 3 investigates auditory and visual integration of congruent cues for target detection using an intersensory facilitation of reaction time (RT) paradigm, on which non-psychiatric individuals are known to be faster to detect bimodal targets, with cues from two sensory modalities, compared to detection times for unimodal targets. Though patients with schizophrenia do show some RT speeding when detecting bimodal targets, it is not to the same extent as non-psychiatric individuals, indicating reduced automatic multisensory integration of these cues. The amount of RT facilitation is related to the symptoms of schizophrenia, as well as the modality of the patient's hallucinations.

Finally, Chapter 4 presents a version of the McGurk illusion, in which auditory speech perception is biased by the presentation of an incongruent visual speech cues. This McGurk paradigm has yielded inconsistent patterns of results in previous studies with schizophrenia patients, and this study design includes many experimental conditions designed to address methodological differences between these earlier

investigations. This study finds no evidence of a difference between schizophrenia patients and non-psychiatric participants on the incidence of the McGurk illusion; however, there is evidence for impaired lip-reading ability in this population. Generally, these results support the idea of a specific impairment in multisensory integration in patients with schizophrenia, above and beyond deficits within individual sensory modalities. As these integration deficits correlate with the symptoms and characteristics of schizophrenia, this is an important area for future research.

## Chapter 1

### Introduction

## Introduction

Schizophrenia is a debilitating psychiatric disorder with a global prevalence rate in the range of 0.5% - 1.5% (1). The disorder is characterized by the presence of psychotic symptoms like delusions and hallucinations, as well as broader impairments in cognitive and social functioning. Traditionally the symptoms of schizophrenia are divided into two categories, positive and negative symptoms. Positive symptoms are experiences and behaviors that are not present in the general population, and include delusions (distorted thought content), hallucinations (distortions in perception), disorganized speech, and grossly disorganized or catatonic behavior. Negative symptoms can be conceptualized as a deficit in normal levels of functioning, and include flat affect, as well as poverty of thought, speech, and goal-directed behaviors (1).

Despite many years of focused research, determining the etiology of schizophrenia is still an ongoing process, due in part to the heterogeneous nature of the disorder in terms of symptom presentation. Schizophrenia runs in families, and genetic linkage studies have identified several genes believed to confer risk for the disorder. However, these genetic interactions, as well as environmental factors, are very complicated, and the current mechanisms have not been fully elucidated (for review see (2)).

Though some attempt has been made to divide patients into subgroups on the basis of their most prominent symptoms, a classification that exists within the current diagnostic system, this has not provided much insight into the etiology of this

symptomatically varied disorder. More recent research approaches using endophenotypes, which are cognitive and electrophysiological differences that are present in patients with schizophrenia, as well as to a lesser degree in first degree relatives, may be more successful as they are better characterized within the clinic, and are more easily associated with genetic variations (3). A number of candidate endophenotypes for schizophrenia have been identified, including atypical performance on an antisaccade task, abnormal smooth pursuit eye movements, deficits in gating of sensory (reduced P50 suppression) and sensorimotor information (abnormal prepulse inhibition, PPI), reduced mismatch negativity (MMN, a preattentive measure of auditory change detection) as well as a number of attention dependent cognitive measures including abnormalities in the P300 event related potential (seen in response to presentation of “oddball” stimuli), poor performance on continuous performance tasks, working memory deficits and increased backwards masking (3-5).

Treatment for schizophrenia is largely pharmacological and is most effective at reducing positive symptoms, whereas negative symptoms are largely unaffected. The first generation of antipsychotic medication was introduced in the 1950’s, and operates by blocking the D2 dopamine receptors (6). These drugs, though effective on psychotic symptoms, carry risks of neurological side effects after long term use, including tardive dyskinesia (repetitive facial tics), tremors, and dystonia (sudden involuntary muscle contractions). The more recently developed “second generation” antipsychotics block serotonin receptors in addition to D2 receptors, which reduces the

risk of neurologic side effects, but increases the risk of obesity, type II diabetes, and hyperlipidemia. Compliance with drug therapy tends to be poor, and most individuals with schizophrenia remain severely disabled throughout their lifetime (2).

Given that researchers are still far from understanding the etiology of the disorder, and that current treatments have not proved effective on the full range of schizophrenia symptoms, there is much need and motivation to continue research in this area.

### **Noisy Sensory Processing in Schizophrenia**

It is known that sensory processing abnormalities exist in schizophrenia at both the behavioral and neural level (for review see (5)). These deficits are usually viewed as problems with sensory and sensorimotor gating. Behavioral studies show deficits in pre-pulse inhibition (PPI), a measure of sensorimotor gating, while electrophysiological studies show reduced P50 suppression of early auditory evoked potentials, which index sensory gating processes. During the PPI paradigm in non-psychiatric individuals, presentation of a weak “prepulse” stimulus 50-300 ms before a strong “startling” stimulus reduces startle response. Patients with schizophrenia, as well as unaffected first-degree relatives and individuals with schizotypal personality disorder (considered to be part of the “schizophrenia spectrum”), do not show the typical reduction in startle (7-13). In the P50 suppression paradigm, individuals are presented with pairs of auditory “click” stimuli separated by 500 ms while neural



activity at the scalp level is recorded via electroencephalography (EEG). In non-psychiatric individuals, the P50 component of the auditory event-related potential is reduced in amplitude to the second click, whereas patients with schizophrenia (as well as relatives and schizotypal individuals) do not show the same reduction (3, 5). An additional early sensory processing deficit that correlates with symptom severity and functional status in patients with schizophrenia are reductions in mismatch negativity (MMN), a measure of early auditory change detection (14-17). Taken together, these deficits in sensory gating and early sensory processing imply that patients with schizophrenia may be less efficient at filtering out irrelevant environmental input, and as a result operate in very “noisy” sensory environments, which is believed to contribute to their cognitive impairments, as well as their psychotic symptoms (3).

While these between-group differences in sensory gating and early processing measures within individual modalities are well replicated findings in schizophrenia research, and appear to be endophenotypes for the disorder, when navigating through a real-world environment, sensory cues rarely occur in isolation. In reality, to interact with a sensory environment most effectively, one must be able to rapidly integrate streams of information from multiple sensory modalities, with appropriate binding and separation of cues from different objects and points of origin. The integrity of multisensory integration is a relatively unexplored area in schizophrenia research. To address this issue, the projects presented in this dissertation explore how schizophrenia patients process and integrate information presented concurrently in more than one sensory modality, and how these tasks may relate to the symptoms of schizophrenia.

## **Processing Sensory Information from Multiple Modalities**

Until fairly recently, perceptual research has focused on understanding how sensory processing occurs for individual modalities in isolation. However, it is undeniable that in the real world, we are constantly bombarded with information from multiple sensory modalities, and to function optimally we must be able to detect, integrate and filter this information to form an accurate perception of our environment. Within the last 10-15 years there has been a dramatic growth in research on how sensory information from different modalities is combined, both in terms of congruent information from different sources, and how events are perceived when presented with conflicting information in different modalities.

Previous research on multisensory integration (MSI) in non-psychiatric individuals has demonstrated that the presentation of congruent information from multiple modalities confers an advantage for speed and accuracy of processing (for review see (18-21). For example, reaction times in a target detection task are faster when auditory and visual cues are presented simultaneously, compared to a cue in a single modality (22). Along similar lines, Frens et al. (23) showed that participants had faster saccades to a visual target when an irrelevant auditory cue was spatially and temporally aligned with the target. In another task, Perrott and colleagues (24) demonstrated that visual search times are improved when an auditory click train is presented at same location as visual target.

In terms of the neural basis of this behavioral enhancement, electrophysiological studies in nonhuman animals have shown cells in the superior colliculus (SC) to be particularly responsive to multisensory stimulation, showing superadditive activity when presented with congruent multisensory cues, and depressed activity to asynchronous cues (25-27). Functional neuroimaging studies of MSI in humans finds the SC (Calvert et al, 2001) as well as a distributed network of cortical areas involved in MSI (for review see (28, 29). For example, the superior temporal sulcus (STS) has been shown to be involved with processing information from vision, audition, and touch (30). When participants are presented with auditory and visual cues, a number of cortical regions are activated and considered to be specifically “multisensory” areas, including the STS, the superior temporal gyrus, the medial temporal gyrus, and parietal regions (29, 31-34). There is also emerging evidence that the presentation of multiple sensory cues also affects activation of and processing in areas previously considered to be “unisensory” regions (for review see 29).

When individuals are presented with cues from multiple sensory modalities that are in conflict with one another, perception tends to be dominated by the most reliable source of input. Early explanations of multisensory integration in conflict situations were based on a modality appropriateness hypothesis (18, 35), in which the modality with the greatest precision for a particular judgment is weighted more heavily. For example, auditory cues have a greater influence than visual information when making temporal judgments, based on the greater temporal resolution of the

auditory system compared to the visual system, whereas vision dominates audition when making spatial localization judgments, as the visual system is generally superior to the auditory system in terms of spatial resolution (18, 36).

However, current research is beginning to show that these dominance patterns can be altered if the reliability of a cue is systematically varied. For example, Heron and colleagues (37) used a spatial localization task in which they systematically varied the uncertainty of the visual and auditory cues. When visual uncertainty was low, auditory cues had relatively little impact on responses, as predicted by modality appropriateness. However, as visual uncertainty increased, influence of auditory cues on localization increased, indicating that the weighting of multisensory information may be driven more by cue reliability, as opposed to an inflexible modality specific rule. Other findings related to the combination of visual and auditory cues e.g. (38, 39), as well as multisensory integration for vision and proprioception (40-42) has led some of these researchers to propose a statistically optimal model of multisensory integration, driven by online assessments of cue reliability.

Given these findings in which cue reliability is systematically varied by the addition of noise to a particular sensory input, it would be of interest to explore how the sensory system of an individual with schizophrenia, known to have noisy sensory input, as indexed by PPI and P50 suppression deficits, would combine information from multiple sensory sources. It is also interesting to consider the effects of years of unreliable sensory experiences, in the form of hallucinations, on the sensory integration abilities of a patient with schizophrenia. For example, if an individual

suffers from auditory hallucinations, an unreliable source of input within that modality, does that affect weighting of information in a multisensory sensory situation? The same question could be asked for patients who experience visual, tactile, or (more rarely) olfactory or gustatory hallucinations. If these perceptual experiences do affect the weighting of multisensory information, then particular patterns of weighting may vary with the quality and intensity of past and/or current symptoms.

### **Multisensory Integration in Schizophrenia: Previous Studies**

To date, there have been very few studies investigating multisensory integration in patients with schizophrenia, although there have been some hints of general sensory integration problems in reviews of neuropsychological testing data. These data indicate patients with schizophrenia and their first -degree relatives have abnormal neurological signs on measures of “integration of higher sensory functions.” This subset of neurological tests includes measures of audiovisual integration (the ability to match a pattern of sounds to a visual diagram); stereognosis (the ability to identify common objects by touch); graphesthesia (the ability to identify numbers written on the skin); extinction (in response to bilateral and simultaneous somatosensory stimulation); and right/left confusion (43, 44). One such study (45) even found a correlation between poor sensory integration and eye tracking difficulties, a prominent marker of schizophrenia.

Experimental studies that have directly tested multisensory integration in patients with schizophrenia have so far been limited, and have yielded inconsistent results. Two groups have explored how patients with schizophrenia combine auditory and visual speech information using variations of the McGurk effect, a striking perceptual illusion wherein participants are presented with conflicting auditory and visual speech cues (46). Previous studies with non-psychiatric individuals have found that for particular audio-visual speech pairings, participants “hear” the phoneme or word matching the visual speech or a blend of the auditory and visual stimuli, as opposed to the actual auditory stimulus. One study (47) found that patients with schizophrenia experience the illusion less than typical controls, indicating reduced multisensory integration, while another study (48) found no difference between groups. The de Gelder (47) study also tested schizophrenia patients on a variation of the ventriloquist illusion, in which typical individuals mislocalize the source of an auditory stimulus when presented with an offset visual flash, and found no difference between patients and control participants.

A more recent study (49) has found that although in non-psychiatric individuals, speech perception under noisy auditory conditions is much improved by the additional of visual speech information, patients with schizophrenia do not show the same degree of benefit. Although both groups showed improved performance on a speech recognition task when both audio and visual cues were given, typical controls benefited more than patients with schizophrenia, despite comparable performance between groups on the auditory alone condition. This pattern of results also provides

support for reduced multisensory integration with schizophrenia. Finally, there are two studies that have explored the integration of auditory voice and visual facial expression cues for emotion perception in schizophrenia patients, and have found abnormal integration of these cues compared to non-psychiatric individuals (50, 51).

Given the small number of previous studies on this topic, as well as an inconsistent pattern of results when testing different participant samples on similar paradigms (47, 48) or testing the same participants on different tasks (47), it is difficult to draw conclusions about the integrity of multisensory integration in patients with schizophrenia. To address this gap in the literature, the projects described in this dissertation further explore how patients with schizophrenia combine cues from multiple sensory modalities, as well as investigating how disordered integration relates to the symptoms of schizophrenia, the modality of hallucinations, and impaired sensorimotor gating. A number of different multisensory integration paradigms were tested on the same groups of participants, which eliminates cohort differences across studies as a potentially confounding source of variability. Current clinical symptoms were assessed at the time of testing, to allow for investigation of how integration deficits relate to the schizophrenia phenotype. Finally, many of the participants included in these studies had been previously tested on electrophysiological measures of sensory gating, and early automatic sensory processing, which allowed for the exploration of how these early deficits might relate to multisensory processing.

Chapter 2 evaluates the strength of the size-weight illusion (SWI) in patients with schizophrenia. In this classic perceptual illusion, when participants are asked to

compare the weights of two objects of identical mass and apparently identical material, one large and one small, the small object will feel substantially heavier (52). As judgments of perceived heaviness involve the integration of visual and tactile cues, the SWI can be used to investigate the integrity of this process, which has not previously been explored with these modalities in schizophrenia patients. Deficits in multisensory integration in schizophrenia patients would result in either a reduced incidence or strength of the SWI, as the illusion depends on the integration of visual and tactile cues. The results of this study provide evidence for reduced multisensory integration in patients with schizophrenia, as well as a correlation between the SWI and sensorimotor gating, as assessed by prepulse inhibition.

The experiment presented in Chapter 3 investigates intersensory facilitation of reaction time, a well-documented behavioral effect first reported by Hershenson (22) in which participants are faster to detect bimodal targets, defined by cues in two sensory modalities, compared to unimodal targets. As most previous studies of multisensory integration in patients with schizophrenia have used incongruent cues from different modalities, that typically cause perceptual illusions or perceptual errors in non-psychiatric individuals, it is of major interest to also test patients on a task in which multisensory integration is expected to result in improved behavioral performance. The results of this study indicate that although schizophrenia patients do show some speeding of reaction times to the bimodal cues, it is not to the same extent as non-psychiatric individuals. On an individual subject level, degree of multisensory integration correlates with overall negative symptoms, and patients who experience



both auditory and visual hallucinations show greater deficits in integration compared to patients who experience only auditory hallucinations.

Chapter 4 presents a version of the McGurk illusion (46), in which auditory speech perception is biased by the presentation of an incongruent visual speech cues. The McGurk paradigm has been tested with schizophrenia patients before, with an inconsistent pattern of results between studies (47, 53). This study design includes many experimental conditions designed to address methodological differences between these previous investigations. With additional control conditions not tested in previous studies, including a target detection condition that assess participants' attention to and focus on the presented stimuli, we find no evidence of a difference between schizophrenia patients and non-psychiatric participants on the incidence of the McGurk illusion. This finding may suggest that "higher level" multisensory integration involving language stimuli may be relatively intact in patients with schizophrenia. Alternatively, more sensitive methods of assessing the extent of multisensory integration may be required to quantify processing differences in this population.

The final section of this dissertation, Chapter 5, summarizes and integrates the findings from Chapters 2, 3, and 4, outlines overall conclusions that can be drawn across the studies, and summarizes how these findings contribute to the general understanding of sensory processing in patients with schizophrenia. Suggestions for further development and extension of these intriguing initial findings are also discussed. Collectively, the pattern of results described in this dissertation provide

evidence for a specific deficit in multisensory integration in patients with schizophrenia, above and beyond what is expected based on unisensory processing disruptions. This disordered integration is related to the schizophrenia phenotype, and is a promising new research area for further investigation.

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## Chapter 2

Superior Size-Weight Illusion Performance in Patients with Schizophrenia:

Evidence for Deficits in Forward Models and Multisensory Integration



### **Abstract**

When non-psychiatric individuals compare the weights of two similar objects of identical mass, one large and one small, the smaller object is often perceived as substantially heavier. This size-weight illusion (SWI) is thought to be generated by a violation of the common expectation that the large object will be heavier, possibly via a mismatch between an efference copy of the movement and the actual sensory feedback received. The SWI also involves multisensory integration, as both visual and tactile cues are combined for weight discrimination decisions. As previous research suggests patients with schizophrenia have deficits in efference copy mechanisms and multisensory integration, we hypothesized that schizophrenia patients would show a reduced SWI. The current study compared the strength of the SWI in schizophrenia patients to matched non-psychiatric participants; weight discrimination for same-sized objects was also assessed.

We found a reduced SWI in schizophrenia patients, which resulted in better (more veridical) weight discrimination performance on illusion trials compared to non-psychiatric individuals. Differences in the SWI cannot be explained by differences in weight discrimination sensitivity alone. The current finding supports the idea of dysfunctional efference copy mechanisms and/or multisensory integration in this population. At an individual subject level, reduced incidence of the SWI is correlated with reduced sensorimotor gating as assessed by prepulse inhibition (PPI).

**Superior Size-Weight Illusion Performance in Patients with Schizophrenia:  
Evidence for Deficits in Forward Models and Multisensory Integration**

**INTRODUCTION**

Schizophrenia is a debilitating psychiatric disorder with a global prevalence rate of approximately 1.0% (1). Individuals with schizophrenia, their unaffected first degree relatives, and individuals with schizotypal personality disorder all exhibit sensory processing abnormalities at both the behavioral and neural level in a number of different modalities (2-5). These deficits, including reduced prepulse inhibition, reduced P50 suppression, and reduced mismatch negativity to auditory stimuli are all deficits of early sensory processing, which may contribute to psychotic symptoms (6) and correlate with symptom severity and functional status (7-10).

Although these sensory and “gating” deficits are well characterized within individual sensory modalities, how schizophrenia patients integrate information from more than one sensory modality is a relatively new and emerging area of study. Previous research on multisensory integration (MSI) has demonstrated that the presentation of cues from multiple modalities that are coincident in time and/or spatial location facilitates localization, detection, and identification of stimuli (for reviews see (11, 12). At the neural level, MSI occurs in temporal and parietal areas of the brain, where information from individual sensory modalities converges (for review see 13).

To date, few studies have directly investigated multisensory integration in schizophrenia, and results have been divergent. Some studies find reduced MSI in

schizophrenia patients compared to non-psychiatric participants on auditory-visual speech integration tasks (14, 15), as well as disrupted integration of emotional faces and voices (16, 17). In contrast, other studies find no difference between these groups on an auditory-visual speech integration task (18) and a non-speech auditory-visual task (14). Given the small number of previous studies, the limited range of modalities tested, and conflicting patterns of results, it is difficult to draw conclusions about how auditory and visual information, or multisensory cues in general, are integrated in this population.

The current study investigated MSI in schizophrenia patients between two previously unstudied modalities, touch and vision as they relate to weight perception, using a classic perceptual illusion (19). When participants are asked to compare the weights of two objects of identical mass and apparently identical material, one large and one small, the small object will feel substantially heavier, even though participants are explicitly asked to compare weight rather than the density. This effect, the size-weight illusion (SWI), is thought to be generated by a violation of expectation. When participants initially view the objects, the brain “expects,” based on previous experience, that the larger object will be heavier than the smaller object. When both are subsequently lifted, the large object feels surprisingly light, and the small object feels surprisingly heavy (20, 21), so the small object is perceived as the heavier of the two. However, it is still debated whether this mismatch occurs at the sensorimotor (20, 21), perceptual (22, 23), and/or cognitive level (24). Crucially, both tactile and visual information contribute to the SWI. Although the SWI can be experienced when

participants are presented with either visual or tactile size information alone, the illusion is stronger when both cues are presented together (25, 26). As judgments of perceived heaviness involve the integration of visual and tactile cues, the SWI can be used to investigate MSI. Deficits in multisensory integration in schizophrenia patients would result in either a reduced incidence or strength of the SWI, as the illusion depends on the integration of visual and tactile cues.

Another potential link between schizophrenia and the SWI are efference copy mechanisms. The sensorimotor mismatch explanation for the SWI has been framed within the context of the forward model of motor control (27, 28), which proposes that when a motor act is initiated, an efference copy of the action is generated and sent to sensory comparator areas of the brain. Comparisons between this copy and actual sensory feedback are used for online movement adjustments, cancelling sensory reafference, and movement prediction and planning (29, 30). The sensorimotor mismatch which causes the SWI may be between this efference copy prediction and conflicting sensory feedback received when the objects are actually lifted. Previous research has argued that patients with schizophrenia have disruptions in forward model/efference copy mechanisms, which may underlie the self monitoring deficits in this population (31-33). As such, we hypothesized that a deficient efference copy/comparator mechanism would result in a reduced SWI in schizophrenia patients, relative to non-psychiatric comparison participants.

As generating these motor predictions involves sensorimotor transformations, we were also interested to investigate whether performance on the SWI task was

related to a sensorimotor gating measure, prepulse inhibition (PPI), which is known to be impaired in schizophrenia patients. PPI is automatic reduction of startle responses that occurs when the startling stimulus is preceded 30 to 500 milliseconds by a weak prepulse (34-36). Reduced PPI in schizophrenia patients compared to non-psychiatric individuals is a consistently replicated finding (37-42), and implies impaired sensorimotor gating processes in this patient population. Reduced PPI is also considered an endophenotype for schizophrenia (6, 43), and similar patterns of dysfunction are present in unaffected, first degree relatives of patients with schizophrenia (42, 44-46). To explore this possibility, relative performance on these two tasks was compared for a subset of the schizophrenia patient group which had previously participated in a PPI study.

## **METHODS AND MATERIALS**

### **Participants**

Participants were 20 schizophrenia patients and 20 non-psychiatric participants recruited via the UCSD Schizophrenia Research Program. All schizophrenia patients had confirmed diagnoses based on the Structured Clinical Interview for *DSM-IV*, with no other Axis I diagnoses nor history of neurologic insult. Current clinical symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS, 47) and the Scale for the Assessment of Positive Symptoms (SAPS, 48). Non-psychiatric participants were recruited through newspaper advertisements and flyers posted at the UCSD medical center, and were screened to rule out past or present Axis I or II

diagnoses and drug abuse. Participants were assessed on their capacity to provide informed consent, and given a detailed description of their participation in the study. Written consent was obtained via a consent form approved by the University of California, San Diego institutional review board (Protocol # 070052).

All schizophrenia patients were clinically stable, and nineteen were prescribed second generation antipsychotics (1 unmedicated). Five patients were living in board-and-care facilities and fifteen patients were living independently or with their family at the time of testing. Patients were diagnosed as having the following schizophrenia subtypes: paranoid (n=11), undifferentiated (n=5), and residual (n= 4). Table 1 contains demographic and clinical information. There were no significant differences between the groups in age (2 tailed t-test,  $p = .71$ ) or years of education (2 tailed t-test,  $p = .06$ ). Participants also completed the Edinburgh Handedness Inventory (Oldfield, 1971); nineteen of the non-psychiatric comparison participants were right-handed (1 left-handed) and eighteen of the schizophrenia patients were right-handed (1 left-handed, 1 ambidextrous).

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Insert Table 1 about here  
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**Methods: Size-weight Illusion**

During the experiment, participants compared the weights of pairs of gray painted wooden disks by holding one in each hand and reporting which of the two was heavier. Disks were all 1.5 inches tall and of two sizes, large (five inches diameter), and small (2 inches diameter). The objects' mass was evenly distributed about their center, and they appeared to be of uniform material. Two disks were simultaneously placed onto participants outstretched hands, and they were given about 10 seconds to chose which disk was heavier.

SWI trials compared a 90 gram small disk to large disks of increasing weights (100 – 210 grams in 10 gram increments). Weight discrimination trials compared same-sized disks in five series, with a standard weight compared against three heavier and three lighter disks, in increments of 10 grams. There were three weight discrimination series with large disks (standards 120, 150, and 180 grams) and two with small disks (standards 120 and 150 grams). Each SWI comparison was tested four times, and each weight discrimination trial was tested twice, counterbalanced for hand, for a total of 118 trials in one of five random orders. As “same weight” judgments were not allowed, 90 g small vs. 90 g large comparisons were excluded from final analyses.

**Methods: Prepulse Inhibition (PPI)**

Ten participants in the schizophrenia group had previously participated in a prepulse inhibition (PPI) in the lab. During that study session, participants abstained from smoking for at least 20 minutes prior to testing and sat in a recliner chair in a sound-attenuated room. Two 4-mm silver–silver chloride electrodes were positioned below and lateral to each eye over the orbicularis oculi (resistance < 10  $\Omega$ ), with a ground electrode behind the left ear. Electromyographic activity was directed through an SRLABORATORY monitoring system (San Diego Instruments, Inc, San Diego) that recorded 250-millisecond epochs starting with startle stimulus onset (1-kHz sampling rate). Electromyographic activity was band-pass filtered (0.1-1.0 kHz).

Startle stimuli were presented binaurally via headphones. The session lasted 23.5 minutes and included a total of 74 active and 18 no-stimulation trials. The session began with a 5-minute acclimation to white noise at a 70-dB sound pressure level that continued throughout. Startle stimuli were 40 ms noise bursts at a 115-dB sound pressure level. Prepulses were 20 ms noise bursts at an 85 dB sound pressure level with an interstimulus interval (isi) between prepulse and pulse of either 30, 60, or 120 ms. Five startle stimuli were presented at the beginning (block 1) and end (block 4) of the session to assess habituation. In blocks 2 and 3, pulse alone (PA) trials and each of the 3 prepulse trial types were pseudorandomly intermixed (range of intertrial intervals, 11-19 seconds; mean intertrial interval, 15 seconds). In 18 no-stimulation trials, data were recorded without stimulus presentation to assess basal



electromyographic activity. Consistent with previously published methods (37, 38), participants with mean pulse alone values of less than 10 digital units in block 2 were classified as non-responders, and excluded from data analysis.

Percent PPI,  $100 - ((\text{prepulse amplitude} / \text{pulse amplitude}) * 100)$ , was calculated for each trial, and data were collapsed across eye and block as no differential effects were observed for these within subjects factors. Average percent PPI at the 60 ms isi, where significant differences between schizophrenia patients and non-psychiatric individuals are most commonly observed (37), was calculated across blocks 2 and 3 (16 total trials).

## **RESULTS**

For all series of comparisons (five weight discrimination and one SWI), data were averaged across group (Schizophrenia vs. Control) and fit with a cumulative normal curve using Matlab (The Mathworks, Natick, MA, Figure 1). For each fit, the slope (the width of the underlying curve, lower values indicate steeper slopes) and the point of subjective equality (PSE) (the mean of the underlying curve) values were calculated (Table 2). The PSE is the point at which subjects cannot discriminate which weight is heavier, and are equally likely to report that one weight is heavier versus the other. As there are relatively few trials per participant for individual comparisons, data fits for individuals are unstable, which makes traditional parametric statistics such as an ANOVA non-optimal for these data. Therefore, statistical significance was assessed using a bootstrap method (49, 50) in Matlab to assess whether the observed differences between groups are more extreme than differences

expected by chance alone. Random groups of 20 participants were selected from the entire sample and compared to the remaining 20 participants. Data were averaged across the randomly selected groups, and fit as described above. Values for each group were subtracted from one another to create a between-groups difference score for each metric. This procedure was repeated 10,000 times for each series of comparisons, and mean difference values were used to create a sampling distribution of mean differences for random assignment to groups. Observed mean differences in each condition were compared to these sampling distributions. Cases in which observed mean differences (Schizophrenia – Control) fell within the upper or lower 2.5% of the sampling distributions, as in a two-tailed hypothesis test at  $\alpha < .05$ , were considered significantly different.

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Insert Figure 1 about here  
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Insert Table 2 about here  
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In all but one of the conditions (Small 120 weight discrimination), slopes for schizophrenia patients were shallower than those of non-psychiatric participants,

indicative of less sensitive weight discrimination (representative example Figure 1A). The PSE did not differ between groups for any weight discrimination series (Table 2). For the SWI trials, however, the PSE for the schizophrenia patients is significantly lighter, at 160.80 g, than the PSE for non-psychiatric individuals, at 174.17 g. The PSE, where the weights are perceived as equal, is the point at which the illusion is “nulled,” with discrimination at 50% (Figure 1B). Thus, this comparison serves as a metric for the strength of the SWI, with higher values indicating a stronger illusion. This pattern of results supports our hypothesis of a reduced SWI in the schizophrenia patient group. Running these analyses excluding the residual schizophrenia patients, the unmedicated patient, and the non-right handed participants respectively did not affect the overall pattern of results, therefore reported values include entire data set.

The less sensitive weight discrimination observed for schizophrenia patients is consistent with previous research (51-53). The fact that these slope differences are present across five of six conditions, whereas the PSE difference appears only in the size-weight condition, implies that differences in the SWI cannot be explained by these sensitivity differences alone. However, to control for the influence of discrimination sensitivity, the analyses described above were also run on a subset of the data, ten participants from each group, who were roughly matched on weight discrimination performance. For the five weight discrimination series with this subset of the data, neither the PSE nor the slope differed between schizophrenia patients and non-psychiatric individuals, indicating that we were successfully able to match for weight discrimination performance within our sample. However, even with this

matching, the PSE for the schizophrenia patient groups was still significantly lighter (154.54 g) than that of non-psychiatric individuals (166.69 g,  $p < .025$ ; slope difference for SWI ns). The fact that this difference in the strength of the SWI persists despite matching for weight discrimination performance provides further evidence that the reduced SWI for schizophrenia patients is not merely due to differences in weight discrimination sensitivity.

To investigate the relationship between performance on the SWI task and sensorimotor gating as measured by percent prepulse inhibition (PPI), a linear correlation was run between the number of trials on which a schizophrenia patient participant experienced the SWI, and their Percent PPI at the 60 ms isi. There was a significant positive correlation between these two factors ( $r^2 = .43$ ,  $p < .01$ ), such that patients who experienced the SWI on the least number of trials also had the smallest PPI, or the most impaired sensorimotor gating. Within the patient group, no significant correlations were found between performance on the SWI task and either positive symptoms, as assessed by global SAPS scores, or negative symptoms, as assessed by global SANS scores.

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Insert Figure 2 about here  
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## **DISCUSSION**

In the size-weight illusion (SWI) condition, the point of subjective equality (PSE), where the illusion is “nulled” and the weights are perceived as equal, differed between groups. The PSE value is a metric for the strength of the SWI, as it represents the perceived weight of the small comparison disk. As such, a smaller PSE (160.80 g) in the patient group compared to the non-psychiatric group (174.17 g) demonstrates that patients with schizophrenia experience a weaker SWI, as the illusion is cancelled out by a lighter weight, confirming our earlier hypothesis. Schizophrenia patients also show consistently more accurate performance on weight discrimination performance across almost the entire range of size-weight stimuli (Figure 1A). In contrast, the PSE does not differ between groups in any of the weight comparison series, supporting the idea of a specific deficit in the illusion condition, above and beyond differences in weight discrimination sensitivity. Within the schizophrenia patient group, a reduced SWI was correlated with reduced sensorimotor gating, as measured by prepulse inhibition (PPI), a measure on which schizophrenia patients are consistently impaired compared to non-psychiatric individuals. This pattern of results indicates there may be a common neural substrate for these disturbances.

For over 30 years, since Sutton and colleagues (54) posed the challenge, neuroscientists have searched for a task in which schizophrenia patients "outperform" non-psychiatric individuals, based on their underlying cognitive and neural dysfunction. This pattern of results offers promise that the SWI may be a unique

paradigm that fits the criterion of "better performance based on a deficit," as patients have more accurate weight judgments on the SWI trials than "normal" comparison participants. The current result also adds to a growing body of literature finding a specific deficit in multisensory integration in schizophrenia patients. Further exploration of these deficits may provide new insights and targets for investigation in schizophrenia research. Specifically, brain areas thought to be involved in the integration of information from vision and touch in typical individuals include the insula, the intraparietal sulcus (IPS) and the lateral occipital tactile-visual (LOtv) region for cross-modal object processing (for review see13).

These results are also consistent with previous studies of abnormal efference copy mechanisms in schizophrenia patients, which have been proposed to underlie some of the positive symptoms of schizophrenia (31-33). Helmholtz (55) originally proposed that when a motor act is initiated, an efference copy (56) of the movement is sent to the relevant primary sensory cortices, initiating a "corollary discharge" that primes the sensory cortex to receive feedback from a self-initiated movement. Indeed, studies have provided evidence for deficient corollary discharge/efference copy mechanisms in both the auditory (32, 57-59) and motor (60) domains in this population.

The results of the current study provide evidence for an efference copy deficit in a new domain - weight perception. It is thought that the SWI is generated due to a mismatch between the expected weights of the objects, and the actual sensory feedback received. As such, a deficient efference copy mechanism could explain the

reduced illusion. One possible neural generator of this mismatch is the right inferior parietal lobule (IPL), which shows increased activation when a lifted object is heavier or lighter than expected (61). Parietal lobe damage can also cause specific impairments that are best explained by disruption of internal model predictions (62). A single neuroimaging study of the SWI itself implicates the ventral premotor area, which receives its main cortical input from parietal areas (63), as a site that adapted to the density (as opposed to size or weight) of lifted objects, and was more active on trials where the SWI was perceived (64). An efference copy deficit explanation of the reduced SWI in schizophrenia patients would implicate the parietal lobe as the possible source of between group differences.

Whether the attenuated SWI in schizophrenia patients is driven by reduced MSI, abnormal efference copy mechanisms, or a combination of both cannot be resolved with these data. However, both of these problems could be explained by dysfunction in parietal lobe networks. Though previous publications have proposed that many of the core features of schizophrenia could be parsimoniously explained by general parietal lobe disruptions (65, 66) and even specific issues with the IPL (67), the broad range of deficits in schizophrenia patients creates an inverse problem, with several possible explanations for a single deficit. As such, the results of the current study make an important contribution, as the processes that likely explain the reduced SWI in schizophrenia patients are specifically linked to parietal regions.

Building on this novel initial finding, there are a number of future directions that may provide more insight into the specific nature of this reduced SWI. To assess

cognitive expectation, we are currently investigating whether, based on visual inspection alone, schizophrenia patients predict the large disk to be heavier, similar to typical individuals. A repeated lifting paradigm with size-weight stimuli would also help to elucidate specific areas of dysfunction; previous studies have shown that typical individuals incorrectly estimate the forces needed to lift the objects on early lifting trials with size-weight stimuli, but rapidly adjust their grip and lift forces for the actual mass of the object (22, 23). Employing this type of paradigm with schizophrenia patients could evaluate whether the reduced illusion is due to poor motor predictions or rather a reduced mismatch between expected and actual sensory feedback based on abnormal actual sensory feedback, or problems with the comparator mechanism. If schizophrenia patients misestimate initial lift forces in a manner similar to non-psychiatric participants, this would imply they are generating a correct motor prediction, but that the mismatch with sensory feedback itself is reduced or absent. In contrast, if patients do not employ differential similar to those of comparison participants, this would indicate abnormal motor predictions are being made. Finally, repeated training with stimuli that have an inverted volume-weight relationship can reduce and even reverse the SWI, indicating that the size-weight prior expectations can be modified with experience (68). Testing this paradigm with schizophrenia patients may be highly informative, as a reduced training effect would support the hypothesis that schizophrenia patients either do not register sensory mismatches or violations of expectations as strongly as do non-psychiatric individuals, or that these prediction errors are not used to revise and update internal models.



Evidence for this type of deficit would have important functional implications, as revisions to internal prediction models are necessary to successfully adapt to a changing environment.

In conclusion, the current study presents a unique finding for schizophrenia research, in which a deficit, either in MSI and/or efference copy mechanisms, results in more accurate than normal performance on a sensory illusion task. This deficit correlates with sensorimotor gating, which is considered to be an endophenotype for the disorder. Both potential sources for this reduced SWI implicate the parietal lobe as a probable site of dysfunction in this population. Future studies using related paradigms and additional levels of investigation (e.g. functional brain imaging) may provide further insight into the specific nature of the efference copy mechanism deficits in schizophrenia patients, as well as potential consequences in terms of perceptual learning and adaptation, relationship with clinical profiles, and to better understand how higher-order cognitive problems in schizophrenia arise from lower-level deficits in multi-sensory processing.

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Table 2.1. Characteristics of non-psychiatric comparison participants (n = 20) and schizophrenia patients (n = 20). Schizophrenia patients and non-psychiatric comparison participants did not significantly differ in either age (2 tailed t-test,  $p = .71$ ) or years of education (2 tailed t-test,  $p = .06$ ). Abbreviations: SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

<b>Characteristic</b>	<b>mean (SD)</b>
Non-psychiatric Comparison Participants (11 females)	
Age, y	50.7 (9.37)
Education, y	14.95 (2.54)
Schizophrenia Patients (8 Females)	
Age, y	51.75 (8.77)
Education, y	13.45 (2.35)
Duration of Illness, y	29.85 (10.5)
Number of Hospitalizations	5.9 (6.7)
SAPS Score	8.2 (5.22)
SANS Score	13.85 (4.85)

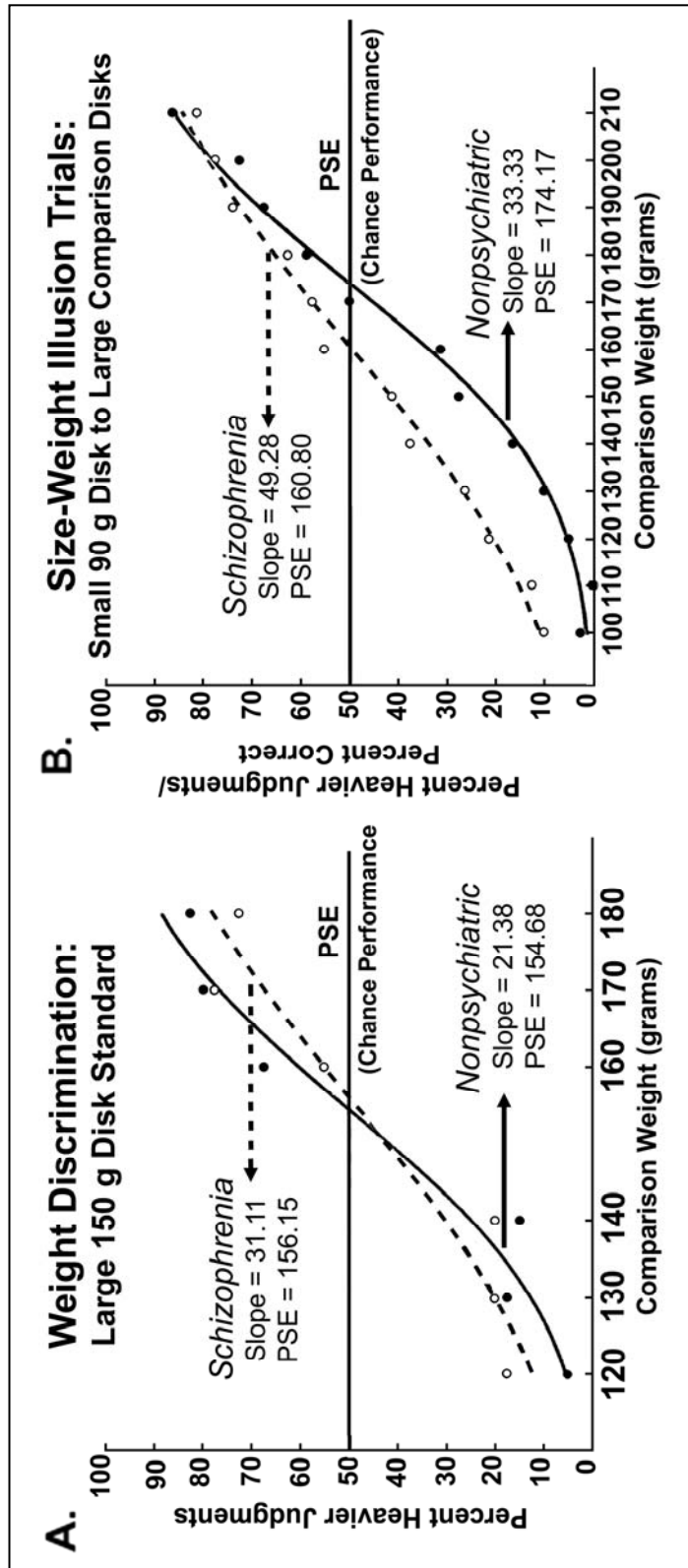


Figure 2.1: Cumulative normal fits for A) a representative example of weight discrimination series with a large disk standard weight of 150 grams and B) size-weight illusion (SWI) trials, which compared a 90 gram small disk to large disks of increasing weights, 100 – 210 grams in 10 gram increments. Closed circles and solid lines represent nonpsychiatric comparison participants, open circles and dotted lines represent schizophrenia patients. Although the slopes differ between groups in both conditions, the point of subjective equality (PSE) – where the weights are perceived as equal and the SWI is nulled – is shifted to the left, with a significantly lighter value for the schizophrenia patients, indicative of a reduced SWI.

Table 2.2. Slope and point of subjective equality values for cumulative normal fits of data across all conditions. Starred difference scores are those that differ between groups at  $\alpha < .05$  (two-tailed), based on a bootstrap analysis.

<b>Comparison Series</b>	<b>Slope</b>			<b>PSE (g)</b>		
	<b>Schizophrenia</b>	<b>Non-Psychiatric</b>	<b>Difference</b>	<b>Schizophrenia</b>	<b>Non-Psychiatric</b>	<b>Difference</b>
Size-Weight Illusion	49.28	33.33	15.95*	160.80	174.17	-13.37*
Weight Discrimination Large 120 Standard	32.53	20.44	12.09*	120.86	121.49	-0.63
Weight Discrimination Large 150 Standard	31.11	21.38	9.73*	156.15	154.68	1.47
Weight Discrimination Large 180 Standard	47.51	25.19	22.32*	176.66	178.31	-1.65
Weight Discrimination Small 120 Standard	23.71	21.98	1.73	122.59	117.36	5.23
Weight Discrimination Small 150 Standard	32.65	23.83	8.82*	149.47	148.74	0.73

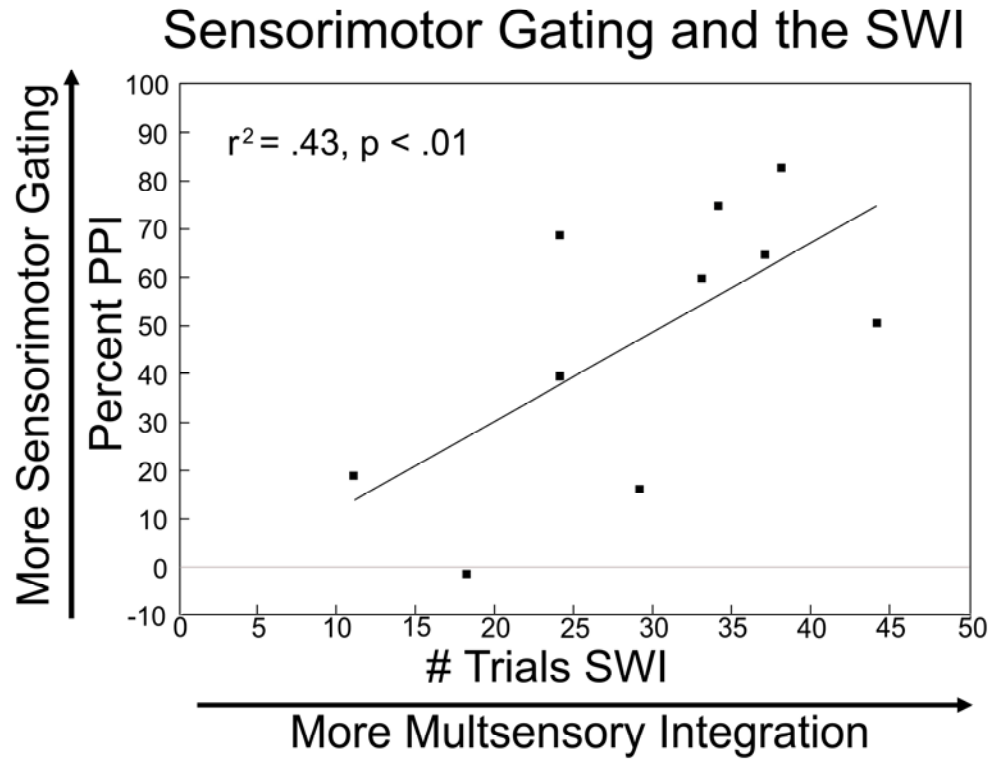


Figure 2.2: Correlation between the number of trials on which a participant experienced the size-weight illusion (SWI) and their percent prepulse inhibition (PPI). There is a significant positive relationship between these two variables, such that schizophrenia patients who experienced the SWI on the fewest trials also had the most impaired sensorimotor gating, indicating a relationship between the two.

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## Chapter 3

### Reduced Multisensory Integration in Patients with Schizophrenia on a Target Detection Task

### **Abstract**

It is known that non-psychiatric individuals are faster to detect bimodal targets, with cues from two sensory modalities, compared to detection times for unimodal targets. This speeding of reaction times (RTs) is attributed to superadditive processing of multisensory cues. The current study assesses the extent of this RT facilitation for a sample of patients with schizophrenia, who are believed to have problems with multisensory integration. RTs to detect bimodal, Audio-Visual targets are compared to a predicted RT distribution, which is a summed probability distribution of RTs to Visual Alone and Auditory Alone targets. Though patients with schizophrenia do show some RT benefit when detecting bimodal targets, it is not to the same extent as non-psychiatric individuals. Within individual participants, RT benefit is correlated with negative symptoms, such that patients with greater negative symptoms show the least RT facilitation. Additionally, schizophrenia patients who experience both auditory and visual hallucinations show less multisensory benefit compared to patients who experience only auditory hallucinations, indicating that the modality of hallucinations may affect multisensory integration.

## **Reduced Multisensory Integration in Patients with Schizophrenia on a Target Detection Task**

### **INTRODUCTION**

Schizophrenia is a debilitating psychiatric disorder with a global prevalence rate of approximately 1.0% (1). Individuals with schizophrenia, as well as their unaffected first degree relatives, and individuals with schizotypal personality disorder all exhibit sensory processing abnormalities at both the behavioral and neural level in a number of different modalities (2-5). Although these sensory and “gating” deficits are well characterized within individual sensory modalities, such as reduced prepulse inhibition, reduced P50 suppression, and reduced mismatch negativity to auditory stimuli, how schizophrenia patients integrate information from multiple sensory modalities is a relatively new and emerging area of study. Although until recently perceptual research in general has tended to focus on sensory processing within individual modalities, it is undeniable that in the real world, we are constantly bombarded with information from multiple sensory modalities, and to function optimally we must be able to detect, integrate and filter this information to form an accurate perception of our environment. Within the last 10-15 years there has been a dramatic growth in research on how sensory information from different modalities is combined, both in terms of congruent information from different sources, and how events are perceived when presented with conflicting information in different modalities. Previous research on multisensory integration (MSI) in non-psychiatric

individuals has demonstrated that the presentation of congruent information from multiple modalities confers an advantage for speed and accuracy of processing (for review see (6-9)). For example, reaction times in a target detection task are faster when auditory and visual cues are presented simultaneously, compared to a cue in a single modality (10). Along similar lines, Frens et al. (11) showed that participants had faster saccades to a visual target when an irrelevant auditory cue is spatially and temporally aligned with the target. In terms of the neural basis of this behavioral enhancement, electrophysiological studies in nonhuman animals have shown cells in the superior colliculus (SC) to be particularly responsive to multisensory stimulation, showing superadditive activity when presented with congruent multisensory cues, and depressed activity to asynchronous cues (12-14). Functional neuroimaging studies of MSI in humans finds the SC (15) as well as a distributed network of cortical areas involved in MSI (for review see (16, 17)). For example, the superior temporal sulcus (STS) has been shown to be involved with processing information from vision, audition, and touch (18). When participants are presented with auditory and visual cues, a number of cortical regions are activated and considered to be specifically “multisensory” areas, including the STS, the superior temporal gyrus, the medial temporal gyrus, and parietal regions (15, 17, 19-21). There is also emerging evidence that the presentation of multiple sensory cues also affects activation of and processing in areas previously considered to be “unisensory” regions (for review see 17).

To date, there have been very few studies investigating multisensory integration in schizophrenia, although there have been some hints of general sensory



integration problems in reviews of neuropsychological testing data. These data indicate patients with schizophrenia and their first -degree relatives have abnormal neurological signs on measures of “integration of higher sensory functions.” This subset of neurological tests includes measures of audiovisual integration (the ability to match a pattern of sounds to a visual diagram); stereognosis (the ability to identify common objects by touch); graphesthesia (the ability to identify numbers written on the skin); extinction (in response to bilateral and simultaneous somatosensory stimulation); and right/left confusion (22, 23). One such study (24) even found a correlation between poor sensory integration and eye tracking difficulties, a prominent marker of schizophrenia.

Of studies that have investigated MSI experimentally in schizophrenia patients, some find reduced integration in schizophrenia patients compared to nonpsychiatric comparison participants on tasks that evaluate the integration of auditory and visual speech cues (25, 26), as well as disrupted multisensory integration of emotional faces and voices (27, 28). However, other studies find no difference between patients and non-psychiatric individuals on auditory visual tasks, including a very similar auditory-visual speech integration task, (29) and a non-speech auditory-visual task (30). As this is a relatively small body of literature with an inconsistent pattern of results, the question of how auditory and visual information, or multisensory cues in general, are integrated in this population is still under investigation.

Importantly, the majority of these previous studies have used paradigms that present sensory cues from different modalities that are in conflict with one another

(27-30), a common experimental approach in MSI research that allows for insight into which cue has the most influence on the final perceptual judgment. However, it is equally important to understand how schizophrenia patients utilize congruent information from multiple sources, which typically confer a behavioral and/or processing advantage, as opposed to the conflict paradigms that often results in perceptual illusions, or errors in processing, in non-psychiatric individuals. Therefore, the current study investigates whether individuals with schizophrenia show similar behavioral benefit as non-psychiatric individuals when presented with bimodal cues.

To evaluate this question, we tested group of patients with schizophrenia on a simple target detection task to assess intersensory facilitation of reaction time, which is a well-documented behavioral effect first reported by Hershenson (10). Participants were asked to respond with a button press as quickly as possible when they detected a simple target, which could be either unimodal (visual alone or auditory alone) or bimodal (auditory + visual). Previous studies of this type of paradigm have found that reaction times to detect the bimodal targets are faster than reaction times to either single stimulus alone.

## **METHODS AND MATERIALS**

### **Participants**

Participants were 20 schizophrenia patients and 20 non-psychiatric participants recruited via the UCSD Schizophrenia Research Program. All schizophrenia patients had confirmed diagnoses based on the Structured Clinical Interview for *DSM-IV*, with

no other Axis 1 diagnoses nor history of neurologic insult. Current clinical symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS, 31) and the Scale for the Assessment of Positive Symptoms (SAPS, 32). Non-psychiatric participants were recruited through newspaper advertisements and flyers posted at the UCSD medical center, and were screened to rule out past or present Axis I or II diagnoses and drug abuse. Participants were assessed on their capacity to provide informed consent, and given a detailed description of their participation in the study. Written consent was obtained via a consent form approved by the University of California, San Diego institutional review board (Protocol # 070052).

All schizophrenia patients were clinically stable, and nineteen were prescribed second generation antipsychotics (1 unmedicated). Six patients were living in board-and-care facilities and fourteen patients were living independently or with their family at the time of testing. Patients were diagnosed as having the following schizophrenia subtypes: paranoid (n=11), undifferentiated (n=6), and residual (n= 3). Table 1 contains demographic and clinical information. There were no significant differences between the groups in age (2 tailed t-test,  $p = .95$ ) or years of education (2 tailed t-test,  $p = .11$ ). Participants also completed the Edinburgh Handedness Inventory (Oldfield, 1971); nineteen of the non-psychiatric comparison participants were right-handed (1 left-handed) and eighteen of the schizophrenia patients were right-handed (1 left-handed, 1 ambidextrous).

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Insert Table 1 about here  
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### **Reaction time task**

Participants were seated in front of an 18" ViewSonic Graphics Series monitor (1024 x 768, 60 Hz) with their eyes 57 cm from the center of the screen. The experiment was programmed in E-Prime (Psychology Software Tools, Inc.) Participants pressed the space bar on a standard computer keyboard to start each trial. Trials began with a fixation cross presented for 1.5 seconds, followed at a variable random delay (500 - 1500 ms) by either a visual stimulus – a red letter X printed in Times New Roman font, 12 pt, subtending 0.7 degrees of visual angle, presented for 100 ms, an auditory stimulus - a brief, 100 ms tone presented binaurally via headphones, or a both cues simultaneously in the bimodal condition. Blank trials were also included to reduce anticipatory responses. Participants were instructed to press the "K" key of a standard PC keyboard with the index finger of their preferred hand (dominant hand for all participants) as quickly as possible when they detected either a visual or auditory target, and the reaction time (RT) to the button press was measured. Participants completed four blocks of 74 trials; each block began with 4 randomly selected trials that were treated as practice trials and excluded from analysis, followed by 20 trials in each condition (auditory, visual, and bimodal) plus 10 blank catch trials, all presented in random order.

As the bimodal targets provide two cues for detection rather than one, comparing the raw RTs for unimodal vs. bimodal stimuli cannot disentangle the effects of redundant stimulation (e.g. the presentation of two cues) from the effect of true multisensory benefit, gained from congruent stimulation in two separate sensory modalities. To test for the presence of actual multisensory gain, RTs in the bimodal condition were compared to predicted RTs generated by the “independent race model” (33, 34), which calculates the summed probabilities of the auditory alone and visual alone conditions ( $Pr \text{ Auditory} + Pr \text{ Visual}$ ) for each individual participant. When RTs in the bimodal condition are significantly faster than this summed race model probability, which is the expected distribution of RTs for presenting two cues as opposed to one, this is considered a violation of the race model and thought to reflect true superadditive multisensory integration (33).

Prior to analysis, individual responses more than 3 standard deviations above or below the mean of a particular condition were excluded and replaced with the mean of the remaining RT's for that condition. This data cleaning did not differentially affect the patient group (total trials excluded: schizophrenia patients 82, non-psychiatric individuals 76). Data analysis was performed with Matlab (The Mathworks, Natick, MA) using a program published by Ulrich, Miller, and Schroter (35). Briefly, for each participant, raw RTs in each experimental condition (auditory, visual, auditory + visual) were used to generate a cumulative density function (CDF). The CDFs for the auditory and visual targets were summed to calculate the race model prediction curve for each individual participant (see 35 for more details of analysis).

These curves were evaluated to determine percentile values at 20 different points (.05 – 1.0) and these percentile values were averaged across individuals for each group (Schizophrenia versus Control). Any given percentile value determines the upper limit for reaction times associated with that percentile. For example, a reaction time value of 300 ms for the .05 percentile indicates that 5% of trials in this condition have a reaction of 300 ms or faster.

Violations of the race model at individual percentiles were evaluated using paired t-tests. As these multiple t-tests inflate the family-wise alpha level, we also report Bonferroni-corrected violations. This is considered a somewhat conservative correction (35), and the general pattern of results is consistent for both non-corrected and corrected comparisons.

## **RESULTS**

False alarm rates were virtually non-existent, and did not differ significantly between groups (0.11% of trials for patients, 0.23% for non-psychiatric;  $t = -0.50$ ,  $p = 0.62$ ). In an attempt to sample the distribution of RT's for each condition equivalently for individual participants, missed trials were rerun at the end of each block, and RT's for the rerun trials replaced misses during analysis. Overall miss rates were calculated based on the number of rerun trials per condition for each participant plus any trials missed again when rerun. These miss rates were relatively low and differed between groups for only the Auditory condition (2.57% patients vs. 0.24% non-psychiatric,  $t = 2.63$ ,  $p = 0.01$ ) but not for Visual condition (1.85% patients vs. 0.97% non-psychiatric,  $t = 1.73$ ,  $p = 0.09$ ), or Bimodal condition (0.41% patients vs. 0.30% non-psychiatric,  $t$

= 0.44,  $p = 0.66$ ). Misses that remained after rerun were extremely rare, and did not differ significantly between groups in any condition (Auditory 0.16% patients, 0% non-psychiatric,  $t = 1.38$ ,  $p = 0.17$ ; Visual 0.11% patients, 0% non-psychiatric,  $t = 1$ ,  $p = 0.32$ ; Bimodal 0.11% patients, 0.06% non-psychiatric,  $t = 0.52$   $p = 0.60$ ). The significant difference in overall misses was primarily driven by one participant in the schizophrenia group; the analyses presented below were run with that participant excluded and results were identical, therefore reported results include all participants.

Reaction time curves for schizophrenia patients and non-psychiatric participants are presented in Figure 1. The data for non-psychiatric individuals (Figure 1 A) replicates many previous findings, in which reaction times (RTs) for the bimodal condition are faster than either of the unimodal (visual or auditory) conditions. In addition, for almost the entire curve, RTs in the bimodal condition are faster than predicted by statistical summation of the two unimodal conditions, which is shown in the race model prediction curve. Individual t-tests for each of the twenty percentiles presented indicate that bimodal RT's violated the race model up through the 80<sup>th</sup> percentile (all  $p$ 's  $< .05$ ; Bonferroni corrected violations also up through 80<sup>th</sup> percentile). In contrast, patients with schizophrenia (Figure 1 B) only show violations of the race model up through the 50<sup>th</sup> percentile (Bonferroni corrected violations up through the 35<sup>th</sup> percentile). This pattern of results indicates that although schizophrenia patients do show some of the expected multisensory benefit on this task is it not to the same extent as non-psychiatric individuals.

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Insert Figure 1 about here  
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One potential limitation to the interpretation of between group differences in multisensory integration is that the unimodal reactions times differ between groups, with overall slower times for the schizophrenia patients across all conditions. Though the fact that the race model predictions are calculated using each groups specific unimodal curves as a base somewhat addresses this issue, it does not completely control for the influence of general slowing of RT's in the schizophrenia group. Therefore, we also ran the same analyses described above on a subset of the data, ten participants from each group, that were roughly matched for unimodal RT's. The curves for relatively slow non-psychiatric participants and relatively fast schizophrenia patients are shown in Figure 2. The difference in violations of the race model between groups persists, and is even amplified with these selected subjects, with violations through the 80<sup>th</sup> percentile for slow non-psychiatric individuals (Bonferroni corrected violations up through the 50<sup>th</sup> percentile), and violations through only the 35<sup>th</sup> percentile for schizophrenia patients (no significant violations of the race model with Bonferroni correction). A direct comparison of the unimodal RT curves for schizophrenia patients and non-psychiatric individuals is presented in Figure 3; individual t-tests for each of the twenty percentiles presented found no significant differences between groups (2 tailed t tests, all p's > .34), indicating that we were able



to successfully match for unimodal RT. As such, it is unlikely that the observed differs in multisensory benefit between groups can be attributed to slower overall reaction times.

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Insert Figure 2 about here  
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Insert Figure 3 about here  
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We were also interested to investigate whether the modality of a patient's hallucinations affected their pattern of multisensory integration. To do this, the patient group was separated into individuals who have experienced both visual and auditory hallucinations ( $n = 10$ ) and those who have experienced only auditory hallucinations ( $n = 10$ ). There results of this comparison are shown in Figure 4; patients who have experienced only auditory hallucinations show violations of the race model up through the 55<sup>th</sup> percentile (Bonferroni corrected violations up through the 40<sup>th</sup> percentile), compared to violations through only the 10<sup>th</sup> percentile for patients who have experienced both auditory and visual hallucinations (no significant violations of the race model with Bonferroni correction). This pattern of results indicates that patients who have experienced both visual and auditory hallucinations may be especially impaired with respect to audio-visual multisensory integration. As the auditory and visual hallucination group also has higher positive symptom scores

than (global SAPS of 10.8 for auditory and visual group, versus 6.4 for only auditory group,  $t = -2.18$ ,  $p < .05$ , 2 tailed), we also examined integration patterns for the patient group with a median split based on global SAPS score. Both the high and low SAPS groups showed similar patterns of multisensory integration (race model violations through the 35<sup>th</sup> percentile for high SAPS, and up through the 40<sup>th</sup> percentile for low SAPS), indicating that the integration differences observed between the different hallucination groups can not solely be explained by positive symptom severity.

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 Insert Figure 4 about here  
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To examine the relationship between multisensory benefit for individual participants and other variables of interest, for each participant we counted the number of percentiles in which the bimodal RT curve was faster than the race model prediction value. This metric has a maximum score of 20 (bimodal faster than race model prediction for all percentiles, multisensory benefit across entire curve) and a minimum score of 0 (race model prediction faster than bimodal for all percentiles, no multisensory benefit). Therefore, higher scores indicate multisensory benefit across a great proportion of the curve. These RT Benefit scores showed a significant negative correlation with negative symptoms ( $r^2 = 0.20$ ,  $p < .05$ , Figure 5), such that participants who showed multisensory benefit over less of the curve had greater global

SANS scores. No significant correlation was found between this bimodal benefit metric and positive symptoms (global SAPS score).

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Insert Figure 5 about here  
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## **DISCUSSION**

Intersensory facilitation of reaction time (RT) is a well-documented behavioral effect first reported by Hershenson (10), in which bimodal stimuli (e.g. auditory and visual, or visual and tactile cues presented simultaneously) are detected faster than to either single stimulus alone. Multiple studies have found that this speeding of RT's for bimodal cues is above and beyond what would be expected by statistical summation of the unimodal RT's (e.g. (33, 34, 36, 37), and is thought to reflect genuine facilitation of processing due to the presentation of congruent cues from multiple sensory modalities.

The current study finds that though patients with schizophrenia do experience some benefit in reaction time to bimodal cues, it is not to the same extent as in typical individuals. For non-psychiatric individuals, reaction times in the bimodal condition violate the race model up to the 80th percentile, indicating a benefit greater than predicted by redundant stimulation for the majority of the reaction time curve. In contrast, the schizophrenia patients only show violations of the race model up to the 50th percentile. This provides evidence that these patients do indeed show behavioral

improvement that is typically attributed to multisensory facilitation, it is to a lesser extent, or on fewer overall trials, than non-psychiatric individuals. When these analyses are performed on a subset of participants matched across groups for RT's in the unimodal conditions, the pattern of results is unchanged, with the non-psychiatric participants showing violations of the race model over a greater proportion of the curve than schizophrenia patients (80<sup>th</sup> percentile vs. 35<sup>th</sup> percentile respectively). This subset analysis is crucial to determine whether this apparent deficit in multisensory integration is driven solely by general slowing on the task. The fact that between group differences persist when participants are matched on performance in the auditory alone and visual alone conditions supports the idea of a specific deficit in multisensory integration in this population, in addition to well studied deficits in unimodal processing. This pattern of results fits with the one previous study that examined multisensory integration in patients with schizophrenia using a paradigm in which bimodal cues facilitate performance in non-psychiatric individuals. Ross and colleagues (26) evaluated how the addition of congruent visual speech cues improved participants' ability to identify degraded (noisy) auditory speech using single word stimuli. Although both non-psychiatric individuals and schizophrenia patients showed better performance with the addition of visual information (compared to auditory alone), the patient group did not benefit as much as the non-psychiatric participants.

We also found that patients with both auditory and visual hallucinations show even further reduced multisensory integration compared to patients who experience only auditory hallucinations, indicating that modality of hallucination may affect this

process. Although this is a preliminary finding that requires further investigation, one possible explanation for this difference is that having two disordered sensory channels in the auditory and visual group, as opposed to only one in the only auditory group, leads to increased variability in the timing of processing signals that enter the brain via those channels. Studies of multisensory integration in non-psychiatric individuals indicate that the timing of input from multiple sensory channels is crucial to elicit the enhanced neural activity associated with multisensory cues (38). As such, small differences in the timing of and synchrony between both the auditory and visual channels could have deleterious cumulative effects. In contrast, having only one disordered channel in the auditory hallucination group may lead to less severe deficits.

As more data accumulate on the topic of multisensory integration in individuals with schizophrenia, it appears that subtle deficits may indeed exist, (25-28), but perhaps that some paradigms do not allow for enough precision to evaluate the degree of MSI in sufficient detail to detect these differences. For example, in the current study, we don't find that schizophrenia patients show no behavioral benefit when responding to bimodal cues, but rather a reduction in the magnitude of benefit. That these deficits are somewhat subtle does not discount their clinical relevance, as RT benefit is significantly correlated with negative symptoms. We also find a similar pattern of reduced, but not absent, multisensory integration using a visual-tactile integration paradigm investigating the size-weight illusion with schizophrenia patients (39). With this size-weight data, simply analyzing the incidence of the illusion did not reveal clear differences between patients and non-

psychiatric individuals, but performing a more precise analysis that estimates the magnitude of integration did yield interesting differences that were associated with another sensorimotor gating measure.

As a number of our participants completed both the current study and this visual-tactile experiment, we investigated whether individual subject performance was correlated across paradigms and modalities, but found no significant relationship. As such, it is possible there are unique neural substrates for the differences observed between schizophrenia patients and non-psychiatric individuals in these studies. In non-psychiatric individuals, the integration of auditory and visual information is thought to occur in a number of regions, including the superior temporal sulcus (STS), the superior temporal gyrus, the medial temporal gyrus, and parietal regions (15, 17, 19-21).

Moving forward with this paradigm, it would be interesting to investigate the neural basis of these between group differences using neuroimaging techniques. For example, electroencephalography (EEG) studies of the this type of reaction time paradigm in non-psychiatric individuals finds evidence for both early and late audio-visual interaction effects (40, 41) but also see (42), as well as enhanced neural synchrony associated with multisensory processing (43). This type of investigation would provide insight into where and when processing differences may arise between these two diagnostic groups. This type of further exploration would also be helpful to discover whether the decreased benefit seen in the average data for the patient group is due to a general reduction in multisensory benefit across all trials, or whether

differences are driven by superadditive multisensory processing on fewer individual trials compared to non-psychiatric individuals. Examining trial-by-trial variability in neural responses could help to discriminate between these possibilities. Finally, it will also be informative to further explore the clinical correlates of these between group differences, such as whether integration deficits are state or trait dependent, or whether they may also be present early in the course of illness.

In conclusion, the current study finds that patients with schizophrenia show a reduced behavioral gain compared to non-psychiatric individuals when detecting bimodal targets, and furthermore that the degree of bimodal benefit received is related to their clinical symptoms. This finding adds to a growing body of literature providing evidence for a specific deficit in MSI in patients with schizophrenia, above and beyond disordered processing within individual modalities. The fact that within individual patients the degree of multisensory benefit was correlated with severity of negative symptoms indicates that these integration problems may contribute to the schizophrenia phenotype.

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Table 3.1: Characteristics of non-psychiatric comparison participants (n = 20) and schizophrenia patients (n = 20). Schizophrenia patients and non-psychiatric comparison participants did not significantly differ in either age (2 tailed t-test, p =.95) or years of education (2 tailed t-test, p =.11). Abbreviations: SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

<b>Characteristic</b>	<b>mean (SD)</b>
Non-psychiatric Comparison Participants (11 females)	
Age, y	50.90 (9.33)
Education, y	14.70 (2.96)
Schizophrenia Patients (8 Females)	
Age, y	51.10 (9.32)
Education, y	13.35 (2.23)
Duration of Illness, y	29.90 (10.65)
Number of Hospitalizations	7.40 (8.44)
SAPS Score	8.6 (4.94)
SANS Score	13.65 (4.70)

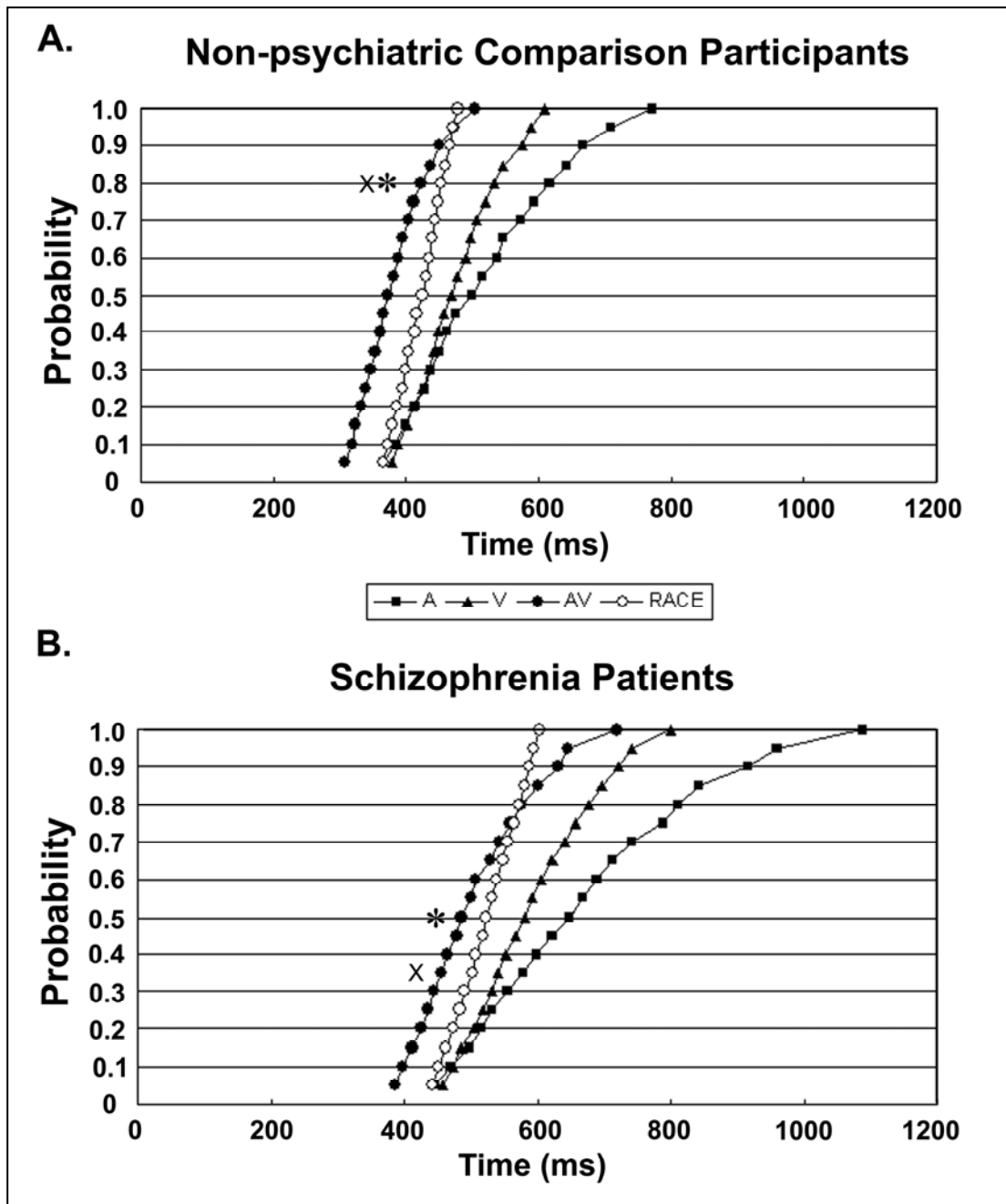


Figure 3.1: Cumulative density functions of reaction times (RTs) for target detection with three cue types; Unimodal Auditory (A), Unimodal Visual (V) and Bimodal Auditory + Visual (AV) as well as Race Model predictions (RACE) based on unimodal RT curves. Panel A shows non-psychiatric comparison participants and panel B shows schizophrenia patients. The percentile up to which the AV curve violates the race model for each group is marked with a star, Bonferroni corrected violation level marked with an X. Schizophrenia patients show intersensory facilitation of reaction time over less of the curve, up to only the 50<sup>th</sup> percentile, compared to non-psychiatric individuals who show race model violations up to the 80<sup>th</sup> percentile.

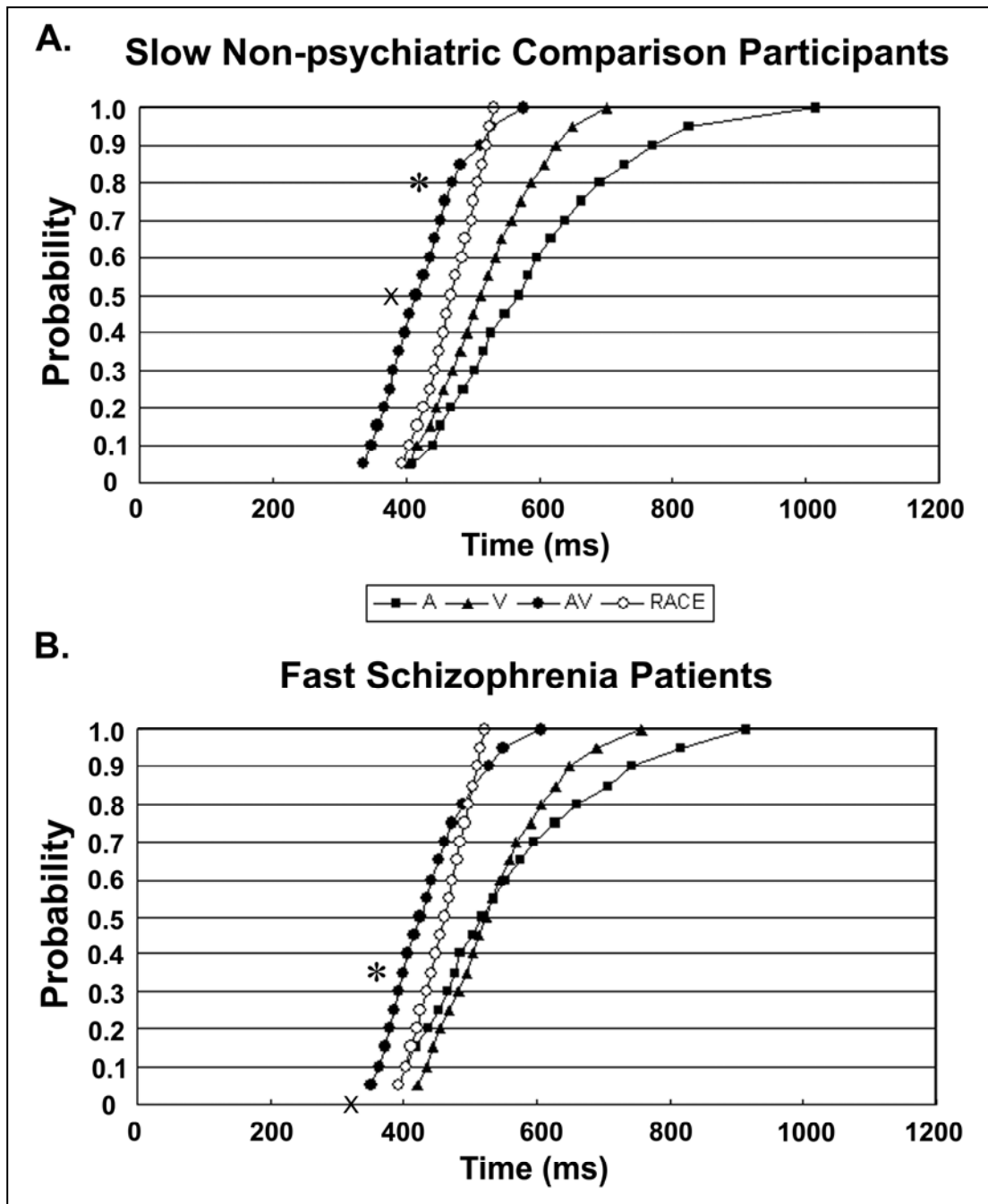


Figure 3.2: Cumulative density functions of reaction times (RTs) for target detection with three cue types; Unimodal Auditory (A), Unimodal Visual (V) and Bimodal Auditory + Visual (AV) as well as Race Model predictions (RACE) based on unimodal RT curves. Panel A shows non-psychiatric comparison participants ( $n = 10$ ) with relatively slow unimodal reaction times, and panel B shows schizophrenia patients with relatively fast unimodal reaction times. The percentile up to which the AV curve violates the race model for each group is marked with a star, Bonferroni corrected violation level marked with an X. Even when groups are matched for unimodal reaction times, schizophrenia patients still show intersensory facilitation of reaction time over less of the curve.

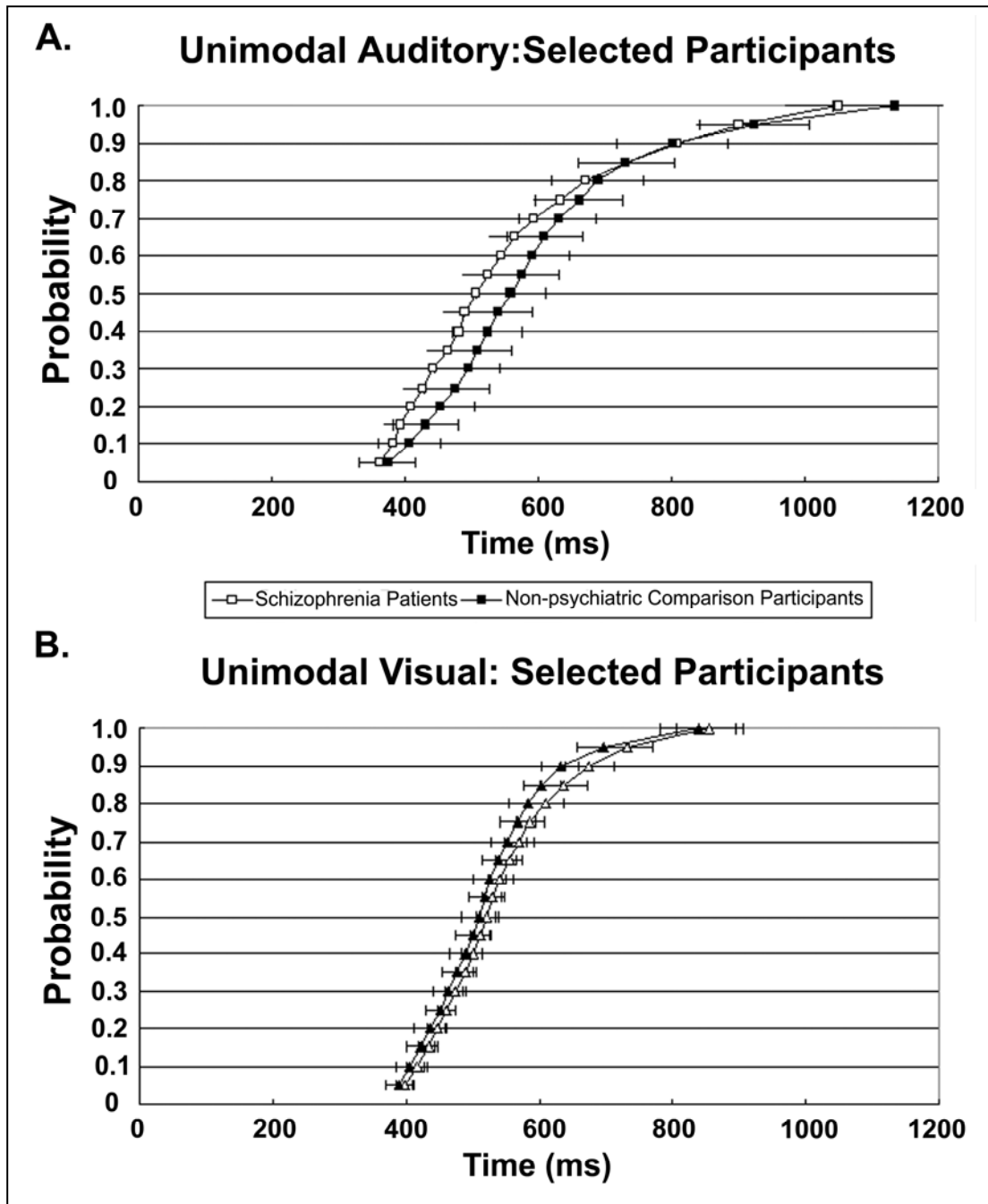


Figure 3.3: Cumulative density functions for unimodal conditions with participants matched on these conditions. In both the A) auditory condition and B) visual condition, no significant differences were found between schizophrenia patients and non-psychiatric comparison participants, indicating that matching was successful.

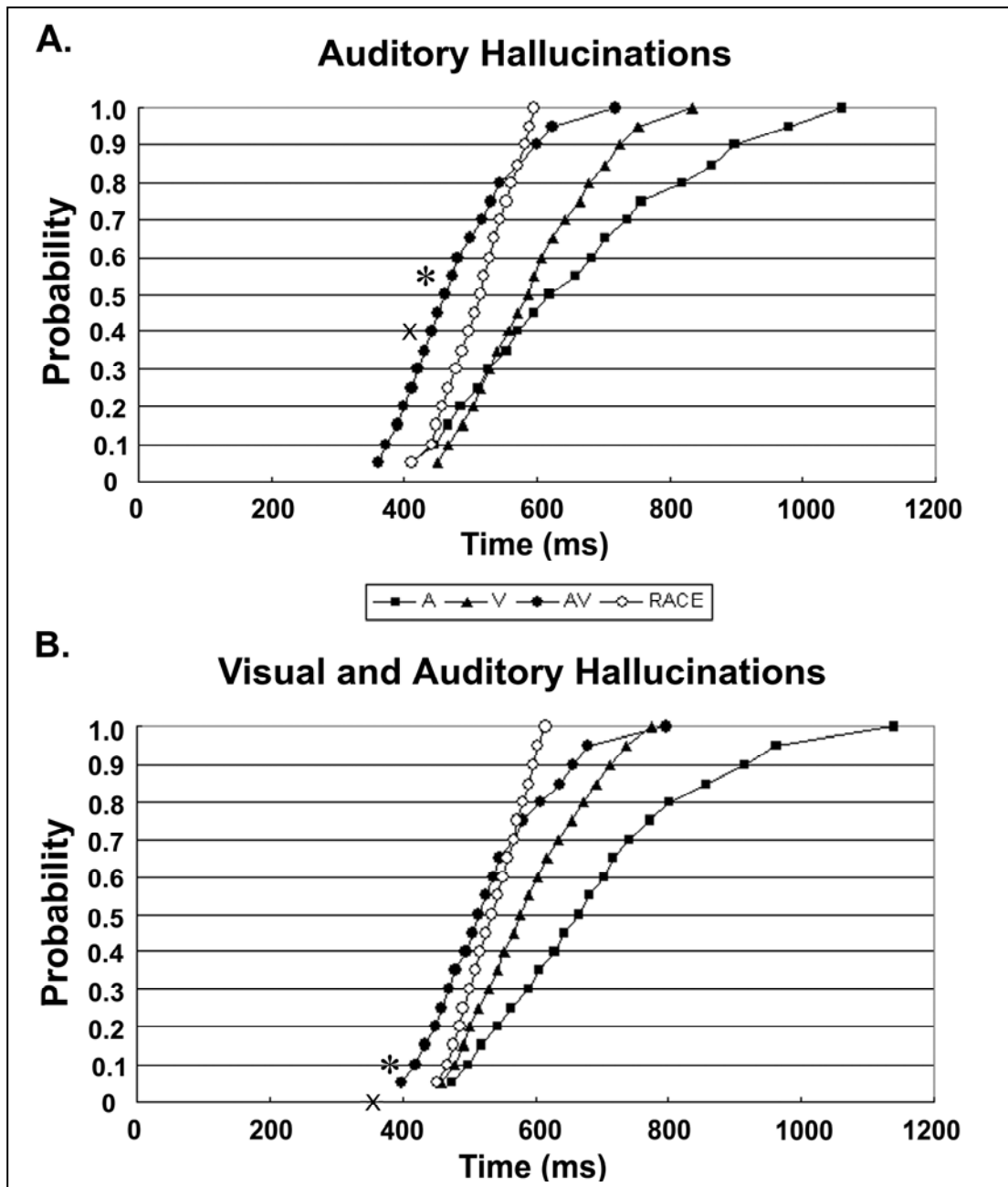


Figure 3.4: Cumulative density functions of reaction times (RTs) for target detection with three cue types; Unimodal Auditory (A), Unimodal Visual (V) and Bimodal Auditory + Visual (AV) as well as Race Model predictions (RACE) based on unimodal RT curves. Panel A shows a sample of schizophrenia patients ( $n = 10$ ) who experience only auditory hallucinations, and panel B shows a sample of schizophrenia patients ( $n = 10$ ) who experience both auditory and visual hallucinations. The percentile up to which the AV curve violates the race model for each group is marked with a star, Bonferroni corrected violation level marked with an X. Patients who experience both auditory and visual hallucinations exhibit reduced multisensory integration compared to patients who only experience auditory hallucinations.

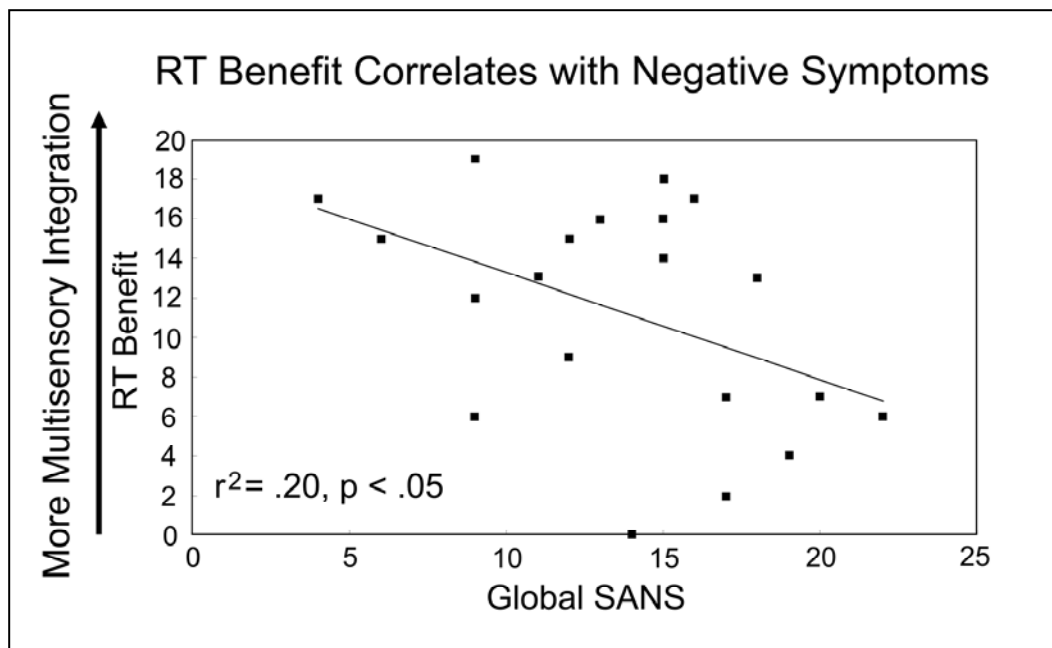


Figure 3.5: Correlation between metric of multisensory benefit (maximum score of 20 with higher scores indicating more multisensory benefit) and negative symptoms (global SANS scores) for individual patients with schizophrenia. There is a significant negative correlation between these factors, such that individuals who exhibited less multisensory benefit had greater negative symptom ratings.

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## Chapter 4

### The McGurk Illusion in Patients with Schizophrenia

### **Abstract**

The McGurk effect is a powerful, audio-visual perceptual illusion in which auditory speech perception is biased by the presentation of an incongruent visual speech cues. The current study investigates the incidence of the illusion in patients with schizophrenia and a non-psychiatric comparison group. Previous investigations of this effect in schizophrenia patients have yielded conflicting patterns of results, with one study indicating a decreased incidence of the illusion, which was interpreted as reduced multisensory integration between auditory and visual speech cues in this population. However, another study found no difference between patients and non-psychiatric participants. The current design includes number of additional control conditions are included to address some of these discrepancies. With the addition of these conditions, we find no difference in the incidence of the McGurk illusion between schizophrenia patients and non-psychiatric participants; however, we do find evidence for impaired lip-reading ability in this population. Findings are discussed in the context of emerging research indicating a specific deficit in multisensory integration in patients with schizophrenia.

## **The McGurk Illusion in Patients with Schizophrenia**

### **INTRODUCTION**

When considering speech perception, it may be natural to assume that the majority of speech processing occurs via auditory input alone. However, there is a large body of evidence indicating that visual cues also play a substantial role in the perception and interpretation of speech. For example, the addition of visual speech cues to auditory speech can improve comprehension, an effect that is amplified when auditory cues are degraded (1-4). Functional neuroimaging studies have also shown that presenting participants with visual speech activates some areas also involved in processing auditory speech (5-7), indicating some common neural mechanisms for the processing of auditory and visual speech.

A powerful behavioral example of how visual speech cues can affect speech perception is the McGurk Effect (8). In this paradigm, auditory speech cues are paired with incongruent visual speech, and for particular combinations what is “heard” corresponds to the presented visual cue, rather than the auditory. For example, individuals listen to the sound /ba/ while they view a video of someone mouthing a different sound, /da/, after which they are asked to report what they heard. For most individuals, the visual information dominates the fused perception, and what is “heard” either match the visual information (/da/), or corresponds to a fusion of the auditory and visual cues, e.g. /ga/. The current study investigates the incidence of the McGurk illusion in individuals with schizophrenia, as a metric of auditory-visual speech integration in this population.

The integrity of multisensory integration (MSI) processes is an emerging area of schizophrenia research. Though there are relatively few empirical studies of this topic to date, there is some data to suggest that schizophrenia exhibit reduced multisensory integration compare to typical individuals (9-13); however, also see (9, 14). The McGurk paradigm has been tested before in patients with schizophrenia by two different groups, but these investigations have yielded conflicting results. In one study de Gelder and colleagues (15) tested a sample of schizophrenia patients on a variation of the McGurk effect using non-word vowel-consonant utterances (e.g. /aba/, /ata/) presented in one of three conditions; auditory alone, visual alone, or audio-visual, in which the visual stimuli were dubbed with an incongruent audio track. They found that compared to non-psychiatric comparison participants, the schizophrenia group exhibited similar accuracy in the auditory condition, impaired lip-reading performance in the visual alone condition, and a reduced visual bias in the auditory-visual condition. The authors interpret this pattern of results as evidence for reduced integration of auditory and visual speech in this population. In contrast, Surguladze et al. (7) tested a sample of schizophrenia patients on a McGurk paradigm as part of a larger fMRI study investigating the neural correlates of auditory-visual speech perception in this population. In this study, participants were presented with auditory tracks of single word stimuli, as well as audio plus incongruent visual single word stimuli. They found no difference between patients and controls in the incidence of the McGurk illusion.

Given the conflicting results of previous studies on this topic, as well as differences in experimental design, the goal of the current study was to run an expanded version of the McGurk paradigm to more fully explore the incidence of this illusion in patients with schizophrenia. A sample of patients with schizophrenia and matched non-psychiatric comparison participants were tested on a large number of word and non-word stimuli in a number of additional perceptual conditions not included in previous studies, such as congruent audio-visual stimuli and incongruent audio-visual stimuli in which the illusion is expected to occur, in addition to the McGurk, auditory alone, and visual alone conditions tested in previous studies. We also include a task at fixation, centered over the mouth of the speaker in the video clips, to evaluate whether there are any measurable differences in attention to the visual stimuli between diagnosis groups.

## **METHODS AND MATERIALS**

### **Participants**

Participants were 19 schizophrenia patients and 18 non-psychiatric participants recruited via the UCSD Schizophrenia Research Program. Only participants with English as a first language were included for this study. Two schizophrenia patients were excluded from analysis from analysis for poor performance in control conditions, and demographic information is listed for only the 17 participants included in final analyses. All schizophrenia patients had confirmed diagnoses based on the Structured Clinical Interview for *DSM-IV*, with no other Axis 1 diagnoses nor history of

neurologic insult. Current clinical symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS, 16) and the Scale for the Assessment of Positive Symptoms (SAPS, 17). Non-psychiatric participants were recruited through newspaper advertisements and flyers posted at the UCSD medical center, and were screened to rule out past or present Axis I or II diagnoses and drug abuse. Participants were assessed on their capacity to provide informed consent, and given a detailed description of their participation in the study. Written consent was obtained via a consent form approved by the University of California, San Diego institutional review board (Protocol # 070052).

All schizophrenia patients were clinically stable, and sixteen were prescribed second generation antipsychotics (1 unmedicated). Five patients were living in board-and-care facilities and twelve patients were living independently or with their family at the time of testing. Patients were diagnosed as having the following schizophrenia subtypes: paranoid (n=9), undifferentiated (n=5), and residual (n= 3). Table 1 contains demographic and clinical information. There were no significant differences between the groups in age (2 tailed t-test,  $p = 0.61$ ), and non-psychiatric individuals had significantly higher years of education (2 tailed t-test,  $p < 0.01$ ).

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Insert Table 1 about here  
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## **McGurk Task**

Stimuli were created by recording a female native English speaker pronouncing a number of single syllable English words, and single syllable non-word stimuli. Auditory and visual components used to create various stimulus types were separated and spliced in Adobe Audition software. During testing audio and visual clips were presented using Macromedia Director 8.5 (Macromedia, San Jose, CA).

During testing, auditory stimuli were presented binaurally via headphones and visual stimuli were presented on an 18" ViewSonic Graphics Series monitor (1024 x 768, 60 Hz). Trials were initiated via a button press by the experimenter, and consisted of a fixation cross for 1500 ms, followed by one of the stimulus set described below.

Stimuli were all similar in length and lasted approximately 2.5 seconds. Video stimuli occupied nearly the entire computer screen.

A large set of possible audio-visual stimuli were piloted with college undergraduate participants from UC San Diego to find audio-visual combinations that would produce a strong McGurk illusion. Fifteen word and sixteen nonword stimuli were selected from this set as McGurk stimuli, as well as fifteen word and fifteen nonword audio-visual combinations that did not elicit a McGurk effect. In order to try and isolate a specific reduction in the McGurk effect in the absence of other differences in language and sensory processing, a number of control conditions were included in the study design, namely Auditory Alone stimuli (audio track presented over headphones, no video clip), Visual Alone stimuli (video clip presented on computer screen, no audio), and Audio-Visual Congruent stimuli where both cues

match and are presented together (natural speech). After the best McGurk and non-McGurk combinations were selected from the large sample of possible combinations, the corresponding Audio, Visual, and Audio-Visual Congruent stimuli were added to the stimulus set. Finally, to provide a measure of attention during the task, and to ensure that all participants were focusing on the mouth of the speaker in the videos to maximize the incidence of the McGurk illusion, twenty trials in which a Target shape (either a square or a circle) appeared over the mouth of the speaker were also included. For Target trials participants were asked to report which shape they saw, as opposed to what the speaker said. All 208 stimuli were presented once in random order.

Participants were told: “You are going to watch some video clips on the computer screen and hear some sounds coming over the headphones; sometimes the sounds would be real words, and sometimes just nonsense syllables, like “ba” or “da,” or “ki” or “ti.” The video clips will be of a woman saying a word or sound. You should watch the computer screen at all times, even when there is no video being played. If there is a video playing, please focus on the mouth of the speaker. Your task is to repeat to me what you hear the person say. On a few of the trials, there will be a small red shape that appears on the mouth of the speaker; on those trials just report what shape you see, you don’t need to tell me what the person said.” The various other conditions were then explained. During the task, an experimenter recorded the participants’ response after each trial, and advanced to the next trial when the participant was watching the computer screen and ready to continue. Any trials on which the participant did not watch the computer screen for the entire stimulus

presentation were excluded from final analyses; these exclusions were very rare as a trial was not initiated until the participant was focused and ready.

After data collection was complete, the data for individual stimuli were inspected for the non-psychiatric participants. Some of the stimuli selected based on pilot data did not maintain their high levels of accuracy during the actual experimental sessions, and these were removed from analyses for all participants; final counts for each stimulus type and number of excluded trials are detailed in Table 2. Performing the statistical analyses described below with these poor stimuli included did not change the overall pattern of results.

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Insert Table 2 about here  
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Participants' responses were compared with the actual stimuli presented. In the Audio Alone, Audio-Visual Congruent, Audio-Visual Incongruent McGurk, and Audio-Visual Incongruent No McGurk conditions, trials were coded as a Match when the report was identical to the presented auditory word or sound, and a Nonmatch where the report differed from the presented auditory word or sound. In the Visual Alone condition, trials were coded as a Match when the reported word or sound began with the same first letter as the presented visual stimulus, and a Nonmatch when the report began with a different initial letter. In the Target condition, trials were coded as a Match when the correct shape was reported and a Nonmatch when an incorrect

shape, or no shape was reported. For each condition, except the McGurk condition, a Percent Correct was calculated for each participant, by dividing the number of Match trials by the total number of trials for each condition. For the McGurk condition, a Percent Illusion was calculated by dividing the number of Nonmatch trials by the total number of trials.

## **RESULTS**

Data were analyzed with a 2 (Group) x 2 (Word Status) x 6 (Stimulus Type) ANOVA. Significant main effects and interactions were further explored post-hoc with Tukey pair-wise comparisons. The overall F test was significant,  $F(23, 396) = 86.1754$ ,  $p < .0001$ . There was a significant main effect of Group ( $F = 9.2067$ ,  $p = .0026$ ), such that non-psychiatric participants were slightly more accurate across all conditions (85.69%, compared to 83.78% for the patients). There was also a significant main effect of Word Status ( $F = 4.62$ ,  $p = .0322$ ), such that Word stimuli were identified slightly more accurately, 85.27%, than Nonword Stimuli, 83.20%. Finally, there was a significant main effect of Stimulus Type ( $F = 383.9486$ ,  $p < .0001$ ), indicating that Visual stimuli were identified less accurately than all other stimuli, that AV Congruent stimuli were identified most accurately (better than all other stimulus types expect for Target condition), and that the incidence of the McGurk illusion was greater than accuracy in the Visual condition, but less than accuracy in all other conditions (Table 3).

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Insert Table 3 about here  
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With respect to interactions, there was no significant interaction between Word Status and Group ( $F = .0633$ ,  $p = .8015$ ), and there was no interaction between all three factors (Group x Word Status X Stimulus Type,  $F = .8598$ ,  $p = .5082$ ). However, there was a significant Word Status x Stimulus Type interaction ( $F = 5.6618$ ,  $p < .001$ ) such that accuracy was significantly higher for Word Stimuli, compared to Nonword Stimuli, in only the Visual (42.15% vs. 33.40%) and No McGurk (97.12% vs. 88.17%) conditions.

There was also a significant Group x Stimulus Type interaction (Figure 1), such that non-psychiatric participants were more accurate than schizophrenia patients for only the Visual stimulus type (42.70% for the non-psychiatric group and 32.84% for the patient group). The groups did not differ in the incidence of the McGurk illusion, with non-psychiatric individuals experiencing the illusion on 85.35% of trials, and schizophrenia patients on 89.47% of trials.

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Insert Figure 1 about here  
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## **DISCUSSION**

The current study does not find any evidence for differences between non-psychiatric individuals and patients with schizophrenia in the incidence of the McGurk illusion. This is consistent with one previous study (7) with this population, and conflicts with another earlier finding of a reduced incidence of the illusion for patients (15). The current design includes a number of additional control conditions that have not been tested in previous investigations. We also tested a large set of stimuli, using both word and non-word combinations, with relatively little repetition of speech combinations compared to previous studies (15). The lack of an attentional control condition in earlier studies is a significant limitation; if schizophrenia patients are not attending to the visual speech cues as they are presented, their responses on the task would be based solely on the auditory cue, a pattern of results that would be consistent with a reduced illusion. Though the Target detection task was very easy for all participants to perform, it provides some empirical verification that patients and non-psychiatric participants did not significantly differ in their attention to visual speech cues, especially in focusing on the mouth of the speaker, which should elicit a strong McGurk illusion. We propose that the absence of an attentional control is a possible explanation for an inconsistent pattern of results with a similar paradigm. Controlling for this in the current study revealed no difference in audio-visual speech integration between groups, as assessed the incidence of the illusion.

One difference between the two previous studies on this topic that was also further explored in the current study was whether the McGurk stimuli were real words,

or non-word phonetic combinations. The previous study that found a difference between patients and controls in the incidence of the McGurk illusion used non-word stimuli (15), as opposed to the real word stimuli used in the study that found no difference between groups (7). Though in the current study there is a significant main effect such that words are identified more accurately than non-words, there was no interaction between Word Status and Group, indicating that this factor apparently does not explain the different patterns of results in previous studies.

We do find that in the Visual Alone condition, which evaluates lip-reading, that patients with schizophrenia perform significantly worse than non-psychiatric individuals. This finding adds to a small body of existing literature on this topic. One previous study (18) found that lip-reading ability was relatively intact in patients when tested with a multiple-choice response format. Lip-reading performance has also been investigated in prelingually deaf and hearing schizophrenia patients using real word stimuli and a free response format (19). This study found that both patient groups were worse at lip-reading compared to deaf and hearing non-psychotic control samples, respectively, though the authors comment that the differences are surprisingly small. The de Gelder et al. (15) study described earlier also finds evidence for slightly reduced lip-reading abilities in schizophrenia patients using non-word phonetic stimuli. The results of the current study follow this same general pattern, with evidence for a statistically significant, but relatively small difference between groups, with 42.70% correct responses for the non-psychiatric group and 32.84% for the patient group. One possible explanation for why differences in this

condition are significant in our study compared to others may be increased task difficulty, with a free response format that resulted in relatively poor performance for both patient and non-psychiatric participants.

The finding of no difference in the incidence of the McGurk illusion is somewhat inconsistent with a growing body of literature finding evidence for reduced multisensory integration in patients with schizophrenia (9-13). One possible explanation is that perhaps schizophrenia patients are selectively unimpaired on the integration of auditory and visual speech information, as opposed to other domains. However, a previous finding (12) conflicts with this idea; using a study that tested how accurately participants could identify degraded (noisy) speech stimuli, as well as how much accuracy improved with the addition of visual speech cues. They found that although in non-psychiatric individuals, speech perception under noisy auditory conditions is much improved by the addition of visual speech information, patients with schizophrenia do not show the same degree of benefit. This study implies that while patients with schizophrenia do show some evidence of audio-visual speech integration, the extent of this integration is less than is observed in non-psychiatric participants. In light of this previous finding, as well as other studies on integration abilities in this population, it is possible that the method of investigation employed in the current study may be too coarse to detect subtle between group differences, and that paradigms which more finely quantify degree of multisensory integration may be better suited for testing this question. Further study of the integration of higher level integration processes, using complex cues such as speech, will be necessary to explore



this further, and determine whether apparent deficits in MSI exhibited by schizophrenia patients using more simple cues are also present for language processes.

### **ACKNOWLEDGEMENTS**

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Table 4.1: Characteristics of non-psychiatric comparison participants (n = 18) and schizophrenia patients (n = 17). Starred values are significantly different between groups at  $p < .01$ . Abbreviations: SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

<b>Characteristic</b>	<b>Mean (SD)</b>
Non-psychiatric Comparison Participants (10 females)	
Age, y	49.29 (9.85)
Education, y	15.00 (2.63)*
Schizophrenia Patients (6 Females)	
Age, y	49.29 (9.98)
Education, y	13.00 (1.94)*
Duration of Illness, y	27.94 (11.48)
Number of Hospitalizations	6.23 (6.82)
SAPS Score	8.67 (4.82)
SANS Score	13.67 (4.59)

Table 4.2: Examples of each stimulus type and expected response for Word and Nonword stimuli. Also reported are the number of stimuli presented in each condition, as well as the number of stimuli excluded from final analyses due to poor accuracy in the non-psychiatric group.

Condition	Word Stimuli			Nonword Stimuli		
	Example Stimulus	Expected Response	# Stimuli: Presented (Excluded)	Example Stimulus	Expected Response	# Stimuli: Presented (Excluded)
Audio Alone	Audio: /pack/ Visual: none	pack	30 (0)	Audio: /ba/ Visual: none	ba	13 (2)
Visual Alone	Audio: none Visual: “pack”	pack	29 (1)	Audio: none Visual: “ba”	ba	13 (0)
Audio Visual Congruent	Audio: /pack/ Visual: “pack”	pack	29 (0)	Audio: /ba/ Visual: “ba”	ba	13 (2)
Audio Visual Incongruent McGurk	Audio: /pack/ Visual: “tack”	tack	15 (3)	Audio: /ba/ Visual: “ga”	da or ga	16 (0)
Audio Visual Incongruent No McGurk	Audio: /rack/ Visual: “din”	rack	15 (4)	Audio: /na/ Visual: “ti”	na	15 (4)
Target	Audio: /beer/ Visual: “beer” + square	square	12 (0)	Audio: /bi/ Visual: “bi” + circle	circle	8 (0)

Table 4.3: Mean Percent Correct and incidence of McGurk illusion for all experimental conditions.

\* Greater than Visual Alone,  $p < .05$

† Greater than McGurk,  $p < .05$

<b>Condition</b>	<b>Mean Percent Correct/ Percent Illusion</b>
Audio-Visual Congruent	99.06%* †
Auditory Alone	93.85%* † #
Audio-Visual Incongruent McGurk	87.41%* †
Audio-Visual Incongruent No McGurk	92.71%* † #
Target	94.66%* †
Visual Alone	37.77% #

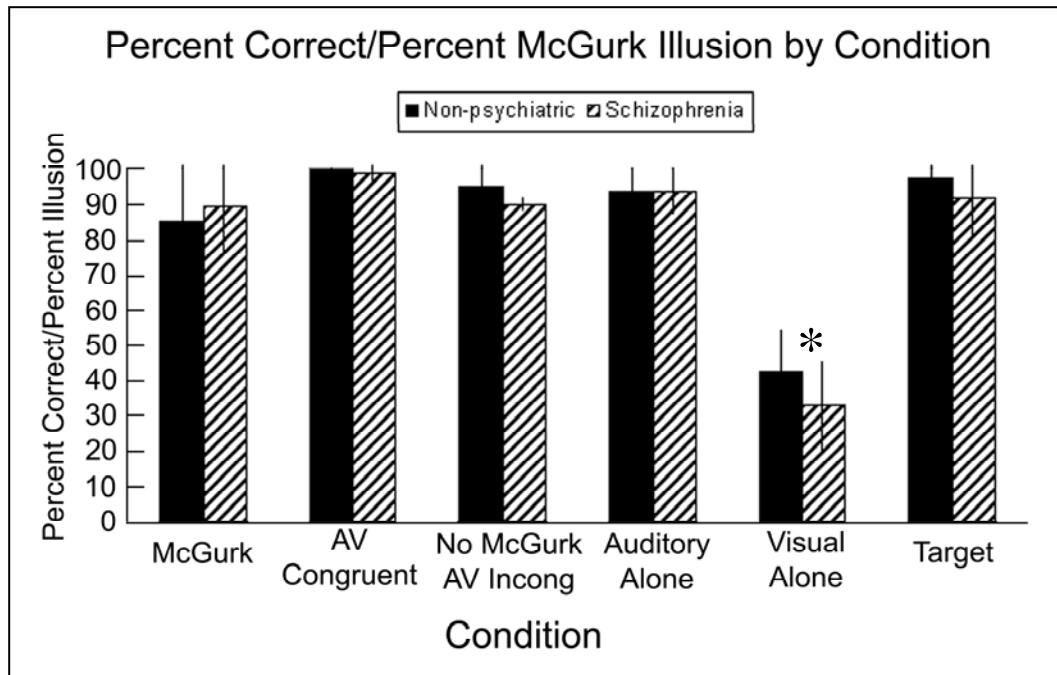


Figure 4.1: Mean percent correct/percent McGurk illusion for all experimental conditions. There was a significant interaction between group and condition such that schizophrenia patients (striped bars) performed significantly worse in the Visual Alone condition compared to the non-psychiatric participants (solid bars). Starred comparison is significantly different between Schizophrenia and Non-psychiatric groups at  $p < .05$ .

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## Chapter 5

### General Discussion

## General Discussion

The studies presented in this dissertation assess multisensory integration (MSI) in patients with schizophrenia using a number of different paradigms within the same participants. There is a small existing body of literature suggesting that MSI may be reduced in these patients (1-5) however, also see (1, 6), and these dissertation studies represent a substantial contribution to this research area. The use of a within-subjects testing design eliminates cohort differences as a potential source of variability between studies, which may limit direct comparisons of results across different studies in a heterogeneous clinical population study as this one. Also, having multiple measures for an individual participant allowed for the investigation of patterns of MSI across paradigms and modalities, although no evidence was found for a central integration deficit across studies within the current data. Evaluation of clinical symptoms at the time of testing also allowed for the exploration of how integration deficits may relate to the symptoms of schizophrenia, which had only been explored in one previous study (6). Finally, including many participants who had been previously tested on electrophysiological measures of sensory gating, and early automatic sensory processing allowed for the exploration of how these early deficits might relate to multisensory processing.

The study described in Chapter 2 evaluates the strength of the size-weight illusion (SWI) in patients with schizophrenia. In this classic perceptual illusion, when participants are asked to compare the weights of two objects of identical mass and apparently identical material, one large and one small, the small object will feel

substantially heavier (7). The SWI can be considered a measure of integration between visual and tactile cues for weight judgments, two modalities that have not been previously probed with an MSI paradigm in this population. The results of this study provide evidence for reduced integration in patients with schizophrenia, as well as a correlation between the SWI and sensorimotor gating, as assessed by prepulse inhibition. A reduced SWI is also consistent with previous studies that have implicated deficient efference copy mechanism in this population (8-10), as an absent or poor quality efference copy would also affect the strength of the illusion.

Further behavioral testing with the SWI paradigm could be fruitful for elucidating the specific nature of the efference copy deficit in this population. For example, previous studies with non-psychiatric participants have shown that when lifting size-weight stimuli, individuals incorrectly estimate the forces needed to lift the objects on early lifting trials with size-weight stimuli, but rapidly adjust their grip and lift forces for the actual mass of the object (11, 12). Employing this type of paradigm with schizophrenia patients could evaluate whether the reduced illusion is due to poor motor predictions or rather a reduced mismatch between expected and actual sensory feedback based on abnormal actual sensory feedback, or problems with the comparator mechanism. If schizophrenia patients misestimate initial lift forces in a manner similar to non-psychiatric participants, this would imply they are generating a correct motor prediction, but that the mismatch with sensory feedback itself is reduced or absent. In contrast, if patients do not employ differential similar to those of comparison participants, this would indicate abnormal motor predictions are being

made. Finally, repeated training with stimuli that have an inverted volume-weight relationship can reduce and even reverse the SWI, indicating that the size-weight prior expectations can be modified with experience (13). Using a training paradigm like this with schizophrenia patients may be highly informative, as a reduced training effect would support the hypothesis that schizophrenia patients either do not register sensory mismatches or violations of expectations as strongly as do non-psychiatric individuals, or that these prediction errors are not used to revise and update internal models. Evidence for this type of deficit would have important functional implications, as revisions to internal prediction models are necessary to successfully adapt to a changing environment. Also, exploring the neural basis of these between group differences, focusing on parietal regions implicated in previous studies (14, 15) would also be an interesting future direction.

The experiment presented in Chapter 3 investigates intersensory facilitation of reaction time, a well-documented behavioral effect first reported by Hershenson (16) in which participants are faster to detect bimodal targets, defined by cues in two sensory modalities, compared to unimodal targets. As most of the previous studies on MSI with schizophrenia patients have tested integration of incongruent cues (Ross et al. (4) is an exception), this study provides an essential additional probe of integration ability using very simple auditory and visual cues. The results of this study indicate that although schizophrenia patients do show some speeding of reaction times to the bimodal cues, it is not to the same extent as non-psychiatric individuals. On an individual subject level, degree of multisensory integration correlates with overall

negative symptoms, and patients who experience both auditory and visual hallucinations show greater deficits in integration compared to patients who experience only auditory hallucinations.

Future investigations of this reaction time difference using neuroimaging techniques such as electroencephalography (EEG) will help to understand where in the brain and when during processing these between-group differences arise. Previous studies of this type of reaction time paradigm in non-psychiatric individuals find evidence for both early and late audio-visual interaction effects (17, 18) but also see (19), as well as enhanced neural synchrony associated with multisensory processing (20). Also, continuing to explore how these reaction time differences relate to the clinical features of the disorder, such as whether MSI deficits are state or trait dependent, or whether they may also be present early in the course of illness would also be of interest.

Chapter 4 presents a version of the McGurk illusion (21), in which auditory speech perception is biased by the presentation of an incongruent visual speech cues. The McGurk paradigm has been tested with schizophrenia patients before, with an inconsistent pattern of results between studies (1, 6). This study design includes many experimental conditions designed to address methodological differences between these previous investigations. With the addition of an attentional control condition, we find no difference in the incidence of the McGurk illusion between schizophrenia patients and comparison participants; however, we do find evidence for impaired lip-reading ability in this population. This finding of no difference in the incidence of the

McGurk illusion is somewhat inconsistent with the literature reviewed earlier, as well as the results of Chapters 2 and 3. One possible explanation is that perhaps schizophrenia patients are selectively unimpaired on the integration of auditory and visual speech information, as opposed to other domains. However, the findings of Ross et al (4) conflict with this idea, as they find evidence for reduced, but not absent, integration of auditory and visual speech cues in schizophrenia patients using a more sensitive behavioral paradigm. As such, we propose that the method of investigation employed in the current study may be too coarse to detect subtle differences, and that paradigms which more finely quantify degree of multisensory integration may be better suited for testing this question.

As more data accumulate on the topic of MSI in individuals with schizophrenia, it appears this population has impaired integration abilities compared to non-psychiatric individuals. One advantage of the within subjects factor of the current set of studies afforded a unique opportunity to investigate whether performance on one integration task, the SWI, correlated with performance on another integration task probing different modalities, the RT task. However, no correlation between performance on these two tasks was found with the current sample, so as yet there is no evidence for a central integration deficit present across paradigms and modalities. The studies presented in this dissertation find evidence for a relationship between MSI ability and a measure of sensorimotor gating in the SWI task, and between integration and symptoms in the RT task, indicating these deficits are relevant for the schizophrenia phenotype. The lack of a difference in integration in the McGurk

experiment highlights the fact that psychophysical methods which can quantify the degree of MSI may be well suited to further investigations on this topic. However, these tasks will need to be carefully selected and designed to allow for the specific evaluation of MSI, while eliciting comparable performance between patients and non-psychiatric participants in perceptual control conditions. As an example, another study that was run in addition to those described earlier, the results of which are not included in this dissertation, was a version of the Shams double-flash illusion (22, 23), in which typical individuals often perceive a single visual flash accompanied by two short auditory beep sounds as two distinct flashes. This is a challenging perceptual task, and a number of schizophrenia participants were excluded due to poor performance in visual alone flash discrimination conditions. When analyzing data from patient participants who reached appropriate performance levels, less accurate performance in the patient group in perceptual control conditions where no illusion was expected precluded an evaluation of specific differences in the incidence of the illusion. These possible difficulties in testing may be an issue in future investigations as well.

Though it may be challenging to find the optimal tasks and testing parameters to continue further investigations into this topic, given the implications of these current studies indicating that MSI deficits may be related to the symptoms and features of schizophrenia make this an important area for further exploration. The studies presented in this dissertation represent an important step in continuing to quantify this relatively unexplored area of schizophrenia research.

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