Humans are constantly bombarded with streams of information from multiple sensory modalities (e.g. auditory and visual) that must be rapidly processed to execute appropriate behaviours. Cognitive control refers to the ability to facilitate goal-directed behaviours while suppressing inappropriate and/or distracting stimuli and behaviours, and has recently been expanded to include working memory paradigms. Although deficits in cognitive control are commonly reported in patients with schizophrenia, the majority of previous schizophrenia studies have utilised unisensory stimuli, with only a single study employing a more realistic multisensory approach. Unisensory studies may not adequately capture the complex environment that is typical in occupational and interpersonal settings where patients with schizophrenia have shown to exhibit deficits associated with cognition. Thus, to understand the underlying neuronal processes of cognitive control in real-world environments, a multisensory approach is needed.

There are two potential theories regarding cognitive control deficits in patients with schizophrenia. The first theory suggests that poor performance in patients results from dysfunction within the cognitive control network (CCN) during trials with conflicting (i.e. incongruent trials) relative to non-conflicting (i.e. congruent trials) information. The core CCN in healthy controls includes the dorsal medial prefrontal cortex, dorsolateral and ventrolateral prefrontal cortex (lateral prefrontal cortex), anterior insula and the inferior parietal lobes. Previous neuroimaging studies have reported abnormalities within the lateral prefrontal cortex, dorsal medial prefrontal cortex, posterior parietal cortex, posterior temporal cortex and thalamus for patients with schizophrenia relative to healthy controls across a variety of tasks. However, reduced and increased prefrontal activation have been reported, as well as a combination of both findings. The single imaging study examining multisensory cognitive control in patients with schizophrenia reported hypoactivation within lateral prefrontal cortex, temporoparietal juncture and medial temporal regions.

Although top-down allocation of attention necessitates the recruitment of the CCN, competent performance is also dependent on the processing of stimuli within the sensory cortex. A second theory therefore suggests that dysfunction within sensory cortex contributes to downstream cognitive control deficits in patients with schizophrenia. These deficits have been observed in both auditory and visual steady state responses, mismatch negativity, abnormal auditory gating and reduced visual evoked potentials. Conversely, hyperactivation of auditory cortex and primary visual cortex has also been reported, suggestive of over-processing of sensory stimuli. Finally, a direct interaction exists between attentionally demanding multisensory conditions (requiring more cognitive control) and the degree of neuronal activation within sensory cortex. These attention-related modulations (ARMs) include enhanced neural responses (i.e. upregulation) within primary and secondary sensory cortices for the attended stimuli and suppressed responses for the ignored stimuli, the appearance of new waveforms, as well as more synchronous neuronal spiking.

Thus, multisensory cognitive control tasks are uniquely poised to distinguish between deficits resulting from top-down abnormalities within the CCN (incongruent auditory/visual trials v. congruent auditory/auditory or visual/visual trials), basic deficits in neurovascular properties within unisensory cortex, and the direct modulation of unisensory cortex (ARMs). We hypothesised that patients with schizophrenia would exhibit deficits within the CCN specifically during cognitive control (incongruent v. congruent trials), whereas deficits within the unisensory cortex would be seen generally (across both incongruent and congruent trials). In addition, we predicted that patients with schizophrenia would fail to exhibit upregulation of unimodal
sensory cortical areas (ARMs) to attended stimuli at increasing cognitive loads (high frequency stimuli relative to low frequency stimuli) as has been observed in healthy populations.\(^1\)

**Method**

**Participants**

Thirty-seven clinically stable patients with schizophrenia and 37 age- and gender-matched healthy controls were included. Data from one patient was lost secondary to acquisition problems, and one patient was an outlier (three standard deviations) relative to their cohort on two of six motion parameters (frame-wise displacement). Two patients with schizophrenia performed below chance levels (based on a binomial distribution) on the task, leaving a total of 33 patients with schizophrenia (29 males; 36.0 years old (s.d. = 13.6)) and 33 matched healthy controls (29 males; 34.6 years old (s.d. = 12.6)) for final analyses. Informed consent was provided according to institutional guidelines.

Inclusion criteria for patients with schizophrenia included a diagnosis of schizophrenia based on the Structured Clinical Interview for DSM-IV-TR and age of 18–65 years. Most patients with schizophrenia (32/33) were on a variety of antipsychotic medications (28/32 patients atypical) such that olanzapine equivalency scores were calculated.\(^23\) Exclusion criteria for both groups included a history of neurological disorder, head trauma with loss of consciousness greater than 5 min, mental retardation, inadequate hearing (tested with the calibrated finger rub auditory screening test), active substance dependence or misuse within the past year and lifetime history of dependence or use within the last 12 months of phencyclidine, amphetamines or cocaine. Additional exclusion criteria for healthy controls included a current or past psychiatric disorder (with the exception of one lifetime depressive episode), depression or antidepressant use within the past 6 months, lifetime antidepressant use of more than 1 year, and history of a psychotic disorder in a first-degree relative. All participants refrained from smoking for at least 1 h before scanning.

**Neuropsychological and clinical assessment**

All participants completed the Wechsler Test of Adult Reading (WTAR). Patients with schizophrenia completed the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery, Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale, Clinical Global Impression, Fagerstrom Test for Nicotine Dependence (FTND), a modified (PANSS), Calgary Depression Scale, Clinical Global Impression, Fagerstrom Test for Nicotine Dependence (FTND), a modified

**Task**

The task was identical to previous publications.\(^24\) Congruent or incongruent multisensory (auditory and visual) numeric stimuli (Fig. 1A and 1B) were simultaneously presented at either low (0.33 Hz; 3 trials/block) or high (0.66 Hz; 6 trials/block) frequency rates in 10-second blocks. For each block, the stream of target numbers (one, two or three) was preceded by a cue word, ‘HEAR’ or ‘LOOK’. If the cue was ‘HEAR’, participants were instructed to respond via a right-handed button press to aurally presented target stimuli and ignore simultaneously presented visual numbers (attend-auditory condition). When the cue was ‘LOOK’, visually presented stimuli were the targets and participants were instructed to ignore auditory stimuli (attend-visual condition). The inter-block intervals varied between 8, 10 and 12 s to decrease temporal expectations and permit modelling of the baseline response. Order of blocks was pseudorandom, with a total of 432 trials presented across six separate imaging runs. Median reaction times were used as measures of central tendency to reduce the influence of skew. Accuracy was analysed using ranking of percentage of errors in each trial type to account for deviations in normality. 2 × 2 × 2 (group (patients with schizophrenia v. healthy controls) × condition (congruent v. incongruent) × frequency (0.33 Hz v. 0.66 Hz)) mixed-measures analysis of variance (ANOVAs) were conducted separately on attend-auditory and attend-visual conditions for both accuracy and response time data.

**Magnetic resonance imaging and statistical analyses**

Magnetic resonance imaging (MRI) data including T1 images and echo-planar imaging (EPI) were collected on a Siemens 3T Trio Tim scanner with a 12 channel head coil. EPI data were collected using a single-shot, gradient-echo sequence (repetition time (TR) = 2000 ms; voxel size: 3.75 × 3.75 × 4.35 mm; see online supplemental Methods), Functional imaging maps were calculated using the Analysis of Functional NeuroImages (AFNI) software (http://afni.nimh.nih.gov). Standard pre-processing steps included motion correction, slice timing correction, smoothing (8 mm full-width at half-max Gaussian kernel) and spatial normalisation. A voxel-wise deconvolution analysis generated a single haemodynamic response function (HRF) for each trial-type relative to baseline (visual fixation plus baseline gradient noise) and was based on the first 22 s post-stimulus onset. Error trials were modelled separately.\(^25\) Percent signal change (PSC) for correct trials was calculated by summing beta coefficients for images occurring 6–14 s post-cue onset and dividing by the average model intercept.

Similar to accuracy and response time data, two parallel whole-brain voxel-wise, 2 × 2 × 2 (group (patients with schizophrenia v. healthy controls) × condition (congruent v. incongruent) × frequency (0.33 Hz v. 0.66 Hz)) mixed-measures analysis of covariance (ANCOVAs) were conducted on auditory and visual modalities separately using 3dMVM in AFNI. In this analytic framework, our predictions of increased abnormalities during cognitive control are specifically tested by the group × condition (increased deficits for patients with schizophrenia on incongruent trials) and group × condition × frequency (worse performance under higher cognitive loads) interactions, whereas our prediction of increased difficulty with processing multisensory stimuli is tested by the main effect of group. All voxel-wise results were corrected for false positives at P < 0.05 based on 10 000 Monte-Carlo simulations implemented in AFNI (cluster level = parametric threshold P < 0.005; minimum cluster size 2431 m). Clusters that survived false positive correction but exhibited greater than 75% overlap with a white matter/ventricular exclusion map were also excluded (see online supplemental Methods).

**ARMS analyses**

Individual T1 data were segmented through the FreeSurfer reconstruction pipeline, with regions of interest (ROI) defined by standard labels (see online supplemental Methods). To calculate how unisensory cortex was attentionally modulated in the presence of identical sensory stimulation (ARMs), PSC data were subtracted in the expected direction of positive modulation for auditory (attend-auditory trials – attend-visual trials) and visual (attend-visual trials – attend-auditory trials) cortex for each frequency, collapsing across congruent and incongruent trials. This was followed by 2 × 2 (group × frequency) ANOVAs and
one-sample t-tests to ensure that resulting subtraction maps were not equivalent to the null distribution (see online supplemental Methods). The group × frequency interaction specifically tested the hypothesis that patients with schizophrenia would fail to exhibit ARMs at increasing cognitive loads (faster rate of stimulus presentation). Multivariate analysis of covariance (MANCOVAs) were performed separately for primary and secondary auditory and visual cortex volumes using intracranial volume (ICV) as the covariate.

Results

Demographics and clinical data

There were no significant differences in age between the two groups (P > 0.10). Significant group differences were observed in education (t_{64} = 2.1, P = 0.05) and estimate of pre-morbid intelligence (t_{40.5} = 2.6, P < 0.05), with patients with schizophrenia exhibiting lower estimated intelligence than healthy controls. See Table 1 for remainder of clinical demographics.

Multisensory selective attention task behavioural data

The ranked accuracy data were analysed separately for attend-auditory and attend-visual trials using 2 × 2 × 2 (group [patients with schizophrenia v. healthy controls] × condition [congruent v. incongruent] × frequency [0.33 Hz v. 0.66 Hz]) ANOVAs. There were no significant effects for any factors or interactions in the attend-visual trials. The three-way interaction was significant for the attend-auditory condition (F_{1,64} = 7.9, P < 0.05), with follow-up analyses indicating that patients were less accurate on high-frequency, incongruent trials.

During attend-auditory trials (Fig. 1C), ANOVA results for reaction time data indicated significant main effects of condition (F_{1,64} = 87.7, P < 0.05), frequency (F_{1,64} = 126.7, P < 0.05) and group (F_{1,64} = 6.1, P < 0.05), with faster response times for congruent (548.0 ms (s.d. = 78.4)) relative to incongruent (607.8 ms (s.d. = 106.0)) and high (546.8 ms (s.d. = 85.2)) relative to low (609.0 ms (s.d. = 98.7)) frequency trials. Healthy controls (551.7 ms (s.d. = 73.2)) also responded faster to targets relative to patients with schizophrenia (604.1 ms (s.d. = 97.4)). Non-significant trends were observed for condition × group (F_{1,64} = 2.9, P = 0.096) and frequency × condition (F_{1,64} = 3.1, P = 0.082) interactions. The non-significant condition × group interaction indicated increased slowing for patients with schizophrenia while ignoring auditory stimuli (incongruent–congruent trials 70.6 ms (s.d. = 57.5)) relative to healthy controls (incongruent–congruent trials 49.0 ms (s.d. = 45.6)) beyond general response slowing.

For attend-auditory trials (Fig. 1D), significant main effects of both condition (F_{1,64} = 78.1, P < 0.05) and frequency (F_{1,64} = 107.4, P < 0.05) were noted, with participants responding
Contrary to a priori predictions, neither the group × condition nor the group × condition × frequency interaction was significant. A mixed-measures ANCOVA was performed for the attend-visual condition. Although the main effect of group was also significant (F(1,64) = 6.6, P < 0.05), with patients with schizophrenia (649.5 ms (s.d. = 98.3)) responding more slowly than controls (594.7 ms (s.d. = 73.8)). No interaction effects were significant (P < 0.10).

**Motion parameter analyses**

Two multivariate analyses of variance (MANOVAs) were performed to examine potential group differences in frame-wise displacement for all six motion parameters. Although the main effect of group was not significant for the translational motion MANOVA (P > 0.10), there was a significant effect for the rotational motion MANOVA (F(3,62) = 4.04, P < 0.05), with univariate measures indicating significantly increased motion for patients with schizophrenia (pitch: F(1,64) = 8.29, P < 0.05; yaw: F(1,64) = 7.67, P < 0.05). The utilisation of covariates in the presence of group differences is actively debated, but motion can produce spurious activation. Primary functional analyses were therefore performed with frame-wise displacement as a covariate, whereas analyses without frame-wise displacement are reported in the online supplement. In addition, more aggressive strategies for eliminating individuals with excessive motion were also evaluated (see online supplemental Results).

**Attend-visual fMRI results**

A voxel-wise, 2 × 2 × 2 (group × condition × frequency) mixed-measures ANCOVA was performed for the attend-visual condition. Contrary to a priori predictions, neither the group × condition nor the group × condition × frequency interaction was significant. Regions exhibiting increased activation for incongruent relative to congruent trials (CCN; see online supplement Fig. DS1 for effects collapsed across group and Fig. DS2 for individual group effects) included bilateral dorsal medial prefrontal cortex (Brodmann areas (BA) 6/9/24/32/33), bilateral anterior insula, lateral prefrontal cortex extending into the precentral gyrus (left BAs 4/6/8/9/10/13/44/45/46/47; right BAs 6/9/13/44/45/46/47), bilateral middle and posterior superior temporal gyri/sulci extending into inferior parietal lobule (BAs 13/21/22/39/40), the left posterior parietal cortex (BAs 19/39/40) and left precuneus/posterior cingulate gyrus (BAs 7/31). Increased activation for incongruent trials was also observed within the bilateral thalamus, basal ganglia and midbrain nuclei during the attend-visual condition.

A main effect of group was also present in several cortical regions during attend-visual conditions (Fig. 2). The findings were represented by two primary patterns of patient hyperactivation and potentially failed deactivation, supporting the hypothesis of a generalised deficit in unisensory cortex activation in patients with schizophrenia. Specifically, patient hyperactivation was observed in the right (BAs 13/38/40/43) auditory cortex, as well as left (BAs 2/3/4/9/5/7/40 and right (BAs 2/3/4/5/6/7/40) sensorimotor cortex, posterior parietal cortex and precuneus. For the second pattern, healthy controls exhibited deactivation within right extrastriate primary visual cortex (BAs 18/19/29/30/31), whereas patients with schizophrenia exhibited baseline activity. Finally, healthy controls displayed increased activation in lobules VII and VIII of the left cerebellum relative to patients with schizophrenia. Similar results were obtained when individuals with greater than 0.50 mean frame-wise displacement were excluded from analyses. Additional regions of patient hyperactivation (left auditory cortex) and healthy control deactivation (left visual cortex, para-central lobule and cingulate cortex) were observed when frame-wise displacement was excluded from the model as a covariate (see online supplemental Results; Fig. DS3). Qualitative examination of the HRF indicated both an increased amplitude and duration of response for patients with schizophrenia, with little evidence of a post-undershoot (online Fig. DS4).

Due to null effects and concerns about insufficient power, supplemental analyses were also conducted on the CCN to determine effect sizes. Specifically, regions within the CCN were first identified by comparing the intersection of the within-participant comparisons for the contrast of incongruent v. congruent trials (see online Fig. DS2 for individual group maps). Table 2 indicates

<table>
<thead>
<tr>
<th>Table 1 Summary of participant neuropsychological performance</th>
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<tr>
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<tr>
<td><strong>Patients with schizophrenia</strong></td>
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<tr>
<td>Mean</td>
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<tr>
<td>-------------------------------------------------------------</td>
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<tr>
<td>Demographics</td>
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<td>PANSS negative</td>
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<td>Clinical Global Impression</td>
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<td>FTND</td>
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<td>0.76</td>
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<tr>
<td>SAS</td>
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<td>AIMS</td>
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<tr>
<td>1.58</td>
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<tr>
<td>BAS</td>
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<td>0.24</td>
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<tr>
<th><strong>Healthy controls</strong></th>
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<tbody>
<tr>
<td>Mean</td>
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<tr>
<td>21.91</td>
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<td>1.15</td>
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<td>0.24</td>
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</table>

| a. Education level was determined based on number of years in school. |
| WTAR, Wechsler Test of Adult Reading; PANSS, Positive and Negative Syndrome Scale; UPSA, UCSD Performance Based Skills Assessment; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; FTND, Fagerstrom Test for Nicotine Dependence; SAS, Simpson Angus Scale; AIMS, Abnormal Involuntary Movements Scale; BAS, Barnes Akathisia Scale. |
the regions of common activation across both patients with schizophrenia and healthy controls for this contrast as well as the respective effects sizes. For all regions within the CCN, effect sizes were typically in the small range (range \(0.22\) to \(0.03\)).

The group \(\times\) frequency interaction (see online Fig. DS5) was significant within the culmen and decline bilaterally and the right posterior parietal cortex (BAs 7/40). Simple effects testing indicated a consistent pattern in which patients with schizophrenia exhibited increased activation within both of these regions as a function of stimulus frequency (both \(P < 0.05\)), whereas healthy controls’ levels remained at the same level of activation regardless of stimulation frequency (both \(P > 0.10\)).

The main effect of frequency and other second-order interactions (attend-visual and attend-auditory conditions) are not central to the current paper and are presented in the online supplementary Results.

**Attend-auditory fMRI results**

Similar to the attend-visual results, neither the group \(\times\) condition nor the group \(\times\) condition \(\times\) frequency interaction was significant for attend-auditory trials. There were two different networks that exhibited either increased activation during incongruent trials (CCN) or increased activation during congruent trials (sensory cortices) for attend-auditory trials (see online Fig. DS6 for effects collapsed across group and online Fig. DS7 for individual group effects). Increased activation for incongruent trials was observed in the bilateral anterior insula extending into the ventrolateral prefrontal cortex (BAs 13/45/47), bilateral dorsal medial prefrontal cortex (BAs 24/32) and the left dorsolateral prefrontal cortex/ precentral gyrus (BAs 4/6/9). Increased activation for incongruent trials was also observed in the posterior aspects of the left middle and posterior superior temporal gyrus/sulcus (BAs 21/22/39/40), bilateral basal ganglia, midbrain nuclei and thalamus. In contrast, regions of increased activation during congruent trials included both the bilateral ‘what’ (fusiform, parahippocampal gyri and lingual gyri; BAs 18/19/36/37) and ‘where’ (middle occipital gyri, precuneus and cuneus; BAs 7/18/19/31) visual streams, as well as bilateral secondary auditory cortex extending into the precentral gyrus (BAs 13/43/4/6) and left putamen.

For the main effect of group (Fig. 3), patients exhibited hyperactivation within right secondary auditory cortex (BAs 13/43) and bilateral sensorimotor cortex/posterior parietal cortex (inferior and superior aspects; left BAs 2/5/7/40 and right BAs 1/2/3/4/5/6/7/40) during attend-auditory trials. In contrast, in healthy controls, hyperactivation was observed in the left cerebellum. Results remained unchanged when participants with greater than 0.50 mean frame-wise displacement were excluded from analyses. Similar to the attend-visual condition, additional clusters of patient hyperactivation (left auditory cortex) and healthy control deactivation (paracentral lobule and cingulate gyrus) were observed when frame-wise displacement was eliminated from the model. In addition, there were no differences between groups in the left cerebellum when the covariate was eliminated (online Fig. DS8). Examination of the entire HRF (online Fig. DS9) indicated a similar pattern of abnormalities as in the attend-visual condition (increased response amplitude/duration and no post-undershoot for patients with schizophrenia).
Table 2  Effect sizes for regions of common activation within the CCN

<table>
<thead>
<tr>
<th>Size, µL</th>
<th>Patients with schizophrenia</th>
<th>Healthy controls</th>
<th>Cohen’s $d$</th>
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<tbody>
<tr>
<td>L lPFC</td>
<td>19383</td>
<td>33 (0.094) 0.105</td>
<td>33 (0.121) 0.134</td>
</tr>
<tr>
<td>L pSTS</td>
<td>7121</td>
<td>33 (0.090) 0.100</td>
<td>33 (0.099) 0.120</td>
</tr>
<tr>
<td>R lPFC</td>
<td>2255</td>
<td>33 (0.082) 0.135</td>
<td>33 (0.078) 0.134</td>
</tr>
<tr>
<td>B ACC</td>
<td>1853</td>
<td>33 (0.056) 0.099</td>
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<td>33 (0.121) 0.134</td>
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</table>

ARMS analyses

Results from two MANCOVAs indicated no significant differences in auditory or visual cortical volume between the two groups (both $P_\alpha > 0.10$).

ARMS analyses (2 (group) × 2 (frequency) ANOVAs) indicated trend-level interaction effects within the primary ($F_{1,64} = 3.88, P = 0.053$) and significant interaction effects within the secondary ($F_{1,64} = 4.05, P < 0.05$) visual cortex (Fig. 4A and 4B). Simple effects tests indicated a trend for increased ARMs for patients with schizophrenia relative to healthy controls within primary visual cortex ($t_{64} = −1.73, P = 0.089$), with significantly increased ARMs in secondary visual cortex ($t_{64} = −2.05, P < 0.05$) during high-frequency trials. There were no significant group differences for low frequency trials ($P > 0.10$). However, one-sample $t$-tests indicated that robust ARMs were not present in primary or secondary visual cortex for either group ($P > 0.10$).

As predicted, the group × frequency interaction was statistically significant for primary auditory cortex ($F_{1,64} = 4.09, P < 0.05$), whereas effects were not significant for secondary auditory cortex (Fig. 4C and 4D). Follow-up simple effects testing indicated no significant ($P > 0.10$) group differences in ARMs for low frequency trials (0.33 Hz). In contrast, patients with schizophrenia exhibited significantly decreased ARMs ($t_{64} = 2.09, P < 0.05$) for auditory trials within primary auditory cortex relative to healthy controls during high-frequency trials. One-sample $t$-tests confirmed that positive modulation (i.e. $PSC > 0$) occurred for healthy controls within primary auditory cortex ($t_{64} = 3.15, P < 0.05$) but was absent for patients with schizophrenia ($P > 0.10$) during high-frequency trials. Qualitative examination of secondary auditory cortex (Fig. 4D) also suggested differences in high-frequency trials for patients with schizophrenia relative to healthy controls. One-sample $t$-tests confirmed the presence of ARMs within secondary auditory cortex for healthy controls ($t_{64} = 3.05, P < 0.05$) which were absent for patients with schizophrenia ($P > 0.10$). Collectively, these findings indicate that patients with schizophrenia failed to upregulate unimodal cortical areas at increasing cognitive loads.

Network, behavioural and clinical interactions

Our next series of analyses investigated whether differences in auditory, sensorimotor and posterior parietal cortex were associated with behavioural or clinical findings. Behavioural and functional results indicated a main effect of group, such that data were first averaged across all trials (reaction time and functional activity) and then across voxels (functional data) separately for attend-auditory and attend-visual conditions. Our first set of analyses indicated a positive relationship between reaction time and auditory/parietal activation for both conditions (attend-visual: $r = 0.29, P = 0.02$; attend-auditory: $r = 0.32, P = 0.008$) when all participants were included in analyses. These relationships were not significant when only patients with schizophrenia were examined ($P > 0.10$).
Discussion

The current study investigated whether unisensory cortex, CCN or ARMs would be associated with functional abnormalities during multisensory cognitive control in patients with schizophrenia. Patients had a lower educational attainment and estimate of intelligence, confirming how the typical disease course affects normal activities (e.g. school) and decreases overall cognitive functions. Current behavioural and functional results indicated successful parametric variation of cognitive load, with high-frequency trials resulting in the expected pattern of increased activation within bilateral unisensory (auditory, visual and sensorimotor) cortex and heteromodal cortex (lateral prefrontal and parietal areas), as well as increased posterior default mode network deactivation during both attend-visual and attend-auditory trials. These findings are consistent with previous results and suggest that the higher frequency trials were more attentionally demanding.

Reaction times were also faster for congruent relative to incongruent trials, and incongruent trials resulted in increased activation within the CCN. Activated nodes from the CCN included the dorsal medial prefrontal cortex, lateral prefrontal cortex, anterior insula, striatum, thalamus and posterior parietal cortex. In addition, the posterior superior temporal sulcus, which plays a critical role in audio-visual sensory integration, also showed evidence of increased activation during incongruent trials. However, the magnitude and volume of differential activation (incongruent>congruent trials) appeared greater for attend-auditory relative to attend-auditory condition, suggesting that ignoring auditory distracters may require increased neuronal resources. Activation was also greater for congruent relative to incongruent trials in secondary auditory cortex and primary visual cortex during attend-auditory trials, suggesting that ignoring incongruent visual stimuli did not place additional loads on sensory cortex.

The most pronounced behavioural result was an overall slowing for patients with schizophrenia relative to healthy controls during both attend-auditory and attend-auditory trials, which has been previously observed for patients with schizophrenia during auditory and visual attentional tasks while attempting to ignore auditory distracters. Specific behavioural deficits in cognitive control in patients with schizophrenia were present during both the attend-auditory (i.e. increased error rate for high-frequency incongruent trials) and attend-auditory trials at a trend level (i.e. increased difference in reaction time between incongruent and congruent trials). In contrast, there were no differences in functional activation within the prefrontal nodes of the CCN or thalamus. Importantly, our a priori prediction of cognitive control deficits was tested through an interaction (group x condition), which requires additional statistical power relative to a main effect. Additional analyses indicated small effect sizes between patients with schizophrenia and healthy controls for all major nodes of the CCN, suggesting clinically unmeaningful effects rather than an under-powered sample.

There are several factors which may explain these results. First, recent studies suggest reactive cognitive control tasks such as the Stroop may not be sensitive for revealing deficits in patients with schizophrenia, and that deficits are more likely to emerge during proactive cognitive control tasks (e.g. AX continuous performance task). Similar behavioural (overall slowing with no...
group x condition interaction) and functional (similar levels of activity within the CCN) results were also recently reported in a large cohort of patients with first-episode schizophrenia. However, others have reported deficits during reactive cognitive control tasks, suggesting that future studies should include both reactive and proactive cognitive control tasks to further probe this controversy. Second, the nature (multisensory vs. unisensory) or difficulty level of the current task may have placed differential demands on cognitive resources relative to previous studies, potentially maximising activation within the CCN.

Consistent with a priori predictions and previous results, patients with schizophrenia exhibited hyperactivation in auditory, sensorimotor and posterior parietal cortex during both attend-visual and attend-auditory trials that were associated with the overall pattern of response slowing across both groups. Similar to previous reports, qualitative examination of the HRF indicated both an increased amplitude and duration of response, with little evidence of a post-undershoot for patients with schizophrenia (online Figs. DS4 and DS9). Thus, current results indicate a larger role for dysfunction in unisensory and parietal cortex relative to the prefrontal CCN during multisensory reactive cognitive control. Previous findings on the direction of unisensory cortex abnormalities in patients with schizophrenia have been mixed. Several studies have reported patient hyperactivation in response to a number of different experimental conditions. Hyperactivation of the auditory cortex may be related to either sensory gating or habituation deficits, and hyperactivation for external stimuli has also been associated with a propensity for auditory hallucinations in healthy controls. Others report auditory cortex hypoactivation for external stimuli as a rationale for hallucinations, as part of the paradoxical enhancement effect. Hypoactivation within the lateral prefrontal cortex, fusiform gyrus, temporal-parietal juncture and hippocampus has also been reported during multisensory cognitive control. These contrasting findings may be secondary to the type of multisensory task and the distracters employed, as distracters in the current study were more directly relevant to the task (i.e. members of the target set).

There were no differential effects of increasing stimulus frequency within auditory or visual unisensory cortex between patients with schizophrenia and healthy controls, suggesting that basic neurovascular coupling in response to increasing sensory demands was similar across both groups. Similarly, there were no differences in primary or secondary unisensory cortical volumes between the two groups. In contrast, similar to previous studies in patients and healthy controls, current results indicated that patients with schizophrenia failed to differentially upregulate auditory cortex (ARMs analyses) under higher cognitive loads. The upregulation of unisensory cortex during multisensory tasks may facilitate the suppression of cross-modal distracters or represent a cross-modal spread of alertness. Failure to ‘tune’ auditory cortex under different attentional demands may contribute to impaired performance in patients with schizophrenia across multiple cognitive domains as well as hallucinations. There was minimal evidence of ARMs within primary visual cortex for either healthy controls or patients with schizophrenia, although responses were increased for patients. This may be secondary to the relative lack of difficulty for ignoring visual distracters, or result from involvement of other visual pathways (outside of V1 and V2) during attentional allocation.

There are several limitations to the current study. First, patients exhibited increased head motion relative to healthy controls, and motion parameters were not used as nuisance regressors in level-one analyses per convention in mixed designs. We conservatively focused our discussions on findings that survived analyses with frame-wise displacement as a covariate, although several supplemental analyses indicated that differences in head motion did not likely affect results. Second, previous results have indicated reduced volume in unisensory cortex in patients with schizophrenia, and the influence of volume loss on brain activations was not examined in the current study. Third, our inability to detect clinician-driven dual-tasking may have been restricted by the stability (low-level symptomatology) of patients and/or the chronic nature of psychosis in the current sample. Thus, current results may not generalise to other patient samples (e.g. acutely psychotic).

Fourth, healthy controls were excluded for recent depressive episodes rather than a lifetime history, and depression has been shown to affect activation within the CCN. Fifth, EPI produces auditory background noise secondary to gradient switching that may have differentially affected auditory cortical activity across the two groups. Finally, the full clinical and cognitive battery was not collected on healthy controls due to well-known differences between patients and controls in cognition, smoking and functional outcomes. However, none of these variables were associated with the magnitude of functional activation in the patient cohort. Controls also differed from patients in terms of educational attainment, which is typical for the disease course but may have also contributed to current results.

In summary, current results indicated overall behavioural slowing and functional abnormalities within auditory, sensorimotor/parietal areas during multisensory cognitive control. These behavioural and functional abnormalities were more pronounced while attempting to ignore auditory distracters, with patients also failing to modulate auditory cortex under different attentional demands. Thus, current results suggest that auditory dysfunction may be important for understanding multisensory cognitive control deficits in patients with schizophrenia. Future studies are needed to elucidate whether this issue extends beyond verbal stimuli and whether it can be replicated in unmedicated patients earlier in the disease course.

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Selective Attention in Schizophrenia-Supplement

Online supplement

Methods

Neuropsychological and Clinical Assessment

Hearing was tested with the calibrated finger rub auditory screening test (CALFRAST).\textsuperscript{1} All participants completed the Wechsler Test of Adult Reading (WTAR).\textsuperscript{2} SP completed the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery,\textsuperscript{3,4} Positive and Negative Syndrome Scale (PANSS),\textsuperscript{5} Calgary Depression Scale,\textsuperscript{6} Clinical Global Impression (CGI),\textsuperscript{7} Fagerstrom Test for Nicotine Dependence (FTND),\textsuperscript{8} Abnormal Involuntary Movements Scale (AIMS)\textsuperscript{9} for tardive dyskinesia, a modified version of the Simpson-Angus Scale (SAS)\textsuperscript{10} for parkinsonism, Barnes Akathisia Scale (BAS),\textsuperscript{11} and the UCSD Performance Based Skills Assessment (UPSA-2).\textsuperscript{12}

MR Imaging

All images were collected on a Siemens 3 Tesla Tim Trio. High resolution T1-weighted images were acquired with a 5-echo multi-echo MPRAGE sequence [TE (echo times) = 1.64, 3.5, 5.36, 7.22, 9.08 ms, TR (repetition time) = 2.53 s, TI (inversion time) = 1.2 s, 7° flip angle, number of excitations (NEX) = 1, slice thickness = 1 mm, FOV (field of view) = 256 mm, resolution = 256 x 256]. Echo-planar images (EPI) were collected using a single-shot, gradient-echo echoplanar pulse sequence [TR = 2000 ms; TE = 29 ms; flip angle = 75°; FOV = 240 mm; matrix size = 64 x 64].

The first three images of each run were eliminated to account for T1 equilibrium effects, resulting in a total of 966 images for the final analyses. Thirty-three contiguous sagittal 3.5-mm thick slices with a gap factor of 1.05 mm were selected to provide whole-brain coverage (voxel size: 3.75 x 3.75 x 4.55 mm).
Analyses

Functional images were generated using Analysis of Functional NeuroImages (AFNI) software package\(^\text{13}\) using standard pre-processing steps. Time series images were spatially registered in two- and three-dimensional space to the fourth EPI image of the first run to reduce the effects of head motion, and were temporally interpolated to the first slice to account for differences in slice acquisition. Mean frame-wise displacement was calculated by first converting the 3 rotational motion parameters derived from the rigid body to millimetres using a 50 mm radius sphere.\(^\text{14}\) For each image, the absolute difference of the rotational and displacement motion parameters from the previous image was averaged across all images. Two MANOVAs were conducted to examine group differences in translational and rotational frame-wise displacement. Data were then converted to standard stereotaxic coordinate space\(^\text{15}\) and spatially blurred using a 8 mm Gaussian full-width half-maximum filter.

A white matter and ventricular exclusion mask was derived from a spatially normalized atlas (FS_Desai_PM from AFNI) containing probabilistic maps of 40 ROI originally parcellated by FreeSurfer.\(^\text{16}\) Voxels that exceeded 80\% probability of being in white matter or the ventricles (with the exception of 5\(^{\text{th}}\) ventricle) were first selected to form a template mask, which was then dilated and eroded by 2 mm to fill small holes and smooth edges.

**ARMS Analyses**

Individual subject T\(_1\) data were first segmented through the standard FreeSurfer reconstruction pipeline (version 5.1). The output was visually inspected to confirm accuracy of registration, surface reconstruction, and segmentation. Regions of interest (ROI) were defined by standard FreeSurfer labels available in the Destrieux atlas.\(^\text{17}\) Primary (Heschl’s gyrus) and secondary (planum temporale, Heschl’s sulcus, planum polare, and superior temporal gyrus)
auditory cortex were defined on the basis of a previous publication.\textsuperscript{17} Visual cortex was defined using standard FreeSurfer labels drawn from multiple previous publications.\textsuperscript{18,19} Our primary visual cortex parcellation was defined as the V1 label\textsuperscript{18} with areas shared by the V2 label\textsuperscript{19} removed. For our secondary visual cortex label, we used the entire area identified by Fischl et al.’s V2.\textsuperscript{19}

One sample t-tests were first conducted on the resulting distributions to ensure that each ARM was different from the null distribution, which represents a more robust metric for quantifying ARMs. A series of four 2 x 2 ANOVAs were conducted to examine a priori predictions of decreased ARMs for SP at higher frequencies of stimulation. Two SP were extreme outliers for secondary auditory cortex data and were therefore removed from this particular analysis.

**Results**

*Additional Analyses Examining the Effects of Head Motion on Functional Results*

Patients exhibited increased head motion relative to HC, and frame-wise displacement was not used as a nuisance regressor in level-one analyses (on individual subject level) per convention in mixed designs.\textsuperscript{20} We therefore conservatively focused our primary findings and discussion section on results that survived analyses with frame-wise displacement as a covariate in the full model. However, the use of covariates must be carefully considered for any analyses in which 1) the covariates are significantly different between the groups or 2) where the difference in the covariate is believed to inherently be part of the grouping variable (i.e., disease process). Classic examples of covariates that meet both of these criteria include increased levels of anxiety in depressive disorders and decreased IQ in schizophrenia.\textsuperscript{21} As HC and SP differed in
frame-wise displacement in the current study, we repeated all functional analyses without the use of frame-wise displacement as a covariate.

For attend-visual trials, a comparison of the main effect of group from the analytic models that either included (Figure 2) or excluded (see SF 3) frame-wise displacement yielded additional regions of patient hyperactivation within the left auditory cortex, precentral gyrus (BAs 6) and postcentral gyrus (BA 43). In addition, the left lingual gyrus (BAs 18, 19), right paracentral lobule and precuneus (BAs 5,7,31) were also significant, with follow-up analyses indicating that deactivation for HC and baseline activity for SP. A comparison of the group by frequency interaction indicated a significant cluster in the bilateral cerebellum when frame-wise displacement was included in the model relative to a cluster in the right insula extending into the basal ganglia when this term was not included.

For the attend-auditory ANCOVA, additional regions of SP hyperactivation were observed within left secondary auditory cortex (BA 13), left postcentral gyrus and left inferior parietal lobule when frame-wise displacement was not used as a covariate (see SF 8). Increased deactivation for HC was observed within right precuneus, bilateral paracentral lobule (BAs 7,31). The cluster of activation in the left pyramid and cerebellar tonsil of the cerebellum was no longer significant.

Previous studies\textsuperscript{14,22} have proposed that participants with excessive motion should be eliminated from analyses. To further reduce the likelihood that current results were secondary to group differences in head motion, an additional 3 HC and 9 SP with greater than 0.50 mean frame-wise displacement were removed from analyses. MANOVAs comparing head motion parameters were not significant in this reduced cohort ($p > 0.10$). fMRI analyses were also repeated for the reduced cohort, with and without frame-wise displacement as a covariate. Our
primary results (i.e., main effect of group) for the reduced group were similar to results with the full cohort currently reported as primary analyses. Results from the Group x Condition interaction also remained negative in the reduced cohort, suggesting that the use of alternative strategies for reducing motion did not significantly affect current results.

**Main Effect of Frequency and Second-Order Interactions**

The main effects of frequency were in the expected direction (0.66 Hz > 0.33 Hz) and similar for both the attend-visual and attend-auditory trials (see SF 10-12). Briefly, increased activation was observed bilaterally for higher frequency trials within primary and secondary auditory/visual cortex, pre-supplementary and supplementary motor areas, ventrolateral and dorsolateral prefrontal cortex, posterior parietal cortex, thalamus, basal ganglia and bilateral cerebellum (Lobules IV-VII) across both the attend-visual and attend-auditory conditions. More lateralized motor-related activity was also observed in the left sensori-motor cortex and right cerebellum (lobule IX). In addition, increased deactivation was observed within the posterior cingulate gyrus/precuneus (attend-visual trials), left hippocampus (attend-auditory trials) and paracentral lobule (attend-auditory trials) during the high frequency trials.

During attend-visual trials, the condition by frequency interaction was also significant in the right cerebellum (Lobules VIII and VII) for the attend-visual condition, with simple effects testing indicating higher activation for incongruent trials during high ($t_{1,65} = -4.75, p < 0.05$) but not low ($p > 0.10$) frequency stimulation.

The ANOVA for attend-auditory trials also found a significant condition by frequency interaction within the bilateral temporoparietal junction (BAs 19/39/40), driven primarily by increased activation during low relative to high frequency incongruent trials (right: $t_{1,65} = 5.98, p < 0.05$; left: $t_{1,65} = 5.41, p < 0.05$).
Selective Attention in Schizophrenia - Supplement

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Fig. DS1: This figure presents regions of the brain showing increased activation for incongruent (IT; warm colors) trials relative to congruent (CT; cool colors) trials during the attend-visual (AV) condition (Panel A). Locations of the sagittal (X) and axial (Z) slices are given according to the Talairach atlas for the left (L) and right (R) hemispheres. Panel B presents the box-and-whisker plots for the mean percent signal change (PSC) for selected regions of interest including bilateral posterior superior temporal gyri (pSTS), bilateral anterior cingulate gyrus (ACC), bilateral pre-supplementary motor area (p-SMA) and bilateral ventrolateral and dorsolateral prefrontal cortex (VLPFC+).
Fig. DS2: This figure presents clusters with significant activation differences between incongruent and congruent trials in the attend-visual (AV) condition. Clusters are presented separately for healthy controls (HC) and patients with schizophrenia (SP) in select axial slices. Clusters are shown in red ($p < 0.005$) and yellow ($p < 0.001$) where activation is greater in incongruent relative to congruent trials and in blue ($p < 0.005$) and cyan ($p < 0.001$) where activation is greater in congruent relative to incongruent trials.
**Fig. DS3:** Panel A displays the regions of the brain showing significant group differences between patients with schizophrenia (SP = warm colors) and healthy control (HC = cool colors) during the attend-visual (AV) condition when mean frame-wise displacement is excluded as a covariate in analysis. Locations of the sagittal (X) and axial (Z) slices are given according to the Talairach atlas for the left (L) and right (R) hemispheres. Panel B displays box-and-whisker plots of the mean percent signal change (PSC) for selected regions of interest. SP showed increased activation relative to HC within the bilateral auditory cortex (Aud), sensorimotor cortex (Sen) extending into the posterior parietal lobule, and precuneus (PrCu). HC also exhibited deactivation within extrastriate visual cortex (Vis) and paracentral lobule (Par), which was largely absent in SP.
Fig. DS4: This figure presents percent signal change (PSC) data for the entire hemodynamic response function (22-second post-stimulus interval) for patients with schizophrenia (SP = red trace) and healthy controls (HC = blue trace). Panel labels (Sen: sensorimotor cortex; PrCu: precuneus; Aud: auditory cortex; Vis: visual cortex; Cbm: cerebellum) correspond to regions that showed a main effect of group in the attend-visual (AV) condition (see Figure 2). Note that scaling is variable across regions. Error bars are based on the standard error of the mean for each image. The grey drop lines indicate the images that were used to measure the peak hemodynamic response.
**Fig. DS5:** Both the right posterior parietal cortex (PPC) and cerebellum (Cbm) exhibited a significant Group x Frequency interaction during the attend-visual (AV) condition (Panel A). The magnitudes of p-values are denoted by red or yellow coloring, and axial slice locations (Z) are given according to the Talairach atlas for both left (L) and right (R) hemispheres. Box-and-whisker plots of the mean percent signal change (PSC) data are presented for both the PPC and Cbm regions for healthy controls (HC = blue) and patients with schizophrenia (SP = red) at 0.33 and 0.66 Hz stimulation frequencies. Asterisk indicates a significant group difference (SP > HC; p < 0.05) present at 0.66 Hz stimulus frequency.
**Fig. DS6:** During the attend-auditory (AA) condition, there were differential patterns of increased activation for either incongruent (IT; warm colors) or congruent (CT; cool colors) trials (Panel A). Locations of the sagittal (X) and axial (Z) slices are given according to the Talairach atlas for the left (L) and right (R) hemispheres. Panel B presents the box-and-whisker plots for the mean percent signal change (PSC) for selected regions of interest, which generally fell into two different patterns. In the first pattern (top row of Panel B), increased activation was observed within bilateral posterior superior temporal gyri (pSTS), bilateral anterior cingulate gyrus (ACC) and bilateral ventrolateral prefrontal cortex (VLPFC+) for IT relative to CT trials. In the second pattern (Panel B: bottom row), increased activation was observed for CT relative to IT trials within extrastriate visual (Vis) and secondary auditory (Aud) cortex.
**Fig. DS7:** This figure presents clusters with significant activation differences between incongruent and congruent trials in the attend-auditory (AA) condition. Clusters are presented separately for healthy controls (HC) and patients with schizophrenia (SP) in select axial slices. Clusters are shown in red ($p < 0.005$) and yellow ($p < 0.001$) where activation is greater for incongruent relative to congruent trials and in blue ($p < 0.005$) and cyan ($p < 0.001$) where activation is greater in congruent relative to incongruent trials.
**Fig. DS8:** Panel A displays the regions of the brain showing significant group differences between patients with schizophrenia (SP = warm colors) and healthy controls (HC = cool colors) during the attend-auditory (AA) condition when mean frame-wise displacement is excluded as a covariate in analysis. Locations of the sagittal (X) and axial (Z) slices are given according to the Talairach atlas for the left (L) and right (R) hemispheres. Panel B presents the box-and-whisker plots for the mean percent signal change (PSC) for selected regions of interest. Increased activation for SP relative to HC was observed within bilateral auditory cortex (Aud), sensorimotor cortex (Sen) extending into the posterior parietal lobule, and right precuneus (PrCu). HC tended to exhibit more deactivation within paracentral lobule (Par) relative to SP.
**Fig DS9:** This figure presents percent signal change (PSC) data for the entire hemodynamic response function (22-second post-stimulus interval) for patients with schizophrenia (SP = red trace) and healthy controls (HC = blue trace). Panel labels (Sen: sensorimotor cortex; PrCu: precuneus; Aud: auditory cortex; Cbm: cerebellum) correspond to regions that showed a main effect of group in the attend-auditory (AA) condition (see Figure 3). Note that scaling is variable across regions. Error bars are based on the standard error of the mean for each image. The grey drop lines indicate the images that were used to measure the peak hemodynamic response.
**Fig. DS10:** This figure displays the brain regions showing significant differences in activation between the low (0.33 Hz: blue/cyan) and high (0.66 Hz = red/yellow) frequency of stimulation trials during the attend-visual (AV; Panel A) and attend-auditory (AA; Panel B) conditions. Locations of the sagittal (X) and axial (Z) slices are given according to the Talairach atlas. Higher frequency trials resulted in increased activation within auditory (Aud), visual (Vis) and sensorimotor (Sen) cortex, as well as supplementary motor areas (SMA), cerebellum and heteromodal cortical areas. Increased deactivation was observed during the high frequency trials within the posterior cingulate gyrus/precuneus (PCC; AV trials), left hippocampus (AA trials) and paracentral lobule (Par; AA trials).
**A) AV: Frequency Effect Within Each Group**

![Brain images](image)

**Fig. DS11:** This figure presents clusters with significant activation differences between low and high frequency trials in the attend-visual (AV) condition. Clusters are presented separately for healthy controls (HC) and patients with schizophrenia (SP) in select axial slices. Clusters are shown in red ($p < 0.005$) and yellow ($p < 0.001$) where activation is greater in high relative to low frequency trials and in blue ($p < 0.005$) and cyan ($p < 0.001$) where activation is greater in low relative to high frequency trials.
**A) AA: Frequency Effect Within Each Group**

![Image showing brain slices with significant activation differences between low and high frequency trials in the attend-auditory (AA) condition. Clusters are presented separately for healthy controls (HC) and patients with schizophrenia (SP) in select axial slices. Clusters are shown in red ($p < 0.005$) and yellow ($p < 0.001$) where activation is greater in high relative to low frequency trials and in blue ($p < 0.005$) and cyan ($p < 0.001$) where activation is greater in low relative to high frequency trials.]

**Fig. DS12:** This figure presents clusters with significant activation differences between low and high frequency trials in the attend-auditory (AA) condition. Clusters are presented separately for healthy controls (HC) and patients with schizophrenia (SP) in select axial slices. Clusters are shown in red ($p < 0.005$) and yellow ($p < 0.001$) where activation is greater in high relative to low frequency trials and in blue ($p < 0.005$) and cyan ($p < 0.001$) where activation is greater in low relative to high frequency trials.
An fMRI study of multimodal selective attention in schizophrenia
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