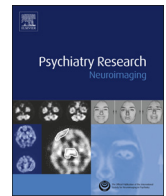




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Neuroimaging investigations of dorsal stream processing and effects of stimulus synchrony in schizophrenia

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ABSTRACT

Impairments in auditory and visual processing are common in schizophrenia (SP). In the unisensory realm visual deficits are primarily noted for the dorsal visual stream. In addition, insensitivity to timing offsets between stimuli are widely reported for SP. The aim of the present study was to test at the physiological level differences in dorsal/ventral stream visual processing and timing sensitivity between SP and healthy controls (HC) using MEG and a simple auditory/visual task utilizing a variety of multisensory conditions. The paradigm included all combinations of synchronous/asynchronous and central/peripheral stimuli, yielding 4 task conditions. Both HC and SP groups showed activation in parietal areas (dorsal visual stream) during all multisensory conditions, with parietal areas showing decreased activation for SP relative to HC, and a significantly delayed peak of activation for SP in intraparietal sulcus (IPS). We also observed a differential effect of stimulus synchrony on HC and SP parietal response. Furthermore, a (negative) correlation was found between SP positive symptoms and activity in IPS. Taken together, our results provide evidence of impairment of the dorsal visual stream in SP during a multisensory task, along with an altered response to timing offsets between presented multisensory stimuli.

1. Introduction

Impairments in perception are recognized as a core deficit of schizophrenia (Green et al., 2004). These include specific deficits in auditory and visual processing (Rojas et al., 2002; Williams et al., 2011; Butler et al., 2008). However, it remains unclear how these types of unisensory deficits impact cognitive functioning and behavioral outcomes in schizophrenia patients (SP) despite studies implicating links. Multisensory integration (MSI) represents an important extension to studies of unisensory processing. MSI is the process whereby information from multiple senses is used by a variety of brain networks to integrate our experience of daily life. By using this combined information, relevant signals should be both easier to identify and easier to distinguish from background noise, with the integration of multiple signals into a coherent percept facilitating adaptive behaviors (Ethofer et al., 2006; Koelewijn et al., 2010).

It has been observed in the unisensory realm that visual deficits for SP occur primarily within the dorsal visual stream (i.e., spatial localization involving the parietal lobe), in contrast to the ventral visual stream (i.e., pattern/object identification involving the temporal lobe) (review: Butler and Javitt, 2005; Martinez et al., 2012). However, there is some evidence that the ventral stream may also be involved (Grent-'t-Jong, et al., 2016). In the visual system, the dorsal and ventral streams

can be preferentially activated through placement of stimuli in peripheral or central visual field locations, respectively (Livingstone and Hubel, 1987; Stephen et al., 2002, 2006; Ungerleider and Desimone, 1986). Therefore, we were able to preferentially activate e.g. the dorsal visual stream by manipulation of the location of the stimulus (i.e. our "near" stimulus activates the peripheral visual field which engages the dorsal visual stream). Our ecologically valid paradigm simulated the near and distant (far) sources in a perspective drawing of a soccer field using both auditory and visual stimuli. Since one aim of the present study was to test whether differences in the dorsal/ventral visual streams of multisensory processing could be observed at the physiological level using MEG we chose to use simple sensory stimuli for our multisensory task, in order to remain largely in the *perceptual* rather than the cognitive domain. In other words, although these multisensory stimuli invoke activation of more complex cortical networks than unisensory stimuli, there is less likelihood that we need to consider confounds associated with higher-order cognitive functions (e.g. differences in strategy by group [Sanfratello, et al., 2014]). Simpler tasks also minimize possibly confounding differences in task performance between groups.

Animal and human studies show that auditory/visual integration occurs within a network of secondary sensory areas and association areas recognized as polysensory [e.g., superior temporal polysensory

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Table 1
Participant demographics. *p < 0.05 significance.

	Age	Male/Female	Olanzapine Equivalent	PANSS Positive	PANSS Negative	IQ	Parental Education
SP (Mean ± SD)	39.5 ± 13.6	44/9	12.6 ± 8.3	14.8 ± 4.9	14.9 ± 5.1	101.2 ± 21.2	4.1 ± 2.0
HC (Mean ± SD)	36.3 ± 12.0	39/17				116.5 ± 13.5	4.6 ± 1.9
TTest, p-value	0.20					0.00007*	0.1

(STP) (Benevento et al., 1977) and in parietal cortices (Andersen et al., 1997; Andersen et al., 2009)]. These multisensory processing sites in turn influence early sensory responses such as the auditory N100 as demonstrated using EEG and MEG (Murray et al., 2005; Schroeder and Foxe 2005; Stephen et al.; 2010). Furthermore, Kayser et al. (2010) demonstrated both feed-forward and feed-back connectivity between auditory cortex and superior temporal sulcus (STS). There is also evidence for direct feed-forward and/or crossmodal influences from early sensory areas (Henschke et al. 2015; King et al. 2012; Aine et al., 1995; Aine et al., 2003). We therefore hypothesized that areas involved in multisensory integration of auditory and visual stimuli would show significantly different brain activity patterns (amplitudes and latencies), between SP and HC. We predicted differences would be evident in temporal (superior temporal gyrus or STG) and parietal areas (superior parietal gyrus [SPG], inferior parietal gyrus [IPG] and in the inferior parietal sulcus [IPS]). Specifically, we hypothesized that there would be reduced activity in dorsal visual stream ROIs (e.g. SPG, IPG, and IPS) for SP when compared to HC, based on the evidence of unisensory dorsal stream deficits described above.

Responses to multisensory stimuli are also highly sensitive to the timing of paired stimuli (Stone et al., 2001; Liu et al., 2011). For example, multisensory facilitation (e.g. an observed decrease in reaction time when one is presented with both auditory and visual information, as opposed to stimuli from only one modality) is maximal when there is no delay between paired stimuli. Facilitation decreases with increasing time between stimuli, with no additional facilitation seen beyond a delay of ~100 ms (Donohue et al., 2011; Shams et al., 2002). Interestingly, multisensory facilitation has been observed to be both impaired (Williams et al., 2010) and enhanced (Stone et al., 2011) in SP relative to healthy controls (HC). Therefore, it is likely that the perception of multisensory stimuli may be altered in SP, perhaps dependent upon the relative timing of the onset of paired stimuli. This idea is consistent with results investigating differences in the "window of simultaneity" of two events. The "window of simultaneity" has been defined as the interval during which our brain perceives two events as occurring together (e.g., Bertelson and de Gelder, 2004; Elliott et al., 2007; Exner, 1875; Poppel, 2004). This window has been studied in SP by Foucher et al. (2007) who found it to be significantly larger for SP (~30%) than HC in simple visual, auditory and auditory/visual conditions. They concluded that SP do not judge the timing of events with the same temporal precision as HC. Furthermore, timing abnormalities have been described when SP are asked to locate, detect or identify a first stimulus, which is followed after a varying delay by a second meaningless stimulus, or a "mask". SP needed a longer time interval than HC between target and mask in order to perform the task successfully (Braff, 1981; Butler et al., 1996; Rund et al., 1993). It has been proposed that this may be due to an inability of SP to differentiate between the stimulus and the mask when both fall within their window of simultaneity (Foucher et al., 2007). Additionally, slowed reaction times (RTs) in SP is one of the most reliable findings across the literature (Benton, 1959; Cancro et al., 1971; Nuechterlein, 1977; Schwartz et al., 1989; Vinogradov et al., 1998). Based on these results, we hypothesized that SP would show *less* difference in activation relative to HC between multisensory stimuli presented synchronously vs. asynchronously in brain regions that have been shown to be responsive to multisensory stimulation. Furthermore, we hypothesized that HC would exhibit a decrease in amplitude of activity in asynchronous relative to

synchronous stimulus conditions. SP, in contrast, would not show this result due to having a longer time window of integration.

Previously, multisensory behavioral facilitation for SP, as compared to HC, was reported by us for a subset of this group in Stone et al. (2011) using high density EEG, and in the full cohort in Stone et al. (2014) where time-frequency analyses of MEG data were conducted. The present study, in contrast, examined the source amplitude and latency of the averaged evoked responses with the manipulation of two parameters during multisensory stimulation (timing and visual field location) to characterize differences in the circuitry of polysensory regions in HC vs SP. Comparisons between HC and SP for multisensory relative to unisensory responses will be reported separately (Stephen et al., in preparation). Therefore, the current study focuses on the manipulation of stimulus parameters within the multisensory conditions, rather than multisensory facilitation per se where one compares RTs for unisensory vs multisensory processing. Our hypotheses are that: 1) responses to peripheral stimuli (dorsal stream) will show reduced amplitude and/or longer peak latencies in SP relative to HC and 2) SP will respond differently than HC to synchronous vs. asynchronous multisensory stimuli.

2. Methods

2.1. Participants

We enrolled 56 SP and 57 HC with good quality MEG data from a larger study. Participant characteristics are presented in Table 1. Participants had no history of neurological disorders (e.g. epilepsy), as determined by a standard neurological exam and review of symptoms. Participants also had no history of significant head trauma (< 10 min loss of consciousness) and no current diagnosis of substance abuse (excluding nicotine). HCs had no history of psychiatric disorder (assessed with SCID-NP) and no first-degree relatives with a history of a psychotic disorder. SPs were confirmed to have a DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder with the SCID-IP. All SP were clinically stable with no recent medication change within one month of study enrollment and no change of medication across the data collection period (cognitive testing and MEG scans were performed at separate visits). Clinical symptoms were assessed using the Positive and Negative Syndrome Scale [PANSS (Kay et al., 1987)], social functioning was evaluated using the University of California Performance Skills Assessment [UPSA (Mausbach et al., 2007)], and anti-psychotic medication dose was recorded and reported as olanzapine equivalents (Gardner et al., 2010) for each patient (Summary in Table 1). The study was approved by the University of New Mexico Health Sciences Center Human Research Review Committee and complied with the Declaration of Helsinki. All participants provided written informed consent prior to the start of their participation in the study.

2.2. MEG behavioral task

During the MEG measurements, participants performed an auditory/visual multisensory integration task (Stone et al., 2011). The stimuli were presented in an ecologically relevant visual background (soccer field; see Fig. 1). Participants were instructed to fixate upon the goalie in the image, which was centered horizontally and vertically with the participants' nasion at a distance of 1 m. Visual stimuli

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