Author's response to reviews

Title: Reduced Duration Mismatch Negativity in Adolescents with Psychotic Symptoms: further evidence for Mismatch Negativity as a possible biomarker for vulnerability to psychosis

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Author's response to reviews: see over
To the Editor,

Please find the changes outlined below as requested by the reviewers.

Kind regards,

Dr. Jennifer Murphy

*Note to the Reviewers: Two authors have been included in this manuscript as it was decided that their respective contributions warranted inclusion as authors. Also, the contributions made by Dr. Kristin Laurens to the task design has been acknowledged in the acknowledgements section of the manuscript.

Reviewer’s report: Patrik Roser

p. 4, l. 24: The abbreviation “PLE” should be preceded by its full name.

   The term “Psychotic-like experiences” or “PLE” has been replaced by the term “psychotic symptoms” when referring to the experiences reported by the participants in our study.

p. 6, l. 15: Interestingly, the participants had no family history of psychotic illness. Was this an exclusion criterion? (Subjects with positive family history and psychotic-like experiences would represent a sample at an even higher risk of psychosis and might possibly demonstrate more pronounced MMN deficits.)

   Although this was not an exclusion criterion, none of the participants in this study sample had a family history of psychotic illness.

p. 6, l. 20: A more detailed introduction into the K-SADS-PL would be helpful for those readers that are not familiar with this measure of psychotic symptoms. How were the statements of the participants and their parents handled in the case of any discrepancy?

   The following more detailed introduction to the K-SADS-PL has now been included in the manuscript: “The K-SADS-PL is designed to measure the severity of symptomatology reported by children and adolescents, and to assess current and past episodes of psychopathology according to DSM-III-R
and DSM-IV criteria.”
The K-SADS-PL manual describes that in the case of discrepancies between parents' and child's reports, the most frequent disagreements occur in the items dealing with subjective phenomena where the parent does not know, but the child is very definite about the presence or absence of certain symptoms. This is particularly true for items like guilt, hopelessness, interrupted sleep, hallucinations, and suicidal ideation. If the disagreements relate to observable behavior (e.g. truancy, fire setting, or a compulsive ritual), the examiner should query the parent(s) and child about the discrepant information. If the disagreement is not resolved, it is helpful to see the parent(s) and child together to discuss the reasons for the disagreement.
(Source: http://www.psychiatry.pitt.edu/research/tools-research/ksads-pl)

p. 7, l. 2: The authors state that the participants' psychotic symptoms have been assessed with regard to hallucinations and delusions. These are quite severe positive symptoms. Some more information on the psychotic symptomatology would be helpful to interpret the results. Have the authors also assessed more subtle psychotic as well as affective and neurocognitive symptoms? How have psychotic symptoms been defined? How was their appearance in terms of severity, duration and frequency?

• The most commonly reported psychotic symptoms in the K-SADS interview were auditory hallucinations, which were accompanied by some form of delusional beliefs. Auditory hallucinations that were deemed as clinically significant included voices commenting on behaviour, a voice giving commands, voices conversing, whispering voices and voices at varying volumes where the words cannot clearly be distinguished by the individual. Examples of non-clinically significant auditory hallucinations included hearing your thoughts aloud, hearing your name being called when no-one has called it, hearing the doorbell or the telephone ring while the TV or radio are playing, and hearing footsteps or knocking. These symptoms became clinically significant when they caused distress or were accompanied by delusional ideation. Clinically significant delusions included feelings of being watched, unfounded ideas that others are saying negative things about the individual (which are distinguished from paranoia and self-consciousness), and a belief that ghost is communicating directly with the individual. Non-clinically significant delusions included beliefs that one can read minds or can predict the future, a strong belief that the world is going to end or a persistent feeling that something strange is going on. The clinically significant examples of hallucinations and delusions are now included on page 8.

• A consensus meeting was held between three raters (i.e. two psychiatrists and one psychologist) to evaluate the interview data. The raters examined the psychosis section of the K-SADS for each participant but did not review any other data and were also blind to any psychiatric diagnoses.
Based on the clinical judgment of the three raters, participants were classified as having psychotic symptoms or not.

- The symptoms were quantified in terms of severity, duration and frequency on the K-SADS interview schedule. When first reported, the interviewer probed to identify the initial onset of the symptom, if it occurred in the past and/or in the present, how often it occurred, how long it lasted for and the strength of the participant’s conviction of the reality of the symptoms reported. The symptoms were rated on a scale of 0-3 with 0 indicating no information, 1 indicating no symptoms present, 2 as subthreshold (likely or suspected) and 3 as threshold (definitely present). When a score of 3 was obtained, a supplement which further probed the different types of hallucinations and delusions.

p. 7, l. 9: The auditory stimuli were presented through the computer speakers at 80 dB. What was the rationale for not using headphones in order to reduce ambient noise and to keep the experimental stimulation set-ups and the SPL at a constant level?

The participants were seated in a sound proof, electrically shielded cubicle which reduced external environmental noise. The SPL was measured with a sound level device to ensure that the auditory stimuli was the same for all participants.

Table 1: Just a small comment on the footnote: the authors presumably mean “microvolts” instead of “millivolts”.
This error has been changed in Table 1.

Table 2: The authors included right- and left-handed participants in the study. Could they give a short statement on this aspect as they included laterality as a within-group factor to their ANOVA?

- The ‘laterality’ within group factor referred to the position or location of the electrodes on the scalp as opposed to controlling for left and right handed participants in the ANOVA. The purpose of including handedness in the table was to ensure that the two experimental groups were completely matched.

- The statistical analysis was based on the paper from Michie et al (2002) where the MMN was examined in biological relatives of patients with schizophrenia. The analysis in this paper included ‘laterality’ as a within-group factor (left, midline, right). As few studies had examined the MMN in high-risk groups, we decided to use the same statistical analysis procedure as this paper.
Reviewer’s Report: Margaret Niznikiewicz

1. In the Introduction, the authors discuss MMN as being elicited independent of attention and then go on to say that its generators form a network subserving change detection and attentional switching – at the very least this is inconsistent. Furthermore, it actually is not true that MMN is free of attentional influences – thus, the statement that its generators belong to attention switching network is correct, but the idea that it is free of attentional influences is not – please rephrase that.

   - The description of the MMN has been altered as follows: “MMN tasks are usually passive and undemanding, and the MMN can be elicited without the participant consciously attending to the auditory stimuli.”

2. Please explain what PLE acronym refers to.

   - The PLE acronym which refers to “psychotic-like experience” has been replaced by psychotic symptoms throughout the manuscript when referring to the experiences reported by the participants in this study.

3. It is rather unfortunate that no task other than looking at a fixation point was used – in a long, passive paradigm like MMN people’s minds wonder and it is a good idea to have them do some kind of uniform task that will not engage their all attentional resources, or the MMN will be drastically reduced.
• It is unfortunate that there was no distracter task used in this study. Due to the relatively short duration of this task, we did not feel it was necessary to provide a distracter task but this is a good point and we will consider this in the future when examining the MMN.

4. When one defines the latency measurement, it is a good idea to say something like: latency was defined as the most negative data point within the x-y msec latency.

• This statement has replaced the previous definition of latency on page 10 of the manuscript.

5. In the statistical section, I would like to see a list of electrodes that went into each factor; from what I read, and I may be wrong – which is why I would like to have the electrodes listed as a function of a factor – some electrodes were entered twice into analysis which is incorrect. I actually quite believe that there was a real reduction in the MMN amplitude but it would be better to arrive at that conclusion with correct stats.

• The statistical analyses in this paper were based on the analysis described in Michie et al (2002) to allow for comparisons across at-risk sample studies. The 2x3x4 mixed factorial statistical analysis of variance of MMN amplitude and latency included “group” (at-risk, control subjects) as the between groups factor and “laterality” (left, right, midline) and “region” (frontal-polar, frontal, frontocentral, central) served as the repeated measures factors. Each electrode was entered once into each factor. Therefore, the factor “region” included the electrodes that belonged to each region (i.e. fp1, fpz, fp2 were included in the frontal-polar region when grouped together in this way for analysis) and it was also possible to group the electrodes according to laterality where, for example, electrodes fp1, f1, fc1 and c3 could be grouped together.

6. The authors found an impaired MMN and an unimpaired P3a. They conclude that this is evidence for disconnection hypothesis – it is not. The fact that one component is impaired and the other is not does not suggest disconnection – it suggests that one brain mechanism – that related to early sensory analyses and passive comparisons between a memory template and sensory evidence is abnormal, while the other mechanism seems to be intact. The evidence that the authors cite for disconnection hypothesis from other authors indeed suggests that disconnection is one of the possible pathological changes in schizophrenia, but it has very little to do with the findings of this paper – please either omit or substantially change that argument.
The section describing the disconnection hypothesis has been omitted and has been replaced with the following section: “P3a amplitude or latency was unaffected in the at-risk group as no group differences were found for this component. Impairments in MMN accompanied by an unaffected P3a may suggest a subtle disruption in the initial automatic detection of change in the auditory environment that is not sufficiently impaired to affect the subsequent attention orienting response.”

7. A minor point – page 12:.. the ability to redirect attention to the novel stimulus .. is not due to the presence of a normal P3a – it is evidenced, or indexed by the a normal P3a.

• This statement has been removed from the manuscript.

8. Finally, as authors point out, it is not clear what relevance these findings have to the future development, or not, of a clinical psychosis, and future studies with larger samples that are longitudinally followed will need to address this issue.