Author's response to reviews

Title: Functional Abnormalities in the Cortical Processing of Sound Complexity and Musical Consonance in Schizophrenia: Evidence from an Evoked Potential study

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Author's response to reviews: see over
A. RESPONSES TO THE COMMENTS OF THE REVIEWERS

Reviewer #1 (Comments to Author):

The manuscript reports on the brain responses in health and schizophrenia evoked by chords and intervals. Using these types of stimuli is relatively new, and the manuscript adds to the body of knowledge concerning processing of auditory stimuli. The manuscript falls somewhat short in the presentation of the methods and the results, and my concerns are outlined below.

Comment 1: The authors imply that auditory EP abnormalities are confined to P50 and P300 (Introduction, and Discussion). However, there is a sizeable body of research showing that N100 and P200 abnormalities exist in schizophrenia (see for example Hu et al., Clin EEG and Neuroscience 43(1) 23-31, 2012 and references therein).

Response: We thank the Reviewer for raising this issue. As indicated by the Reviewer, numerous studies have reported that patients with schizophrenia have a reduction of P300 and gating deficit of P50. In addition, there is also evidence for a gating deficit in the N100 and P200 range. As suggested, we have added the findings of these studies, modified the Introduction and cited these studies in our revised manuscript accordingly. Please refer the yellow highlighted sections on Pages 3 and the cited references #12, #13 and #14).

Comment 2: Schizophrenia is a wide spectrum disorder, and it would be helpful to further specify the nature of the disease in the population studied.

Response: Schizophrenia is a catastrophic psychiatric disorder involving chronic or recurrent psychosis. It is indeed associated with wide spectrum of clinical manifestations. As suggested by the Reviewer, We have added the description about the nature of the disease into the revised Introduction section. (Please refer the yellow highlighted section on Page 3).

Comment 3: How many trials remained for each of the stimulus categories/ channels/ populations after artifact removal? Also, using a 100 micro Volt artifact rejection level is rather high.

Response: A typical adult human EEG signal is about 10µV to 100 µV in amplitude when measured from the scalp (Aurlien, 2004 #1). In this study, we set HEOG and VEOG electrodes to record EOG signal, then set 100mv as rejection level to detect eye artifact (includes eye blinks, eye movements and extra-ocular muscle activity), and remove trials .It is an EEG signal standardization processing before ERP analysis (Croft, 2000 #2; Semlitsch,
After artifact rejection, there has saved 5467 trails in health people, 5729 trails in schizophrenia, both over 70% (total 7500) saved.

Cited references:

Comment 4: It is unclear how the N1 and P2 amplitudes have been defined. Are they measured from baseline or from preceding peak? Also, the 100-150ms in which the authors searched for N1 is rather late and may cause some N1 components to be missed or incorrectly identified.

Response: N1 and P2 are indicating the first large negative amplitude and second large positive amplitude after onset of stimulus. N1 is also known as N100~N180, and P2 is known as P180~P280 (Luck, 2005 #4). And in this study, due to different subjects and event, we find the N1’s latency range is located between 100~150ms, and 180~250ms in P2.

Cited references:

Comment 5: The statistical analysis may not be optimal. It seems that a three factor ANOVA (repeated measures), using population, stimulus type, and EEG channel as factors, or three (one for each EEG channel) two-factor ANOVAS (population and stimulus type) should be performed for N1 and P2 separately. However it seems that a large number of one-factor ANOVAs were done without apparent correction for multiple testing. Also, one would expect to see F-statistics, with degrees of freedom, and some tests to show sphericity of the data (or to correct for the lack of sphericity).

Response: As suggested by the Reviewer, we conducted a three-way analysis of variance (ANOVAs) to rework the statistical analyses. Repeated-measures ANOVAs were used to evaluate the group effects with group (patients/controls) as a between-subjects factor, and stimulus type (perfect fifth, tritone, major triads, diminished triads and atonal chords) and region (each EEG channel) as within-subjects factors. Separate ANOVAs were conducted for N1 and P2. The results showed there were no significant interactions in group × stimulus ×
region (F(2,104)=1.20, p=0.084) and group × stimulus ( F(1,104)=1.95, p=0.109 )
corresponding to N1 component. We also cannot find significant interactions in group ×
stimulus although there were significant interactions in group × stimulus × region
(F(2,104)=1.32, p=0.017) corresponding to P2. However, we found significant interactions in
group × region for each music stimulus (perfect fifth (F(1,26)=4.54, p<0.001), tritone
(F(1,26)=2.504, p<0.001), major triads (F(1,26)=4.72, p<0.001), diminished triads
(F(1,26)=1.96, p=0.003) and atonal chords (F(1,26)=2.37, p<0.001)). Further post-hoc
analyses showed the number of EEG channels which could detect the significant difference
between patients and controls were observed to be greatest for major triads and lowest for
atonal triads. This finding demonstrated consonant sounds might cause the more number of
EEG channel to detect the difference between two groups than dissonant sounds. Because the
N1 and P2 amplitudes presented the largest values at the frontocentral sites and appeared
equally present at electrode sites over each hemisphere based on topographical analysis, we
performed one-way ANOVA for the anterior (Fz electrode), central (Cz), and posterior (Pz)
sites to analyze the effects of chord and interval stimuli on the amplitudes of the N1 and P2
components.

**Comment 6:** The significance levels of a number of the differences are rather low (5%) but
the text uses rather broad language to describe the significance.

**Response:** This study showed that schizophrenic patients exhibited significant reductions in
the amplitudes of the N1 and P2 components elicited by musical stimuli, to which consonant
sounds contributed more significantly than dissonant sounds. Schizophrenic patients could
not perceive the dissimilarity between interval and chord stimuli as compared with the
healthy controls. Statistical significance was set at the level of p < 0.05.

**Comment 7:** I do not understand what Figure 4 shows. The text and caption mention
'difference in the reduction of the P2 amplitude' but there is no exposition on how this was
computed.

**Response:** Schizophrenic patients exhibited significant reductions in the amplitudes of the
N1 and P2 components elicited by both chord and interval stimuli. We then conducted
separate analyses of reductions in amplitudes for intervals (perfect fifth and tritone) and
chords (major triads, diminished triads and atonal chords) respectively. The results showed
the greater reductions in the P2 amplitude elicited by intervals were caused by perfect fifth
intervals than tritons; the reductions in the N1 and P2 amplitudes elicited by chords were
observed to be greatest for major triads and lowest for atonal triads. Namely, the reductions in
amplitude were greater for consonant sounds than dissonant sounds regardless of intervals or
cords. This may reflect a basic deficit in auditory processing of sound consonance in schizophrenia. Figure 4 represented difference in reduction of P2 amplitude evoked by different intervals or chords in schizophrenic patients.
Reviewer #2 (Comments to Author):

**Comment 1:** Functional and structural differences in the temporal lobes – especially the STG - have been well demonstrated in the brains of people with schizophrenia, and are hypothesised to at least partially underlie pathophysiological processes such as auditory verbal hallucinations. Less work has explored specific perceptual differences between those with schizophrenia and healthy controls in the processing of musical sounds. This work looked at evoked auditory potentials in response to intervals and chords of varying complexity and demonstrated abnormalities of processing in those (n=12) with schizophrenia, particularly to consonant (as opposed to dissonant) sounds, compared to matched controls.

Pathophysiology of the temporal lobes and STG are well established findings, including P3 amplitude in evoked potential studies. There is novelty to this study insofar as most electrophysiology studies focus on modestly simple sound paradigms rather than the complexity of full musical chords.

Given the task explores complex tonal and pitch variations in music it would be interesting for future work to compare participants that do not speak a tonal language such as the Chinese languages, though this was not the task of this piece of research, especially as prosodic differences between those speaking tonal and non-tonal languages has previously been demonstrated.

The task paradigm appears reasonable for the authors’ stated aims, with a well-defined question and appropriate methodology. The results appears statistically sound.

The results demonstrate abnormalities in N1 and P2 amplitudes. However the N1 abnormality is a reasonably well-established finding, albeit in typically more simplistic acoustic paradigms, and the study’s main strength is the use of a more complex test paradigm in adding to the existing data on temporal lobe deficits in those with schizophrenia.

My major comment is that the study might not be of broad enough interest to the readership of the journal BMC Psychiatry and better suited to a more neuroscience-based journal.

**Response:** We appreciate your comments.