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Comparison of Auditory and Visual Oddball fMRI in Schizophrenia

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Abstract

Individuals with schizophrenia often suffer from attentional deficits, both in focusing on task-relevant targets and inhibiting responses to distractors. Schizophrenia also has a differential impact on attention depending on modality: auditory or visual. However, it remains unclear how abnormal activation of attentional circuitry differs between auditory and visual modalities, as these two modalities have not been directly compared in the same individuals with schizophrenia. We utilized event-related functional magnetic resonance imaging (fMRI) to compare patterns of brain activation during an auditory and visual oddball task in order to identify modality-specific attentional impairment. Healthy controls ($n = 22$) and patients with schizophrenia ($n = 20$) completed auditory and visual oddball tasks in separate sessions. For responses to targets, the auditory modality yielded greater activation than the visual modality (A-V) in auditory cortex, insula, and parietal operculum, but visual activation was greater than auditory (V-A) in visual cortex. For responses to novels, A-V differences were found in auditory cortex, insula, and supramarginal gyrus; and V-A differences in the visual cortex, inferior temporal gyrus, and superior parietal lobule. Group differences in modality-specific activation were found only for novel stimuli; controls showed larger A-V differences than patients in prefrontal cortex and the putamen. Furthermore, for patients, greater severity of negative symptoms was associated with greater divergence of A-V novel activation in the visual cortex. Our results demonstrate that patients have more pronounced activation abnormalities in auditory compared to visual attention, and link modality specific abnormalities to negative symptom severity.

Keywords

Auditory attention; Visual attention; Oddball; Magnetic resonance imaging

1. Introduction

Individuals with schizophrenia suffer from deficits in sustained attention and working memory (Braff, 1993; Lee and Park, 2005; Mathalon et al., 2004). Sustained attention involves both the ability to focus on task-relevant targets and to inhibit responses to task-irrelevant novel distractors; the three-stimulus variant of the oddball task assesses both

components (Donchin, 1981; Laurens et al., 2005; Liddle et al., 2006; Squires et al., 1975). The neural correlates of target detection and novelty processing have been characterized by event-related potentials (ERP), and prior ERP studies have directly compared auditory and visual oddball activation in schizophrenia (Huang et al., 2011). In ERP, patients demonstrate robust ERP reductions only in the auditory P3, and not the visual P3 (Ford, 1999; Wood, 2006). Relative to ERP, functional magnetic resonance imaging (fMRI) allows for the direct evaluation of the brain regions preferentially engaged during oddball processing (Kim, 2013). To our knowledge, auditory and visual attention deficits have not been directly compared in schizophrenia using fMRI.

Schizophrenia has a differential impact on attention depending on modality: auditory and visual. Prior work using fMRI addressed auditory and visual oddball activation separately in patients (Gur et al., 2007a, 2007b; Wolf et al., 2008), however it is unclear how modality-specific task activation affects oddball performance when these two modalities are directly compared. In ERP, patients demonstrate robust ERP reductions only in the auditory P300 (P3, elicited by the task), and not the visual P3 (Ford, 1999; Wood, 2006; Huang et al., 2011). The deficits in auditory P3 (relative to visual P3) are associated with amplitude reductions in frontal, left temporal and right parietal subcomponents (Jeon & Polich, 2003; Turetsky, Colbath & Gur, 1998; Ohyama et al., 1993).

In fMRI, auditory and visual modalities have been directly compared in healthy individuals (Stevens et al., 2000). Together, these studies showed that auditory targets elicited activation in the right middle frontal gyrus, right superior temporal gyrus and left inferior parietal lobule, whereas visual targets elicited activation in right middle frontal gyrus, bilateral inferior frontal gyrus and right middle temporal gyrus. Auditory novels elicited stronger responses than visual novels in the dorsolateral frontal cortex, inferior parietal lobule, and cingulate cortex (Kiehl, et al., 2001; Stevens et al., 2000; Yoshiura et al., 1999).

Not only has the differential impact of schizophrenia on attention been shown to more severely impair auditory relative to visual attention, as discussed earlier, it has been related to clinical symptomatology. Attentional impairment has been associated with the severity of negative symptoms (Bozikas et al., 2004; Chen and Faraone, 2000; Nieuwenstein et al., 2001; Wolkin et al., 1992). Specific to oddball processing, fMRI activation to auditory novels in schizophrenia correlated inversely with severity of negative symptoms within left dorsolateral frontal cortex and bilateral ventral striatum (Wolf et al., 2008). Thus, clinical symptomatology, specifically negative symptoms, may be particularly related to attentional activation deficits in the auditory modality.

We utilized event-related fMRI to directly compare patterns of brain activation during auditory versus visual oddball tasks, in an effort to elucidate the regions, beyond the respective perceptual processing regions, that might contribute to modality-specific processing of targets and novels in patients with schizophrenia. We aimed to identify which modality yielded more abnormal activation during the oddball task, in an effort to replicate and extend oddball findings from the ERP literature. Consistent with the ERP literature (Ford, 1999; Wood, 2006), we hypothesized that patients would demonstrate greater abnormalities of fMRI activation during auditory compared to visual oddball processing.

Moreover, we aimed to determine whether such modality-specific abnormalities related to the severity of negative symptoms.

2. Methods

2.1. Participants

The sample included 22 healthy controls (13 males) and 20 patients with schizophrenia or schizoaffective disorder (11 males). The sample was drawn from a larger sample that included 23 healthy controls and 24 patients that completed both auditory and visual scans. We removed 5 participants (1 control, 4 patients) due to non-response during the auditory task, resulting in the group of 42 participants used in this report. All participants were right-handed volunteers at the University of Pennsylvania Schizophrenia Research Center. Participants underwent standard assessment, including medical, neurological, psychiatric, neurocognitive and laboratory tests. Psychiatric evaluation included a clinical interview, structured interview (SCID-P, First et al., 1996), and collateral history from family, caregivers and records. Patients had a DSM-IV diagnosis of schizophrenia (N= 17) or schizoaffective disorder depressed-type (N= 3), determined by consensus conference based on all available information and were all on antipsychotic medication (predominantly on second generation antipsychotics; Clozaril, Risperdal, Seroquel, Loxitane, and some on first generation antipsychotics; Haldol or combination. Some patients also received mood stabilizer and anxiolytic agents; Prozac, Xanax, Paxil, Lithium. Patients were clinically stable outpatients with mild symptoms at the time of study, as assessed with the Scale for Assessment of Negative Symptoms (SANS, Andreasen, 1984a) and Scale for the Assessment of Positive Symptoms (SAPS, Andreasen, 1984b). Patients had no history of other disorders or events affecting brain function (i.e., current or history of substance abuse). Seven patients had a history of smoking whereas five had never smoked (the smoking history of the remaining 8 patients is unknown). After a complete description of the study, written informed consent was obtained from the participants.

2.2. Procedure

Participants completed an auditory and visual oddball task during separate scans an average of 4 weeks apart, with order of modality counterbalanced across the participants. The clinical assessments scales were administered once prior to the first scan. The auditory oddball task included standard, target and novel stimuli with distinct auditory tones. 140 frequent standard stimuli (1000 Hz tones), 30 infrequent target stimuli (2000 Hz tones), and 30 infrequent novel stimuli (unique, generally unrecognizable environmental sounds) were presented binaurally via headphones. Each of the stimuli was presented at 75 dB.

Before the test phase, participants were trained on an abbreviated task that contained no novel stimuli. During the test phase, stimuli were presented in a pseudo-random order, 150 milliseconds duration with a 1.85 second inter-stimulus interval. Participants responded with a yes or no button press to the “Target Present?” probe after each stimulus presentation. Responses and reaction times were recorded.

The visual oddball task included standard, target and novel stimuli with distinct visual orientations and colors. 140 frequent standard stimuli were images of a circular arrangement

of small bright red Gabor elements, arranged in a red circle, contrasted against a gray textured background. The light-gray Gabor elements in the background were randomly distributed. 30 infrequent target stimuli were similar to the standard stimuli except they featured a bright green circle. 30 infrequent novel stimuli were fractal images with similar luminance as the standard and target stimuli. The training and test phases were administered similar to the auditory oddball procedure. Visual stimuli were presented in a random order on the screen for 1 second each with a 1 second inter-stimulus interval.

2.3. Image Acquisition

Functional blood-oxygen-level-dependent (BOLD) data was acquired on a 3-T Siemens Tim Trio scanner using a quadrature head coil. Structural images were acquired axially using a magnetization prepared rapid acquisition gradient-echo (MPRAGE), T1- weighted sequence (TR/TE = 1630/3.87 ms, FOV=240 × 180 mm, matrix=256 × 192, slice thickness/gap = 1/0 mm) with a voxel resolution of 0.9375 × 0.9375 × 1.00 mm. This sequence was used for spatial normalization and for anatomic overlays of functional data. Functional images (178 images for the oddball task and 126 images for the recognition memory task) were acquired axially using a 40-slice gradient-echo (GE) echo-planar imaging (EPI) sequence (TR/TE = 3000/30 ms, FOV = 240 × 240 mm, matrix = 64 × 64, slice thickness/gap = 3/0 mm) with a nominal voxel resolution of 3.00 × 3.00 × 3.00 mm.

2.4. Image Processing

The fMRI data was preprocessed and analyzed using FEAT (FMRI Expert Analysis Tool v 5.0.2.1), part of FSL (FMRIB's Software Library, www.fmrrib.ox.ac.uk/fsl). The functional images were slice-time corrected, motion-corrected to the median image with tri-linear interpolation, high-pass filtered (100 s), spatially smoothed (5 mm FWHM Gaussian isotropic kernel), and grand mean scaled. A brain extraction tool was used to remove non-brain areas from the high-resolution structural image (Smith, 2002). The functional images were coregistered to the structural image and transformed by trilinear interpolation into standard anatomical space (Jenkinson et al., 2002; Jenkinson and Smith, 2001) using the T1 Montreal Neurological Institute (MNI) template.

2.5. Statistical Analysis

Subject-level time-series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al. 2001). Condition events were modeled with a canonical (double-gamma) hemodynamic response function and its temporal derivative. The first level analysis focused on target – standard baseline and novel- standard baseline contrasts in each modality, auditory and visual separately.

The design matrix also included 6 motion parameters derived from motion correction, to reduce residual motion effects. Groups did not differ significantly in head motion for auditory ($t = 1.07$, $df = 21$, $p = 0.29$) or for visual scans ($t = .70$, $df = 21$, $p = 0.49$). Head motion did not differ across modalities ($t = .66$, $df = 41$, $p = 0.51$). After preprocessing, whole brain statistical analysis was completed for each individual in subject space, and resulting contrast maps were spatially normalized as mentioned above. Group –level random

effects analyses were performed in FSL, using FMRIB's Local Analysis of Mixed Effects (FLAME 1) (Beckmann et al., 2003; Woolrich et al., 2004). Within-group analyses were accomplished by entering whole brain contrasts into one-sample t-tests. The primary contrasts of interest were Auditory target- Visual target (A-V target), Auditory novel- Visual novel (A-V novel), Visual target- Auditory target (V-A target) and Visual novel- Auditory novel (V- A novel). Between-group analyses used two-sample t-tests. For the A-V contrast we were interested in areas that were lower in patients than controls and similarly for V-A. Jointly these two comparisons would identify any group differences in the modality effect (A-V or V-A). We also examined basic contrasts, target > standard and novel > standard, for each stimulus modality and these findings confirm well-known activation patterns and are presented in the supplement. Significance thresholds were based on spatial extent and we used a minimum height threshold $z > 2.33$ and a cluster $p < 0.05$.

We extracted percent signal change values from clusters that demonstrated significant between-group differences (i.e., prefrontal cortex and putamen). Moreover, to assess the relationship between fMRI BOLD activation and clinical symptoms in patients, separate group level covariate analyses were performed in the whole brain during each condition (A-V target, A-V novel) with negative symptoms (SANS) (Andreasen, 1984a, 1984b). We calculated a total score and a score for each of the subscales for the SANS.

3. Results

3.1. Behavioral Performance

Healthy controls correctly identified 26.9 ($SD = 6.5$) auditory targets (89.7%) and 25.3 ($SD = 5.8$) visual targets (84.3%). There was no difference between auditory compared to visual target detection in accuracy ($t(21) = .87, p = .40$) or response time (auditory: $M = 603.0$ ms, $SD = 80.2$, visual: $M = 648.5$ ms, $SD = 91.6, t(21) = 1.77, p = .09$). Patients correctly identified 27.8 ($SD = 2.0$) auditory targets (92.7%) and 26.0 ($SD = 4.6$) visual targets (86.7%). There was no difference between auditory compared to visual target detection in accuracy ($t(19) = 1.59, p = 0.13$) or response time (auditory: $M = 660.0$ ms, $SD = 111.5$, visual: $M = 670.5$ ms, $SD = 103.8, t(19) = .31, p = 0.77$).

Healthy controls did not differ from patients in auditory target detection ($t(19) = .61, p = .55$) or visual target detection ($t(19) = .45, p = .65$). Moreover, healthy controls and patients did not differ in response times to auditory target ($t(19) = 1.90, p = 0.07$) or visual target detection ($t(19) = .73, p = 0.47$).

3.2. Task Activation within Auditory and Visual Modalities

Functional activation for auditory and visual modalities was consistent with prior literature for target and novel detection, with prominent activation in both modalities in the dorsal and ventral prefrontal cortex and supramarginal/angular gyrus (Gur et al., 2007a, 2007b; Wolf et al., 2008). Widespread group differences were present in the auditory modality, with much more limited group differences in the visual modality. Regions showing within-group and between-group effects for individual modalities (visual, auditory) and conditions (target, novel) are provided in Supplementary Table 1.

3.3. Auditory - Visual (A-V) Direct Comparison

For targets, both groups demonstrated greater auditory than visual activation in the auditory cortex (superior temporal gyrus, Heschl's gyrus, planum temporale) as expected, as well as in the insula and the parietal operculum. There were no significant group differences in the A-V target contrast.

For novels, both groups demonstrated greater auditory than visual activation in the auditory cortex, insula and supramarginal gyrus. Compared to controls, patients demonstrated reduced A-V differential activation to novel stimuli in two clusters with peaks in the prefrontal cortex and putamen (Figure 1). To further characterize this group difference, we extracted percent signal change values from these clusters. The group difference in A-V novel in prefrontal cortex reflects deactivation to visual but not auditory stimuli in controls, while patients deactivate to auditory but not visual stimuli. In the putamen, the group difference reflects activation to auditory but not visual novel stimuli in controls, with the reverse pattern in patients (Figure 2).

3.4. Visual- Auditory (V-A) Direct Comparison

For targets, both groups demonstrated greater visual than auditory target activation in visual cortex (lateral occipital cortex, occipital fusiform cortex). There were no significant group differences in the V-A target contrast.

For novels, both groups again showed greater visual than auditory activation in the same visual cortex regions (lateral occipital cortex, occipital fusiform cortex), as well as in other areas of the temporal lobe (inferior temporal gyrus, parahippocampal gyrus), and parietal cortex (superior parietal lobule, precuneus, lingual gyrus). There were no significant group differences in the V-A novel contrast.

3.5. Correlation with Clinical Symptoms

The average global SANS score was 1.5 and SAPS score was 1.5 for the patient sample. There was a positive correlation between severity of negative symptoms (alogia and avolition subscales) and A-V novel activation in the visual cortex (lingual gyrus, precuneus, fusiform cortex). The more severe the speech and motivational deficits, the more differential activation was found for novelty processing in visual cortex. There were no significant correlations between severity of positive symptoms and A-V novel activation, nor any correlation between positive or negative symptoms and A-V novel activation in the prefrontal cortex and putamen regions where patients had shown abnormalities in modality-specific activation.

4. Discussion

We utilized event-related fMRI to directly compare patterns of brain activation engaged during an auditory and visual oddball task in an effort to elucidate the regions, beyond the respective perceptual processing regions, that are involved during modality-specific processing of targets and novels in patients and to identify modality-specific attentional impairment in patients with schizophrenia. Moreover, we aimed to identify which modality

is associated with more abnormal activation during the oddball task and to determine whether negative symptoms relate to those abnormalities in patients.

Behaviorally, patients performed at a level similar to controls. Our task was designed to be easy in order to avoid performance confounds and enable an investigation of how patients, compared to controls, engage different brain regions during oddball task performance. However, this is not to say that patients do not demonstrate deficits in attention. Patients performed more poorly than controls on a battery of neuropsychological tests administered outside of the scanner, including tests of executive function and attention. Imaging revealed a broad network of functional activation for both auditory and visual target detection and novelty processing consistent with prior literature (Gur et al., 2007b; Kiehl et al., 2005; Wolf et al., 2008). Widespread group differences were present in the auditory modality, with much more limited group differences in the visual modality. There are fundamental differences between the mechanisms of auditory and visual attention (Posner, 1984). Modality determines how items are interpreted, either based on frequency and temporal dimensions as in the auditory modality or based on spatial and temporal dimensions as in the visual modality. Auditory processing, at the early stage, evaluates the frequency information of sounds and subsequently attention can be directed to both the frequency and temporal components. Visual processing analyzes spatial images and orients toward salient features in the spatial environment (Shinn-Cunningham, 2008).

To illuminate modality-specific activation, we used a subtraction paradigm identifying the neural substrates specifically involved in processing auditory versus visual stimuli (Kim et al., 1999). Beyond expected auditory processing regions in the auditory cortex, we found greater auditory than visual activation in the insula and parietal operculum for targets, and in the insula and supramarginal gyrus for novels. Beyond expected visual processing in the visual cortex, we found greater visual than auditory activation in no other regions for targets but in the parietal cortices for novels.

Schizophrenia has been associated with deficits in auditory attention (Gallinat et al., 2002; Kiehl, 2005; Kim et al., 2009; Wolf et al., 2008) and visual attention (Butler et al., 2001; Gur et al., 2007) and we now demonstrate with an fMRI paradigm that the nature of abnormal brain activation differs based on modality; relative to visual attention, auditory attention appears to be associated with greater activation abnormality in schizophrenia. During A-V novelty processing, controls engaged the prefrontal cortex and putamen more than patients. The group difference in the prefrontal cortex reflects deactivation to visual but not auditory stimuli in controls, while patients deactivate to auditory but not visual stimuli. In the putamen, the group difference reflects activation to auditory but not visual novel stimuli in controls, with the reverse pattern in patients. Unlike A-V activation, there were no group differences for V-A activation in either condition, further supporting our hypothesis predicting greater deficits in auditory attention while visual attention remained largely unaffected in patients.

The activation in the prefrontal cortex, putamen and insula, where we found the greatest patient abnormalities for A-V novel processing, is congruent with reports that these regions form a saliency detection network and contribute to processing novels (Bledowski et al.,

2004; Linden et al., 1999; Ragland et al., 2009). Saliency is either extracted by similar mechanisms in both modalities or by the same multimodal cortical areas, whereby a single supra-modal representation of environmental events may be constantly updated (Farah et al., 1989). Saliency (attentional allocations) in the auditory modality is likely controlled by a supra-modal mechanism whereas in the visual modality it is controlled by a modality specific mechanism (Kayser et al., 2005). Our data support that claim; it appears that beyond modality specific auditory activation (in the auditory cortex), auditory attention is modulated by supra-modal mechanisms that involve activation in the prefrontal cortex, putamen and insula. Patients with schizophrenia may have difficulty extracting salience from stimuli, and we demonstrated that they have an impaired ability to process novels, specifically auditory novels.

We further examined whether clinical symptom severity relates to the activation abnormalities. Negative compared to positive symptoms contribute more to cognitive deficits (Addington, Addington, and Maticka-Tyndale, 1991; Gur et al., 2006; Keefe et al., 2006). However, few studies have investigated the relationship between schizophrenia symptomatology and BOLD activation during an oddball task (Garrity et al., 2007; Gur et al., 2007; van Lutterveld et al., 2013; Wolf et al., 2008). We found that negative symptoms (namely, speech and motivational deficits) were associated with greater activation abnormalities to novelty processing in the visual cortex. This finding suggests that activation of visual areas during the processing of auditory novel stimuli may relate to difficulties in paucity of speech and motivation. Further studies are needed to examine this link.

A limitation of our study is that patients were on antipsychotic medications, which might influence our results. However, prior studies have investigated the influence of medication on P3 activity and found that reduced P3 amplitude was evident regardless of age, medication status, illness duration, or symptom change over time (Jeon and Polich, 2003; Pfefferbaum et al., 1989)(Turetsky, Colbath and Gur, 1998). In addition, in our study antipsychotic dosage did not significantly correlate with activation in the clusters showing significant group differences or negative symptom correlations.

Given the statistical power afforded by our sample size, and the relatively mild level of symptoms in our patient sample, we may have been unable to identify some group differences or symptom correlations, and larger studies including a broader range of illness severity might identify additional abnormalities.

The major strength of our study is the application of both auditory and visual oddball fMRI tasks in the same subjects, allowing us to directly compare modality-specific patterns of brain activation. Most prior studies in schizophrenia applying oddball paradigms to investigate target detection and novelty processing have only examined the auditory modality (Wood et al., 2006). Despite a wealth of ERP studies addressing auditory and visual oddball activity in schizophrenia and other disorders, and the many fMRI studies with this paradigm in other disorders (Barry et al., 2009; Doi et al., 2007; Johnson, 1989; Neylan et al., 2003; Van der Molen et al., 2012) no prior fMRI study in schizophrenia has directly compared these modalities using the oddball paradigm.

Our findings yield novel insights into modality-specific attentional impairment in schizophrenia and suggest the nature of abnormal brain activation differs based on stimulus modality. Regions outside of known modality-specific sensory processing regions also show differential engagement during auditory versus visual oddball fMRI. Our results indicate that auditory attentional processing, particularly for novel distractors, is more abnormal than visual attentional processing in schizophrenia, potentially related to altered modality-specific processing in the prefrontal cortex and putamen.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Voxel-wise whole brain clusters with significant between group differences in A-V novel condition (cluster-corrected $p < 0.05$, voxel height threshold $Z > 2.3$) are overlaid on the MNI template brain. Clusters with peak activation were found in the prefrontal cortex and putamen and sub-clusters extended to the superior frontal gyrus and insula, respectively. There were no significant patients > controls clusters.

Figure 2. Percent signal change in the prefrontal cortex and the putamen for auditory and visual novel stimuli during an oddball task in healthy controls and patients with schizophrenia. Percent signal change was extracted from the significant clusters in Figure 1.