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Methods

Clinical Measures

All participants completed the Wechsler Test of Adult Reading (WTAR) as an estimate of premorbid intelligence. SP also completed urine drug screening and a battery of other neuropsychological tests including the Measurement and Treatment Research to Improve Cognition in Schizophrenia battery (MATRICS), Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale, Clinical Global Impression (CGI), Fagerstrom Test for Nicotine Dependence (FTND), Abnormal Involuntary Movements Scale (AIMS) for tardive dyskinesia, a modified version of the Simpson-Angus Scale (SAS) for parkinsonism, Barnes Akathisia Scale (BAS) and the UCSD Performance Based Skills Assessment test (UPSA-2).

MR Imaging

All images were collected on a 3 Tesla Siemens 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]. 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).
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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 for task data and 149 images for connectivity data. Motion correction, slice timing correction, smoothing and spatial normalization were performed for both task and resting state data. Data were then blurred with either an 8 (task) or 6 (rest) mm full-width at half-max Gaussian kernel.

Results

The main effect of Frequency (Supplementary Figure S1) was significant within the primary and secondary auditory cortex, primary and secondary visual cortex, the bilateral paracentral lobule, basal ganglia, cerebellum and left posterior parietal cortex, with increased activation for high relative to low frequency trials. A main effect of Frequency was also observed within the bilateral medial/superior frontal gyri, the left posterior cingulate gyrus and the left angular gyrus extending into the precuneus, but this was primarily driven by greater deactivation during the low frequency trials.

Finally, the Frequency by Congruency (Supplementary Figure S2) interaction was significant in the bilateral medial and superior frontal gyrus (BA 8) as well as the right middle temporal gyrus (BAs 20/21/38). Simple effects testing in the bilateral superior frontal gyrus indicated deactivation for incongruent trials at the lower frequency trials coupled with activation at the higher frequency trials ($p < 0.05$), with no effect of frequency for congruent trials ($p > 0.10$). In the right middle temporal gyrus, there was activation for congruent trials at low
frequency trials coupled with deactivation at high frequency trials \((p < 0.05)\), whereas this pattern was reversed for incongruent trials \((p < 0.05)\).

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References


### Supplementary Table 1: Single regression of clinical variables with SMC activation.

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<th>Measure</th>
<th>Left SMC</th>
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<th>Right SMC</th>
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<tr>
<td></td>
<td>Pearson’s r</td>
<td>t</td>
<td>p</td>
<td>Pearson’s r</td>
<td>t</td>
<td>p</td>
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<td>Olanzapine equivalent</td>
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</table>

Notes: SMC = Sensorimotor cortex; FTND = Fagerstrom Test for Nicotine Dependence; SAS = Simpson Angus Scale; AIMS = Abnormal Involuntary Movements Scale; BAS = Barnes Akathisia Scale.
Figure S1: This figure presents regions with increased activation during high (0.66 Hz) relative to low (0.33 Hz) frequency trials. Selected axial (Z) slices are displayed at 4 mm intervals according to the Talairach atlas. Red (p < 0.005) and yellow (p < 0.001) coloring are used to denote the magnitude of the voxel-wise p values. There were no regions that exhibited increased activation for low frequency trials.

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Figure S2: Panel A displays regions that exhibited a significant interaction between congruency (CON) and frequency (FRQ). The location of the sagittal cutaway is provided according to the Talairach atlas. Panels B and C display box-and-whisker plots of the average percent signal change (PSC) for both low (0.33 Hz; white) and high (0.66 Hz; grey) trials. In bilateral superior frontal gyrus (B SFG), the interaction resulted from deactivation for lower relative to higher frequency stimulation during incongruent trials (IT) only. The relationship between low and high frequency trials was significantly inverted for incongruent (IT; 0.66 Hz > 0.33 Hz trials) relative to congruent (CT; 0.33 Hz > 0.66 Hz trials) within the right middle temporal gyrus (R MTG). Brackets and asterisks indicate a significant difference between specified contrasts (p < 0.05).