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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.

Keywords

multisensory integration; schizophrenia; dorsal visual stream; parietal lobe; visual field; magnetoencephalography

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

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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 (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 and Logothetis (2009) 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. 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., 2006; 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 I. 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 (representations of soccer balls) were presented at one of two positions along the vertical meridian, centered at 1.8° and 8° below fixation for "far" and "near" stimuli, respectively. The Far and Near stimuli were scaled (stimuli subtended a visual angle of 1° and 2.7°, respectively) to conform with the cortical magnification factor (Rovamo and Virsu, 1979); that is, to activate an equivalent patch of primary visual cortex across the two stimuli. It is important to note that "Far" and "Near" stimuli represent stimuli placed in the central and peripheral visual fields, respectively (i.e., with respect to the subject viewing the display). The auditory stimulus was a 550 Hz tone (200 ms duration with 30 ms Hanning ramp up/down) presented at two different sound intensity levels [45 dB (Far) and 63 dB (Near) above hearing threshold] to mimic the perception of a soccer ball bouncing near or far from the participant, and the tones were either synchronous or asynchronous (50ms delay) with the visual stimuli. Therefore the visual stimulus is always presented first. In line with the goal of developing an ecological paradigm, the visual stimulus always preceded the auditory stimulus based on the faster speed of light vs. sound. However, the stimuli are ultimately perceived as synchronous in all conditions since the delay was shorter than the time window of simultaneity for the stimuli. Hearing threshold was determined independently for each ear of each participant just prior to beginning the task (i.e., within the shielded room), which helped to eliminate perceived

volume differences across subjects due to poor ear insert placement or peripheral hearing deficits. To determine the hearing threshold, 1000 Hz tones were randomly presented above and below threshold in a step-wise fashion. The participant was required to press a button whenever they heard a tone. Participants with hearing thresholds greater than 37 dB, after two separate ear insert placement attempts, were excluded from the study.

Eight conditions were presented to the participants during the task: auditory (A) alone for Near and Far conditions, visual (V) alone for Near and Far conditions, multisensory (AV) synchronous for Near and Far conditions, and (AV) asynchronous for Near and Far conditions. A and V stimuli were always congruent during AV conditions; that is, Near and Far conditions never conflicted between stimulus modalities during multisensory presentation. All conditions were presented randomly with an inter-stimulus interval (ISI) of 1500–1900 ms. Stimuli were presented in six 6-minute blocks to provide the participants with regular breaks. The participants were each presented with ~150 trials per condition. Participants were asked to indicate whether the stimulus was near to them or far from them by pressing one of two buttons on a response device with either their right index finger or right middle finger, respectively. AV conditions with a correct response were used for the analyses presented here. Since the task was designed with high contrast stimuli to ensure that the stimuli provided robust neurophysiological responses and the choice was simple accuracy rates were high. Both HC and SP groups averaged only 2–3 “misses” in each task condition of ~150 trials.

The Neurobehavioral Systems Presentation program was used for determining hearing threshold, presentation of the stimuli, and recording of behavioral data (reaction time and number of correct, incorrect and false alarm button presses). Coincident stimulus triggers generated by ‘Presentation’ were sent to the MEG data acquisition computer to mark stimulus timing in the MEG dataset. A practice run was presented in the MEG room prior to data collection to ensure that the participant understood the task. During the practice session, the participant was provided with feedback on correct/incorrect trials to facilitate learning. This feedback (i.e., a soccer ball rolled into the goal and a cheering sound was heard for correct trials, or the ball missed the goal and a disappointed crowd sound was heard for incorrect trials) was also provided for 20% of the trials during the MEG task to encourage compliance throughout data collection. For data quality purposes, online eye-tracking was performed in a subset of participants (approximately 30%) to confirm compliance with fixation instructions across groups. No quantitative analyses were conducted on the eye-gaze data as this was done as an online observation only, however no qualitative differences between HC and SP groups were observed. That is, participants reliably fixated on the goalie, as instructed.

2.3 MEG

MEG data were collected using an Elekta Neuromag 306-channel biomagnetometer located in a magnetically shielded room (Vacuumschmelze, Hanau, Germany). Electrocardiogram electrodes (ECG — placed just below the left and the right clavicle) and electrooculogram electrodes (EOG — one electrode placed just above the left eye-brow and one placed lateral to the outer canthus of the right eye) were also used to provide signals for artifact rejection

of heartbeat and eye-movements, respectively. MEG head position indicator (HPI) coils were placed around the head and secured with tape. HPI coil location and head shape information was obtained using the Polhemus 3-D tracking device. Three fiducial points (left and right preauricular and nasion) were identified to define the head-centered coordinate system in addition to approximately 200 points around the scalp to co-register the MEG data to the MRI structural image. The MEG data were digitized at 1000 Hz (0.03–300 Hz anti-aliasing filter). Continuous HPI monitoring was enabled throughout MEG data collection. MEG data were preprocessed to eliminate artifacts. In particular, the head center for each participant was identified using Neuromag MRILAB software by co-registering the MEG HPI data with the participant's MRIs. This participant-specific head center was used for the scripted Neuromag Maxfilter processing (Taulu and Kajola, 2005). The temporal signal space separation version of the Maxfilter software was employed to 1) minimize noise signals outside a sphere centered around the brain and 2) compensate for subject head movements during the MEG data collection. Eyeblink artifacts were identified using the EOG channel or anterior temporal MEG channels. A subject-specific averaged eyeblink was identified and modeled (i.e., creating an eyeblink projector) using the signal space projection method (Uusitalo and Ilmoniemi, 1997) within the Minimum Norm Estimate (MNE) python software. Using a scripted program, MNE (<http://www.martinos.org/mne/>) was employed to reject bad trials, apply the eyeblink projectors, and average the data by stimulus condition.

We next performed source space analysis of the MEG data using MNE. The cortical surface was reconstructed from MPRAGE MRIs using FreeSurfer for the automatic segmentation of the skull and scalp surfaces. A repeatedly subdivided icosahedron was used as the subsampling method which resulted in 10,242 locations per hemisphere. Coordinate system alignment was accomplished by first manually identifying fiducial landmarks and second by refining the alignment using the additional digitized scalp surface points. Each segmentation and alignment was visually inspected for reasonableness before proceeding.

Source space analysis was conducted using dynamic statistical parametric mapping (dSPM) from within MNE software; dSPM is an anatomically constrained linear estimation approach (Dale et al. 2000). The regularization parameter was set to correspond to a signal-to-noise-ratio of 3 in the whitened data. Source orientation had a loose constraint of $\beta=0.2$, and a depth weighting of 0.8 was used. The forward solution was calculated using a single layer boundary element method (BEM) (Hamalainen and Sarvas, 1989; Mosher and Leahy, 1999) and the brain surface was tessellated with 5120 triangles. Activation at each vertex of the cortical surface was mapped using a noise-normalized minimum norm estimate (Dale et al. 2000). In essence, dSPM identifies where the estimated current differs significantly from baseline noise; this method also acts to reduce the location bias of the estimates (Gramfort et al. 2014). Spatial normalization was accomplished using FreeSurfer (Dale et al. 1999; Fischl et al. 2012) for group comparisons. Spatiotemporal source distribution maps were then evaluated for group differences (Fig. 2B). For ROI analysis (time window 0–500 ms poststimulus) the 'Destrieux' cortical atlas was used (Destrieux et al., 2010). It is based on a parcellation scheme that first divided the cortex into gyral and sulcal regions, the limit between both given by the curvature value of the surface. A gyrus only includes the cortex visible on the pial view, the hidden cortex (banks of sulci) are marked sulci. The Destrieux atlas is shown in Fig. 2A and was used to determine individuals' timecourses within each

ROI. The ROIs investigated were bilateral: occipital pole, insula, STS, STG, SPG, IPG, and IPS. These ROIs were chosen since they are either primary auditory or visual areas or have been shown to be involved in multisensory integration of auditory and visual stimuli, as discussed in the Introduction. Maximum peak amplitude and peak latency for each ROI was determined by a Matlab script. The peak ROI always occurred between 120 and 250 ms (see Fig. 2C for examples of averaged waveforms showing ROI peaks of activation). We note that this window was not corrected for the delay due to the stimulus projector. Furthermore, since the auditory stimulus was also appropriately delayed to ensure that it was either truly synchronous or delayed by 50ms, the peak latency window is closer to 80–210ms after true stimulus onset. If peak amplitude or latency for an individual was $> 2SD$ from the mean these data were discarded from further analysis, this resulted in between 2–4 individuals being excluded from each ROI. Results were corrected for multiple comparisons using the Hochberg (false discovery rate, FDR) method (Hochberg & Benjamini, 1995).

A 3-way mixed ANOVA was conducted, for both amplitude of activation and for peak amplitude latency, with group entered as a between-subjects factor, and hemisphere (right, left), location of stimulus (near, far), and presentation of stimuli (synchronous, asynchronous) entered as within-subjects factors. Next, a hierarchical regression analysis was performed with RT as the independent variable; amplitude was entered first, followed by group, and the interaction term last. A second hierarchical regression analysis was performed for latency, with RT as the independent variable; latency was entered first, followed by group, and the interaction term last. Lastly, MEG peak amplitudes in parietal areas of interest were correlated with medication dose [as olanzapine equivalents; (Gardner et al., 2010)], positive symptoms (sum of first 7 PANSS symptoms: delusions, disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness, and hostility), and negative symptoms (sum of second 7 PANSS symptoms: blunted affect, withdrawal, poor rapport, social withdrawal, difficulty in abstract thinking, lack of spontaneity, stereotyped thinking). These results were corrected for multiple comparisons using the Hochberg (false discovery rate, FDR) method (Hochberg & Benjamini, 1995).

3. Results

3.1 Amplitude of peak activation

We found no significant group differences for any primary sensory or temporal ROIs. For SPG we found a significant main effect of group ($F(1,95)=7.63, p=.007$), such that SP had a smaller amplitude of activation than HC (Fig. 3A). Other main effects for SPG were found as follows: location ($F(1,95)=53.77, p<.001$) and hemisphere ($F(1,95)=7.92, p=.006$). An additional interaction effect of synchrony*hemisphere ($F(1,95)=6.154, p=.015$) was found. For IPG we found a similar significant main effect of group ($F(1,95)=4.49, p=.037$), such that SP had a smaller amplitude of activation than HC (Fig. 3B). Group differences can also be seen in the sample timecourses shown for SPG and IPG in Fig. 2C. Other main effects for IPG were found as follows: location ($F(1,95)=53.06, p<.001$). There was an additional two-way interaction of synchrony by group ($F(1,95)=3.92, p=.05$, Fig. 4A) for IPG whereby amplitude was greater in the asynchronous task condition relative to the synchronous task condition for SP, with the reverse being observed for HC.

For IPS we found a significant main effect of group ($F(1,95)=7.48, p=.037$), such that SP had a smaller amplitude of activation than HC (Fig. 3C). There was an additional two-way interaction of location by group ($F(1,95)=4.94, p=.029$, Fig. 4B), where both SP and HC showed reduced amplitude of activation in IPS for the far relative to the near task conditions; however, the decrease was greater for HC relative to SP. Lastly, we found a significant interaction of hemisphere*sync*location*group ($F(1,95)=5.28, p=.024$). The simple effects are presented in Table II. We see that for all task conditions there was a significant group difference in activation for right IPS, where asynchronous near and synchronous far show the largest group differences. For left IPS these effects were seen in the near task condition only (for both synchronous and asynchronous stimulus presentations). Lastly, it was found that for all ROIs, in all conditions, SP showed a lower amplitude of peak activation in comparison to HC. Other main effects for IPS were found as follows: location ($F(1,95)=54.52, p<.001$) and hemisphere ($F(1,95)=15.04, p<.001$). Full statistical results may be found in Supplementary Material (Tables I & II).

3.2 Latency of peak activation

Again, we found no significant group differences for any primary sensory or temporal ROIs. For SPG peak latency we found no main effect of group, however we did observe a significant 3-way interaction of hemisphere*sync*group ($F(1,95)=6.544, p=.012$). We see in Table III, the interaction is driven by group differences in right SPG in the synchronous task condition, with latency being delayed for SP relative to HC. Other main effects for SPG were found as follows: synchrony ($F(1,95)=35.43, p<.001$), location ($F(1,95)=15.82, p<.001$) and hemisphere ($F(1,95)=6.95, p=.01$). We found no main effect of group, nor any significant interactions for IPG peak latency. Other main effects for IPG were found as follows: synchrony ($F(1,95)=78.68, p<.001$) and location ($F(1,95)=38.86, p<.001$).

IPS is the only region where we found a main effect of group for latency of activation ($F(1,95)=5.24, p=.024$, Fig. 5A). We also found a location by group effect ($F(1,95)=11.9, p<.001$, Fig. 5B) on latency, where clear group differences in latency are present for the Near condition that are not present for the Far condition. By collapsing across hemisphere and synchronous versus asynchronous conditions, we found a significant group difference between HC and SP ($p=.002$) solely for the near task condition. Other main effects for IPG were found as follows: synchrony ($F(1,95)=42.1, p<.001$), location ($F(1,95)=26.78, p<.001$), and hemisphere ($F(1,95)=7.39, p=.008$). Full statistical results may be found in Supplementary Material (Tables I & II).

3.3 RTs and activation

We performed a hierarchical regression analysis for relevant parietal ROIs (right SPG, right IPG, left IPS, and right IPS), to determine if RT was predictive of the interaction between amplitude and group, with amplitude entered first, followed by group, and then the interaction term (amplitude*group). No interaction terms were found to be significant. For latency we found a significant interaction term in right IPG solely for the asynchronous far task condition ($p=0.026$), where faster reaction times were predictive of shorter latencies. Full statistical results may be found in Supplementary Material (Table III).

3.4 Medication dose, clinical symptoms, task and amplitude of activation

A significant negative correlation was found for SP between left IPS peak amplitude in the synchronous near condition and positive symptoms. There were no significant correlations with medication dose or negative symptoms (Table IV).

4. Discussion

4.1 Evidence of dorsal stream visual processing deficits in SP

Recent work examining the ventral and dorsal visual streams in auditory/visual integration suggest that both parallel visual pathways may play a role in the auditory/visual interaction (Kaposvari et al., 2015); however most studies have reported a specific dorsal visual stream deficit in SP (e.g. Butler and Javitt, 2005). Consistent with these prior studies, we found significant differences between SP and HC that were clustered in parietal cortex many of which represent an endpoint for dorsal visual stream projections. We did not reveal any group differences in the sensory areas tested, nor in temporal areas (i.e. an endpoint projection of the ventral visual stream). Our results show reduced activation in IPG, SPG, and IPS regions for SP relative to HC, as predicted (Fig. 3). Furthermore, in IPS we saw a significant location by group interaction (i.e. near vs. far task conditions) for amplitude of activation (Fig. 4B), where there was a larger group difference for the near as opposed to the far task conditions, as predicted. Finally, we found that peak latency in IPS for the near condition was significantly delayed in SP relative to HC (> 10 ms, Fig. 5B). We did not observe a significant difference in the far condition, i.e. a deficit wasn't present in response to the foveal presentation of visual stimuli which preferentially activates the ventral visual stream. It is possible however that our methodology was not as sensitive to ventral visual stream processing and we therefore cannot rule out the possibility of additional, perhaps more subtle, deficits for SP in the ventral visual stream. We also note the possibility that individuals may have been taking medications that could impair visual processing, such as anticholinergic/antihistaminergic drugs. Overall, we note the greatest amplitude and latency differences between HC and SP in IPS, for the near condition.

In addition to the dorsal stream effects, both HC and SP groups showed brain activation in parietal areas during all multisensory conditions. These findings are consistent with neuroimaging studies demonstrating that parietal cortex is activated during multisensory auditory/visual attention and working memory tasks. For example, it was demonstrated by Brang et al. (2013) that there is a relationship between anatomical connectivity and multisensory processing in healthy individuals, where increased connectivity between parietal regions and early sensory areas was associated with facilitation of auditory/visual multisensory RTs. Zmigrod (2014) underscored the role of right posterior parietal cortex (PPC) in multisensory integration by showing a disruption of multisensory processing when tDCS (anodal or cathodal stimulation over the right PPC) was used during an auditory/visual task. Furthermore, the complex hemisphere by synchrony by location by group interaction for amplitude of activation in IPS (Table II), revealed group differences in right IPS (SP < HC) in all task combinations, whereas for left IPS significant group differences were observed only in the near condition (i.e., activation of the putative dorsal stream). These results are consistent with the proposed role that right posterior parietal cortex plays in the

multisensory integration of auditory/visual stimuli as described by Zmigrod et. al (2014). In other words, based on the more general result showing SP<HC for both near and far conditions in right IPS, we infer that right parietal cortex is more generally related to multisensory processing. In contrast the left IPS differences were only observed for the peripheral 'near' stimulus suggesting a more specific dorsal stream deficit. Finally, we reiterate that in all task conditions and in all ROIs investigated SP had reduced amplitude of activation relative to HC, highlighting the possibility of a more global deficit for SP consistent with other work reported in the literature.

4.2 Synchrony of stimuli

Of additional interest is the result that only IPS revealed a significant hemisphere*sync*location*group interaction for amplitude (Table II). While 4-way interactions are challenging to interpret, the results indicate that synchrony impacts the response differently depending on the location of the stimulus. The general pattern shows that SP have increased IPS amplitude during the asynchronous condition except for right IPS during the Near condition, whereas HC show reduced amplitude response for the asynchronous response, as expected by the literature in HC. That is, multisensory response amplitudes tend to decrease with increasing asynchrony (Meredith et al., 1987). The exception here is for right IPS where HC show increased response for asynchronous Near and SP show a decreased response. Consistent with the group differences in IPS responses described above, this may indicate a general alteration in right IPS functioning relative to HC. IPS is also a key area for processing attention and MSI (Calvert and Lewis, 2004). Anderson et al. (2010) found that there is a topographical architecture of multisensory attention in the IPS which may represent a mechanism for specificity in top-down control of attention, and that IPS may therefore have the ability to organize multisensory representations in the brain. Taken together these and the above results suggest that IPS plays a vital role in SP multisensory processing deficits evoked by combined auditory/visual stimuli.

Others have shown the temporal sensitivity of behavioral multisensory facilitation by manipulating stimulus onset asynchrony (SOA) between auditory/visual stimuli (Donohue et al., 2011; Shams et al., 2002) where maximal facilitation was observed with SOA = 0 and no AV RT facilitation at >100 ms SOA. Our study examined onset asynchrony in the center of this range, where some multisensory facilitation is to be expected but where there is no perceptual difference in the onset of the auditory and visual stimuli from the participants' point of view. Furthermore, Foucher's (2007) work with SP determined that the time window for AV facilitation was consistently larger for SP relative to controls and that this time window correlated with symptoms of disorganization (i.e. the time window for AV facilitation was larger for individuals with worse symptoms of disorganization). They suggested these timing differences could directly lead to difficulties in determining cause and effect. Our results showed that the latency of the highest amplitude peak was significantly delayed in SP relative to HC during synchronous but not during asynchronous task conditions for right SPG (Table III). We take this as further evidence that timing perception is altered in SP relative to HC. Contrary to expectations, IPG amplitude was found to be more similar between SP and HC during the asynchronous tasks (Fig. 4A).

However, in contrast to this overall result, when looking at the near condition we found that SP showed little change between the synchronous and asynchronous task conditions in activation of right IPG, whereas HC shows a marked increase in peak activation in this area in the asynchronous relative to the synchronous near conditions (Fig. 2C). Clearly, more work needs to be done to tease apart the differing effects of stimulus synchrony on responses. We note the importance of having a method, in this case MEG, which can detect such timing differences (i.e. on the timescale of neuronal firing) in the investigation of multisensory deficits in SP.

4.3 Medication dose, clinical symptoms, task and amplitude of activation

A significant negative correlation was found between the left IPS activity in SP for the synchronous near condition and positive symptoms, but no other significant correlations with medication dose or negative symptoms (Table IV) were found. This indicates that reduced amplitude IPS activation was associated with higher positive symptoms consistent with the group effects showing that reduced IPS amplitude can be viewed as an impairment in MSI. This result is also consistent with the results of Foucher (Foucher et al., 2007), who found a correlation between “disorganization”, a positive symptom, and MSI impairment in SP. This result may also relate to working memory impairment in SP, since working memory maintenance is associated with activation in the IPS (McNab and Klingburg, 2008) and may be associated with auditory hallucinations (Wible et al., 2009). We also note that IPS is where we observed group differences and interactions between the location (near or far) of the stimuli and both reduced amplitude and delayed peak activation for SP relative to HC. As an integrative region, reduced activity in IPS may have direct implications for proper brain functioning.

4.4 Conclusions

Despite many years of available antipsychotic treatments for SP to address positive symptoms, there has been an unfortunate lack of improvement in the quality of life for many individuals. This is arguably due to the fact that quality of life is in many cases more closely related to cognitive functioning than it is to the alleviation of positive symptoms. It is therefore of importance to better understand the factors and underlying neural correlates of cognitive deficits in SP. Here we have begun by providing a step up in complexity from unisensory investigations, to multisensory integration in schizophrenia while maintaining equivalent attention demands across conditions. Our work here provides evidence of significant brain activation differences in SP vs HC in parietal areas, e.g. areas involved in multisensory integration, particularly IPS. Our results provide additional evidence of a dorsal visual stream impairment in SP. Furthermore, it was only our near task condition (which activated the dorsal visual stream by engaging the peripheral visual field) that correlated with positive symptoms, irrespective of medication dose. However, it is possible that our method was preferentially sensitive to dorsal stream activity, therefore an impairment of the ventral visual stream cannot be ruled out based on the current results. This work also provides evidence that sensitivity to synchrony of sensory stimuli is altered in SP relative to HC. Determining sensitivity to specific task parameters may indicate ways to optimize information delivery to patients with schizophrenia to help minimize deficits within the perceptual realm.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Andersen RA. 1997; Multimodal integration for the representation of space in the posterior parietal cortex. *Philos Trans R Soc Lond B Biol Sci.* 352(1360):1421–1428. DOI: 10.1098/rstb.1997.0128 [PubMed: 9368930]
- Andersen RA, Cui H. 2009; Intention, action planning, and decision making in parietal-frontal circuits. *Neuron.* 63(5):568–583. DOI: 10.1016/j.neuron.2009.08.028 [PubMed: 19755101]
- Anderson JS, Ferguson MA, Lopez-Larson M, Yurgelun-Todd D. 2010; Topographic maps of multisensory attention. *Proc Natl Acad Sci U S A.* 107(46):20110–20114. DOI: 10.1073/pnas.1011616107 [PubMed: 21041658]
- Benevento LA, Fallon J, Davis BJ, Rezak M. 1977; Auditory–visual interaction in single cells in the cortex of the superior temporal sulcus and the orbital frontal cortex of the macaque monkey. *Exp Neurol.* 57(3):849–872. [PubMed: 411682]
- Benjamini YH, Yosef. 1995; Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society, Series B.* 57(1):289–300.
- Benton AL, Jentsch RC, Wahler HJ. 1959; Simple and choice reaction times in schizophrenia. *AMA Arch Neurol Psychiatry.* 81(3):373–376. [PubMed: 13626289]
- Bertelson, P, de Gelder, B. The psychology of multimodal perception. In: Driver, CSJ, editor. *Crossmodal space and crossmodal attention.* Oxford: Oxford University Press; 2004.
- Brang D, Taich ZJ, Hillyard SA, Grabowecy M, Ramachandran VS. 2013; Parietal connectivity mediates multisensory facilitation. *Neuroimage.* 78:396–401. DOI: 10.1016/j.neuroimage.2013.04.047 [PubMed: 23611862]
- Butler PD, Javitt DC. 2005; Early-stage visual processing deficits in schizophrenia. *Curr Opin Psychiatry.* 18(2):151–157. [PubMed: 16639168]
- Butler PD, Silverstein SM, Dakin SC. 2008; Visual perception and its impairment in schizophrenia. *Biol Psychiatry.* 64(1):40–47. DOI: 10.1016/j.biopsych.2008.03.023 [PubMed: 18549875]
- Calvert, GA, L, J. Hemodynamic studies of audiovisual interactions. In: S, C, Calvert, GA, Stein, BE, editors. *The handbook of multisensory processes.* Cambridge (MA): MIT Press; 2004.
- Cancro R, Sutton S, Kerr J, Sugerman AA. 1971; Reaction time and prognosis in acute schizophrenia. *J Nerv Ment Dis.* 153(5):351–359. [PubMed: 5145497]
- Chen YC, Shore DI, Lewis TL, Maurer D. 2016; The development of the perception of audiovisual simultaneity. *J Exp Child Psychol.* 146:17–33. DOI: 10.1016/j.jecp.2016.01.010 [PubMed: 26897264]
- Dale AM, Fischl B, Sereno MI. 1999; Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage.* 9(2):179–194. DOI: 10.1006/nimg.1998.0395 [PubMed: 9931268]
- Dale AM, Liu AK, Fischl BR, Buckner RL, Belliveau JW, Lewine JD, Halgren E. 2000; Dynamic statistical parametric mapping: combining fMRI and MEG for high-resolution imaging of cortical activity. *Neuron.* 26(1):55–67. [PubMed: 10798392]
- Destrieux C, Fischl B, Dale A, Halgren E. 2010; Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage.* 53(1):1–15. DOI: 10.1016/j.neuroimage.2010.06.010 [PubMed: 20547229]
- Donohue SE, Roberts KC, Grent-'t-Jong T, Woldorff MG. 2011; The cross-modal spread of attention reveals differential constraints for the temporal and spatial linking of visual and auditory stimulus

- events. *J Neurosci.* 31(22):7982–7990. DOI: 10.1523/JNEUROSCI.5298-10.2011 [PubMed: 21632920]
- Elliott MA, Shi Z, Surer F. 2007; The effects of subthreshold synchrony on the perception of simultaneity. *Psychol Res.* 71(6):687–693. DOI: 10.1007/s00426-006-0057-3 [PubMed: 16614834]
- Ellison-Wright I, Bullmore E. 2009; Meta-analysis of diffusion tensor imaging studies in schizophrenia. *Schizophr Res.* 108(1–3):3–10. DOI: 10.1016/j.schres.2008.11.021 [PubMed: 19128945]
- Ellison-Wright I, Bullmore E. 2009; Meta-analysis of diffusion tensor imaging studies in schizophrenia. *Schizophr Res.* 108(1–3):3–10. DOI: 10.1016/j.schres.2008.11.021 [PubMed: 19128945]
- Ethofer T, Pourtois G, Wildgruber D. 2006; Investigating audiovisual integration of emotional signals in the human brain. *Prog Brain Res.* 156:345–361. DOI: 10.1016/S0079-6123(06)56019-4 [PubMed: 17015090]
- Fischl B. 2012; FreeSurfer. *Neuroimage.* 62(2):774–781. DOI: 10.1016/j.neuroimage.2012.01.021 [PubMed: 22248573]
- Foucher JR, Lacambre M, Pham BT, Giersch A, Elliott MA. 2007; Low time resolution in schizophrenia Lengthened windows of simultaneity for visual, auditory and bimodal stimuli. *Schizophr Res.* 97(1–3):118–127. DOI: 10.1016/j.schres.2007.08.013 [PubMed: 17884350]
- Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. 2010; International consensus study of antipsychotic dosing. *Am J Psychiatry.* 167(6):686–693. DOI: 10.1176/appi.ajp.2009.09060802 [PubMed: 20360319]
- Gramfort A, Luessi M, Larson E, Engemann DA, Strohmeier D, Brodbeck C, Hamalainen MS. 2014; MNE software for processing MEG and EEG data. *Neuroimage.* 86:446–460. DOI: 10.1016/j.neuroimage.2013.10.027 [PubMed: 24161808]
- Green MF, Kern RS, Heaton RK. 2004; Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res.* 72(1):41–51. DOI: 10.1016/j.schres.2004.09.009 [PubMed: 15531406]
- Hamalainen MS, Sarvas J. 1989; Realistic conductivity geometry model of the human head for interpretation of neuromagnetic data. *IEEE Trans Biomed Eng.* 36(2):165–171. DOI: 10.1109/10.16463 [PubMed: 2917762]
- Hua K, Zhang J, Wakana S, Jiang H, Li X, Reich DS, Mori S. 2008; Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. *Neuroimage.* 39(1):336–347. DOI: 10.1016/j.neuroimage.2007.07.053 [PubMed: 17931890]
- Kaposvari P, Csete G, Bognar A, Csibri P, Toth E, Szabo N, Kincses ZT. 2015; Audio-visual integration through the parallel visual pathways. *Brain Res.* 1624:71–77. DOI: 10.1016/j.brainres.2015.06.036 [PubMed: 26165152]
- Kay SR, Fiszbein A, Opler LA. 1987; The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 13(2):261–276. [PubMed: 3616518]
- Kayser C, Logothetis NK, Panzeri S. 2010; Visual enhancement of the information representation in auditory cortex. *Curr Biol.* 20(1):19–24. DOI: 10.1016/j.cub.2009.10.068 [PubMed: 20036538]
- Koelewijn T, Bronkhorst A, Theeuwes J. 2010; Attention and the multiple stages of multisensory integration: A review of audiovisual studies. *Acta Psychol (Amst).* 134(3):372–384. DOI: 10.1016/j.actpsy.2010.03.010 [PubMed: 20427031]
- Liu B, Jin Z, Wang Z, Gong C. 2011; The influence of temporal asynchrony on multisensory integration in the processing of asynchronous audio-visual stimuli of real-world events: an event-related potential study. *Neuroscience.* 176:254–264. DOI: 10.1016/j.neuroscience.2010.12.028 [PubMed: 21185358]
- Livingstone MS, Hubel DH. 1987; Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. *J Neurosci.* 7(11):3416–3468. [PubMed: 3316524]
- Martinez A, Revheim N, Butler PD, Guilfoyle DN, Dias EC, Javitt DC. 2012; Impaired magnocellular/dorsal stream activation predicts impaired reading ability in schizophrenia. *Neuroimage Clin.* 2:8–16. DOI: 10.1016/j.nicl.2012.09.006 [PubMed: 24179753]

- Mausbach BT, Harvey PD, Goldman SR, Jeste DV, Patterson TL. 2007; Development of a brief scale of everyday functioning in persons with serious mental illness. *Schizophr Bull.* 33(6):1364–1372. DOI: 10.1093/schbul/sbm014 [PubMed: 17341468]
- McNab F, Klingberg T. 2008; Prefrontal cortex and basal ganglia control access to working memory. *Nat Neurosci.* 11(1):103–107. DOI: 10.1038/nn2024 [PubMed: 18066057]
- Mosher JC, Leahy RM, Lewis PS. 1999; EEG and MEG: forward solutions for inverse methods. *IEEE Trans Biomed Eng.* 46(3):245–259. [PubMed: 10097460]
- Murray MM, Molholm S, Michel CM, Heslenfeld DJ, Ritter W, Javitt DC, Foxe JJ. 2005; Grabbing your ear: rapid auditory-somatosensory multisensory interactions in low-level sensory cortices are not constrained by stimulus alignment. *Cereb Cortex.* 15(7):963–974. DOI: 10.1093/cercor/bhh197 [PubMed: 15537674]
- Nuechterlein KH. 1977; Reaction time and attention in schizophrenia: a critical evaluation of the data and theories. *Schizophr Bull.* 3(3):373–428. [PubMed: 335494]
- Owen JP, Marco EJ, Desai S, Fourie E, Harris J, Hill SS, Mukherjee P. 2013; Abnormal white matter microstructure in children with sensory processing disorders. *Neuroimage Clin.* 2:844–853. DOI: 10.1016/j.nicl.2013.06.009 [PubMed: 24179836]
- Perrin MA, Butler PD, DiCostanzo J, Forchelli G, Silipo G, Javitt DC. 2010; Spatial localization deficits and auditory cortical dysfunction in schizophrenia. *Schizophr Res.* 124(1–3):161–168. DOI: 10.1016/j.schres.2010.06.004 [PubMed: 20619608]
- Poppel E. 2004; Lost in time: a historical frame, elementary processing units and the 3-second window. *Acta Neurobiol Exp (Wars).* 64(3):295–301. [PubMed: 15283473]
- Rauschecker JP. 1998; Parallel processing in the auditory cortex of primates. *Audiol Neurotol.* 3(2–3):86–103. [PubMed: 9575379]
- Rauschecker JP, Tian B. 2000; Mechanisms and streams for processing of “what” and “where” in auditory cortex. *Proc Natl Acad Sci U S A.* 97(22):11800–11806. DOI: 10.1073/pnas.97.22.11800 [PubMed: 11050212]
- Rojas DC, Bawn SD, Carlson JP, Arciniegas DB, Teale PD, Reite ML. 2002; Alterations in tonotopy and auditory cerebral asymmetry in schizophrenia. *Biol Psychiatry.* 52(1):32–39. [PubMed: 12079728]
- Rovamo J, Virsu V. 1979; An estimation and application of the human cortical magnification factor. *Exp Brain Res.* 37(3):495–510. [PubMed: 520439]
- Sanfratello L, Caprihan A, Stephen JM, Knoefel JE, Adair JC, Qualls C, Aine CJ. 2014; Same task, different strategies: how brain networks can be influenced by memory strategy. *Hum Brain Mapp.* 35(10):5127–5140. DOI: 10.1002/hbm.22538 [PubMed: 24931401]
- Schroeder CE, Foxe J. 2005; Multisensory contributions to low-level, ‘unisensory’ processing. *Curr Opin Neurobiol.* 15(4):454–458. DOI: 10.1016/j.conb.2005.06.008 [PubMed: 16019202]
- Schwartz F, Carr AC, Munich RL, Glauber S, Lesser B, Murray J. 1989; Reaction time impairment in schizophrenia and affective illness: the role of attention. *Biol Psychiatry.* 25(5):540–548. [PubMed: 2920189]
- Shams L, Kamitani Y, Shimojo S. 2002; Visual illusion induced by sound. *Brain Res Cogn Brain Res.* 14(1):147–152. [PubMed: 12063138]
- Stephen JM, Aine CJ, Christner RF, Ranken D, Huang M, Best E. 2002; Central versus peripheral visual field stimulation results in timing differences in dorsal stream sources as measured with MEG. *Vision Res.* 42(28):3059–3074. [PubMed: 12480075]
- Stephen JM, Knoefel JE, Adair J, Hart B, Aine CJ. 2010; Aging-related changes in auditory and visual integration measured with MEG. *Neurosci Lett.* 484(1):76–80. DOI: 10.1016/j.neulet.2010.08.023 [PubMed: 20713130]
- Stephen JM, Ranken DF, Aine CJ. 2006; Frequency-following and connectivity of different visual areas in response to contrast-reversal stimulation. *Brain Topogr.* 18(4):257–272. DOI: 10.1007/s10548-006-0004-z [PubMed: 16845594]
- Stone DB, Coffman BA, Bustillo JR, Aine CJ, Stephen JM. 2014; Multisensory stimuli elicit altered oscillatory brain responses at gamma frequencies in patients with schizophrenia. *Front Hum Neurosci.* 8:788.doi: 10.3389/fnhum.2014.00788 [PubMed: 25414652]

- Stone DB, Urrea LJ, Aine CJ, Bustillo JR, Clark VP, Stephen JM. 2011; Unisensory processing and multisensory integration in schizophrenia: a high-density electrical mapping study. *Neuropsychologia*. 49(12):3178–3187. DOI: 10.1016/j.neuropsychologia.2011.07.017 [PubMed: 21807011]
- Stone JV, Hunkin NM, Porrill J, Wood R, Keeler V, Beanland M, Porter NR. 2001; When is now? Perception of simultaneity. *Proc Biol Sci*. 268(1462):31–38. DOI: 10.1098/rspb.2000.1326 [PubMed: 12123295]
- Taulu S, Kajola M, Simola J. 2004; Suppression of interference and artifacts by the Signal Space Separation Method. *Brain Topogr*. 16(4):269–275. [PubMed: 15379226]
- Ungerleider LG, Desimone R. 1986; Projections to the superior temporal sulcus from the central and peripheral field representations of V1 and V2. *J Comp Neurol*. 248(2):147–163. DOI: 10.1002/cne.902480202 [PubMed: 3722456]
- Uusitalo MA, Ilmoniemi RJ. 1997; Signal-space projection method for separating MEG or EEG into components. *Med Biol Eng Comput*. 35(2):135–140. [PubMed: 9136207]
- Vinogradov S, Poole JH, Willis-Shore J, Ober BA, Shenaut GK. 1998; Slower and more variable reaction times in schizophrenia: what do they signify? *Schizophr Res*. 32(3):183–190. [PubMed: 9720123]
- Werner S, Noppeney U. 2010; Superadditive responses in superior temporal sulcus predict audiovisual benefits in object categorization. *Cereb Cortex*. 20(8):1829–1842. DOI: 10.1093/cercor/bhp248 [PubMed: 19923200]
- Wible CG, Lee K, Molina I, Hashimoto R, Preus AP, Roach BJ, Fbirm. 2009; fMRI activity correlated with auditory hallucinations during performance of a working memory task: data from the FBIRN consortium study. *Schizophr Bull*. 35(1):47–57. DOI: 10.1093/schbul/sbn142 [PubMed: 18990710]
- Wible CG, Preus AP, Hashimoto R. 2009; A Cognitive Neuroscience View of Schizophrenic Symptoms: Abnormal Activation of a System for Social Perception and Communication. *Brain Imaging Behav*. 3(1):85–110. DOI: 10.1007/s11682-008-9052-1 [PubMed: 19809534]
- Williams TJ, Nuechterlein KH, Subotnik KL, Yee CM. 2011; Distinct neural generators of sensory gating in schizophrenia. *Psychophysiology*. 48(4):470–478. DOI: 10.1111/j.1469-8986.2010.01119.x [PubMed: 20735757]
- Xu L, Groth KM, Pearlson G, Schretlen DJ, Calhoun VD. 2009; Source-based morphometry: the use of independent component analysis to identify gray matter differences with application to schizophrenia. *Hum Brain Mapp*. 30(3):711–724. DOI: 10.1002/hbm.20540 [PubMed: 18266214]
- Zmigrod S. 2014; The role of the parietal cortex in multisensory and response integration: evidence from transcranial direct current stimulation (tDCS). *Multisens Res*. 27(2):161–172. [PubMed: 25296477]
- Zundorf IC, Lewald J, Karnath HO. 2016; Testing the dual-pathway model for auditory processing in human cortex. *Neuroimage*. 124(Pt A):672–681. DOI: 10.1016/j.neuroimage.2015.09.026 [PubMed: 26388552]

Highlights

- Evidence of impairment of dorsal visual stream in SP during simple multisensory task.
- Significantly different activity in parietal areas dependent on stimulus synchrony for SP vs HC.
- Negative correlation between IPS activity and positive symptoms in SP.

Fig 1.

Visual stimuli. A static background (field, sky, goalie and net) was present throughout data collection. Participants were instructed to fixate on the goalie. During visual conditions a soccer ball was presented in 1 of 2 locations. The soccer ball is shown here in the Near position. The Far visual stimulus location is outlined (dashed circle).

Fig. 2.

A. 'Destrieux' cortical atlas showing ROIs. ROIs investigated included: Insula=peach; STG=pink; STS=yellow; SPG=pale purple; IPS=Dark purple; IPG=blue; Occipital pole=maroon. **B.** dSPM difference maps of cortical activity (HC minus SP activity) for 4 AV conditions: synchronous Near/Far and asynchronous Near/Far. Orange/yellow colors indicate greater amplitudes for HC compared to SP. **C.** Examples of averaged timecourses for ROIs.

Fig. 3.

Main effects of Group on amplitude of peak activation identified between 120 and 250 ms.

A. Main effect of group on amplitude of activation in SPG, where SP activation ($Mean \pm SE = 7.36 \pm 0.473$) is reduced relative to HC ($Mean \pm SE = 9.195 \pm 0.468$). **B.** Main effect of group on amplitude of activation in IPG, where SP activation ($Mean \pm SE = 9.233 \pm 0.506$) is reduced relative to HC ($Mean \pm SE = 10.758 \pm 0.512$). **C.** Main effect of group on amplitude of activation in IPS, where SP activation ($Mean \pm SE = 8.191 \pm 0.541$) is reduced relative to HC ($Mean \pm SE = 10.273 \pm 0.546$). All effects, $p < 0.05$.

Fig 4.

Interaction effects for amplitude of activation. **A.** IPG amplitude exhibits a stimulus synchrony (synchronous, asynchronous) by group interaction effect [$Mean \pm SE$: $HC_{sync} = 10.858 \pm 0.519$; $SP_{sync} = 8.969 \pm 0.514$; $HC_{async} = 10.658 \pm 0.537$; $SP_{async} = 9.498 \pm 0.531$]. **B.** IPS amplitude exhibits a stimulus location (near, far) by group interaction effect [$Mean \pm SE$: $HC_{near} = 11.577 \pm 0.642$; $SP_{near} = 8.891 \pm 0.649$; $HC_{far} = 8.969 \pm 0.484$; $SP_{far} = 8.891 \pm 0.649$]. All effects, $p < 0.05$.

Fig. 5.

A. Main effect of group for IPS latency. SP shows a longer latency ($Mean \pm SE = 189.023 \pm 2.14$) than HC ($Mean \pm SE = 182.13 \pm 2.118$). **B.** Significant location*group interaction for IPS latency, where HC and SP become more similar in the far condition [$Mean \pm SE: HC_{near} = 173.342 \pm 2.566$; $SP_{near} = 187.266 \pm 2.592$; $HC_{far} = 190.918 \pm 2.549$; $SP_{far} = 190.781 \pm 2.575$]. All effects, $p < 0.05$.

Table 1

Participant demographics.

	Age	Male/Female	Olanzapine Equivelant	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

* p < 0.05 significance.

Table II

Simple effects for hemisphere*sync*location*group interaction for amplitude of activation in IPS.

ROI/Condition	Amplitude (Mean±SD)		
IPS Left	HC	SP	p-value
<i>sNear</i>	12.6±6.9	9.5±4.5	0.002 *
<i>asNear</i>	12.0±6.5	9.8±4.3	0.007 *
<i>sFar</i>	9.7±4.9	8.1±4.1	0.06
<i>asFar</i>	9.5±4.8	8.5±4.6	0.2
IPS Right			
<i>sNear</i>	10.7±5	8.4±4.3	0.01 *
<i>asNear</i>	11.1±5.5	8.1±3.9	0.0007 *
<i>sFar</i>	8.5±4.4	6.3±2.5	0.001 *
<i>asFar</i>	8.2±4.7	7.0±3.5	0.03 *

* p < 0.05 significance.

Table III

Significant 3-way interaction of hemisphere*sync*group for peak latency in SPG.

ROI/Condition	Latency (Mean±SD)		
SPG Left	HC	SP	p-value
<i>sync</i>	174.4±4.5	171.3±4.5	0.93
<i>async</i>	191.6±2.8	195.6±2.8	0.40
SPG Right			
<i>sync</i>	181.5±3.9	193.4±3.9	0.023 *
<i>async</i>	192.8±3.2	193.2±3.2	0.54

* p < 0.05 significance.

Table IV

Correlations between medication dose/symptoms in SP and parietal activity (MEG signal amplitude) for each of the four task conditions. FDR corrected

ROI/Condition	Olanzapine Equivalent	Positive symptoms	Negative symptoms
Superior Parietal Right			
<i>sNear</i>	-0.09	0.05	-0.15
<i>asNear</i>	-0.08	-0.03	-0.08
<i>sFar</i>	0.04	-0.04	-0.03
<i>asFar</i>	0.00	0.03	0.13
Inferior Parietal Right			
<i>sNear</i>	-0.01	-0.21	0.01
<i>asNear</i>	-0.14	-0.18	-0.04
<i>sFar</i>	0.01	-0.12	-0.12
<i>asFar</i>	-0.03	-0.19	-0.09
IPS Right			
<i>sNear</i>	0.02	-0.01	-0.02
<i>asNear</i>	-0.10	-0.22	-0.01
<i>sFar</i>	0.00	-0.09	-0.09
<i>asFar</i>	-0.11	-0.21	-0.11
IPS Left			
<i>sNear</i>	-0.03	-0.29*	0.10
<i>asNear</i>	-0.08	-0.15	-0.22
<i>sFar</i>	0.05	-0.08	-0.02
<i>asFar</i>	-0.20	-0.22	-0.19

* indicates significance at $p < 0.05$.