Schizophrenia Research 191 (2018) 95–100

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Impaired mismatch negativity to frequency deviants in individuals at ultra-high risk for psychosis, and preliminary evidence for further impairment with transition to psychosis

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ARTICLE INFO

Article history:
Received 11 July 2017
Received in revised form 1 November 2017
Accepted 1 November 2017
Available online 11 November 2017

Keywords:
Event-related potential (ERP)
Transition
Psychosis
Ultra high risk (UHR)
Mismatch negativity (MMN)

ABSTRACT

Background: There is evidence to suggest that people with established psychotic disorders show impairments in the mismatch negativity induced by a frequency-deviant sound (fMMN), and that these impairments worsen with the deterioration of psychotic symptoms. This study aimed to test whether individuals at ultra-high risk (UHR) for psychosis show pre-morbid impairments in fMMN, and if so, whether fMMN continues to deteriorate with transition to psychosis.
Method: fMMN was recorded in a cohort of UHR individuals (n = 42) and compared to healthy controls (n = 29). Of the 27 UHR participants who returned for a second EEG session, six participants had transitioned to psychosis by 12-month follow-up (UHR-T) and were compared to the 21 participants who did not transition (UHR-NT).
Results: fMMN amplitude was significantly reduced, relative to healthy controls, in the UHR cohort. Furthermore, UHR-T individuals showed a significant decrease in fMMN amplitude over the period from baseline to post-transition; this reduction was not observed in UHR-NT.
Conclusions: These results suggest that fMMN is abnormal in UHR individuals, as has repeatedly been found previously in people with established psychotic disorders. The finding that fMMN impairment worsens with transition to psychosis is consistent with the staging model of psychosis; however, caution must be taken in interpreting these findings, given the extremely small sample size of the UHR-T group.

1. Introduction

Mismatch negativity (MMN) is an event-related potential (ERP) elicited pre-attentively in response to an unexpected deviant stimulus presented in a stream of invariant standard stimuli (Näätänen et al., 1978). The impairment in MMN amplitude constitutes one of the most robust and replicable findings in schizophrenia (for recent reviews see Erickson et al., 2016; Michie et al., 2016; Randeniya et al., 2017), and has been described as a "break-through biomarker" (Naatanen et al., 2015; see also Naatanen et al., 2016). Different forms of the MMN have been argued to be related to different facets of schizophrenia. For example, the MMN brought about by a change in the duration of the deviant sound compared to the standard appears to be related to more longstanding "trait" features of schizophrenia (McGorry et al., 2014). Furthermore, several studies have shown that the duration-MMN (dMMN) is reduced in individuals at ultra-high risk (UHR) for developing psychosis when compared to controls (Atkinson et al., 2012; Bodatsch et al., 2011; Higuchi et al., 2014; Jahshan et al., 2012; Murphy et al., 2013; Nagai et al., 2013; Pantlin and Davalos, 2016; Perez et al., 2014; Shaikh et al., 2012; Shin et al., 2009; Solís-Vivanco et al., 2014), with only two studies showing conflicting results (Higuchi et al., 2013; Mondragon-Maya et al., 2013). Most interestingly, comparing dMMN in UHR individuals who transition to psychosis (UHR-T), relative to those that do not transition (UHR-NT), have revealed that the decrease in dMMN amplitude is significant only in UHR-T (Atkinson et al., 2012; Bodatsch et al., 2011; Higuchi et al., 2014; Higuchi et al., 2013; Perez et al., 2014; Shaikh et al., 2012). As such, it has been suggested that this impairment could be used as a predictor of future transition to psychosis.

In comparison, the MMN brought about by a change in the frequency of the deviant sound compared to the standard is regarded as more of a

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https://doi.org/10.1016/j.schres.2017.11.005
0920-9964/

state marker of psychosis (McGorry et al., 2014). A meta-analysis of 32 studies on the MMN in schizophrenia and first-episode psychosis reports that effect sizes of frequency MMN (fMMN) were significantly correlated with duration of illness, indicating that the fMMN amplitude attenuation could reflect disease progression (Umbricht and Krljes, 2005). While some studies have found the fMMN to be intact in first-episode psychosis patients (Devrim-Ucok et al., 2008; Koshiyama et al., 2017; Magno et al., 2008; Mondragon-Maya et al., 2013; Salisbury et al., 2007; Salisbury et al., 2002; Todd et al., 2008; Umbricht et al., 2006; Valkonen-Korhonen et al., 2003), other studies have identified fMMN abnormalities in first-episode psychosis patients (Bodatsch et al., 2011; Oades et al., 2006; Perez et al., 2014). This latter finding is consistent with numerous previous studies which have identified fMMN abnormalities in patients with chronic schizophrenia (See meta-analysis by Umbricht and Krljes, 2005). A few studies have also observed reduced fMMN in UHR when compared to healthy controls (Carrion et al., 2015; Perez et al., 2014). In light of the evidence for fMMN abnormalities in patients with long-term psychotic disorders, combined with the preliminary evidence for fMMN deficits in UHR individuals, the first aim of the current study was to investigate whether UHR individuals also exhibit fMMN deficits relative to healthy controls.

In regards to the question of whether fMMN is a state marker of psychosis: Salisbury et al. (2007) suggested that fMMN impairment worsens with deterioration of illness in chronic schizophrenia patients. This hypothesis has only been directly tested once in UHR individuals (Atkinson et al., 2017). In this study, a relatively low proportion (10%) of UHR participants transitioned to psychosis, and no significant decline in fMMN amongst these individuals was observed. Thus, the second aim of the present study was to replicate the longitudinal design of Atkinson et al. (2017) (2017), and measure the course of fMMN amplitudes in UHR individuals who transitioned to psychosis (UHR-T) over the follow-up period, compared to those UHR individuals who did not transition to psychosis over this period (UHR-NT). Consistent with previous studies (Bodatsch et al., 2011; Brockhaus-Dumke et al., 2005; Mondragon-Maya et al., 2013; Nagai et al., 2013), it was anticipated that fMMN would not be impaired at baseline in UHR-T participants compared to UHR-NT participants, but that a between-group difference would emerge as a decline in fMMN magnitude over time in the UHT-T group, consistent with the staging model of psychosis (McGorry et al., 2014).

The present study formed part of a larger clinical trial investigating the effects of exposure to omega-3 polyunsaturated fatty acids (ω-3 PUFAs) on brain function and transition to psychosis rates in UHR individuals. The concern that "false-positive" individuals (who would never have developed the illness) may be unduly exposed to antipsychotic medication and their potential side-effects has justified the use of more benign approaches such as ω-3 PUFAs (Nelson et al., 2014; van der Gaag et al., 2013). Furthermore, ω-3 PUFA treatment in UHR has been shown to significantly reduce the transition-to-psychosis rates, and improve positive and negative symptoms relative to placebo (Amminger et al., 2010; Amminger et al., 2015), although these results have failed to replicate (McGorry et al., 2017). While the present study was not geared towards addressing this research question, and was underpowered to identify the efficacy ω-3 PUFAs on fMMN or transition rates, we nevertheless present the data here in case it could be of use in future meta-analytic studies investigating the efficacy of these compounds.

To summarize, the two primary aims of the current study were to: (1) determine whether our UHR cohort displayed aberrant fMMN compared to healthy controls; and (2) investigate whether there was any deterioration of the fMMN response following transition to psychosis. The third, supplementary aim of the study was to present our data on the association between ω-3 PUFA exposure and fMMN in the UHR group, in case it could be useful in future meta-analytic studies.

2. Method

2.1. Study design

Participants for this study were recruited from a larger pool of participants from the Neurapro study, a multicenter randomized-controlled trial of ω-3 PUFAs in UHR (Markulev et al., 2017; McGorry et al., 2017). Full clinical assessment, including an interview with the Comprehensive Assessment of At-Risk Mental States (CAARMS; Yung et al., 2005) to determine UHR status were conducted at baseline. Transition-to-psychosis status was assessed every month during the 6-month treatment period and again at the 9- and 12-month follow-ups, using the exit criteria of the CAARMS of daily threshold psychotic symptoms for more than one week.

Participants received either 2.8 g/day of marine fish oil, or placebo capsules, twice a day for 6 months. All participants also received 6–20 sessions of cognitive behavioural case-management (cognitive behavioural therapy within case-management framework) administered by experienced clinicians. Full details about the Neurapro study, including clinical outcome measures and inclusion/exclusion criteria can be found elsewhere (Markulev et al., 2017; McGorry et al., 2017).

EEG recordings were conducted at baseline, immediately following the treatment period (6 months), and/or as soon as possible after transition to psychosis. The EEG side study was approved by the Melbourne Health—Human Research Ethics Committee. Written informed consent was obtained for every participant. Participation was voluntary and participants were reimbursed for their time.

2.2. Participants

Participants were recruited from the Personal Assessment and Crisis Evaluation (PACE) clinic at Orygen Youth Health (OYH) in Parkville, Victoria and from Western headspace in Sunshine, Victoria. They were eligible for inclusion in the study if they were aged 15–25 years, and satisfied one or more of the three operationally defined and validated UHR criteria: attenuated psychotic symptoms; Brief Limited Intermittent Psychotic Symptoms (BLIPS); and/or a trait risk factor. They also had to present with a 30% decrease or sustained chronically low functioning over the past year (Yung et al., 2004) as measured with the Social and Occupational Functioning Assessment Scale (SOFAS; Goldman et al., 1992). Of the 106 participants recruited in the Neurapro study at the Melbourne site, 56 agreed to participate in the EEG side study.

A group of 29 healthy controls was recruited via online advertisements or from a pool of control participants at Orygen. Healthy controls were also aged 15–25 years old but had no past or current mental illness.

2.3. EEG acquisition

EEG data were recorded using Neuroscan software and a Neuroscan SynAmps 2 amplifier (Neuroscan, El Paso, Texas) with internal filters set to 0.5–1000 Hz. Data were continuously sampled at a rate of 1000 Hz from a 64-electrode Quick Cap in accordance with the 10–10 system. Eye movements were measured by placing non-standard electrodes on the outer canthus of each eye for horizontal movement, and above and below the left eye for vertical movement. Each electrode was referenced to an electrode placed on the nose.

fMMN was elicited using an auditory oddball paradigm using the following parameters: standard sounds (90% of trials; 1000 Hz; 50 ms); frequency-deviant sounds (10% of trials; 1200 Hz; 50 ms). 3000 stimuli were presented in a pseudo-randomized order (never two frequency-deviants in a row) with a stimulus onset asynchrony of 500 ms. All stimuli were presented binaurally through professional headphones (Sennheiser HD 280 Pro) while participants sat in a sound-proof room watching a silent video.

2.4. EEG data processing

Data were processed using BrainVision Analyzer version 2.1. Data measured at each electrode were re-referenced to the linked mastoids and filtered using a 0.1 to 20 Hz phase-shift free Butterworth filter (48 dB/Oct slope), as well as a 50 Hz notch filter. Epochs from −100 to 600 ms relative to stimulus onset were extracted and baseline-corrected to their mean voltage from −100 to 0 ms. Epochs were corrected for eye blink and movement artefacts (Gratton et al., 1983). All epochs with signals exceeding peak-to-peak amplitudes of 200 μV at any channel were excluded, as well as any standards that immediately followed a frequency-deviant. ERPs for each stimulus (standard, frequency-deviant) were computed for each participant. The fMMN was defined on the grand-averaged ERPs as the negative peak in the difference waves between frequency-deviants and standards (i.e., frequency deviant-minus-standard) between 130 and 200 ms at the frontal electrode Fz (Duncan et al., 2009; Näätänen et al., 2007).

2.5. Statistical analyses

Differences in baseline characteristics of participants were assessed by Student's *t*-test or chi-squared test as appropriate using IBM® SPSS® Statistics Version 22.

EEG data analyses were conducted using Dell Statistica version 13. The first analysis only used the baseline data and compared the fMMN response of all UHR individuals (regardless of subsequent transition) against that of controls within a 2 × 2 ANOVA, with a single repeated-measures factor (stimulus type: standard or frequency-deviant) and a single between-subjects factor (group: UHR or controls).

The second analysis made use of both measurement occasions in order to assess whether fMMN magnitude differed between UHR-T and UHR-NT participants, and between measurement occasions (prior to transition, post-transition). The data were analyzed using a 2 × 2 mixed factors ANOVA, with a single centered, nuisance covariate. The between-subjects factor was group (transitioned, no transition), the repeated-measures factor was time of measurement (baseline, post-transition), and the nuisance covariate was delay (the number of days between baseline and post-transition measurements). The covariate was added because the time of the "post-transition" measurement differed between individuals, although the same inferential conclusions held if the raw data were analyzed without this covariate. Type I error was controlled at $\alpha = 0.05$ throughout.

As discussed above, our study also explored the question of whether fMMN response of those UHR individuals exposed to ω-3 PUFA treatment differed from those who were allocated to the placebo group. This research question formed part of a larger study investigating the efficacy of ω-3 PUFAs in improving clinical outcome in UHR individuals (McGorry et al., 2017). Unfortunately the present study was underpowered to detect between-group differences, and thus we did not perform statistical analyses on this data and do not interpret the results below. However, we have provided the descriptive statistics and effect sizes in the Results section.

3. Results

3.1. The UHR group displays aberrant fMMN when compared to controls

Comparisons between controls and UHR participants were conducted using the baseline recordings, i.e., prior to the start of treatment in the UHR group, to avoid any confounding effect of treatment. Out of the 56 Neurapro participants who agreed to participate in the EEG side study, 10 did not attend their baseline recording session and the baseline data from four participants had to be excluded from analyses due to poor data quality. Analyses were conducted on the remaining 42 UHR participants and 29 healthy controls. The female:male ratio was not different between the two groups (controls, 15:14; UHR, 26:16). Mean age was slightly lower in the UHR group (17.6 ± 2.3 years) than in the control group (18.7 ± 2.1 years; $p = 0.038$). As expected, functioning score determined with the SOFAS were much lower in the UHR group (56.9 ± 10.4) compared to the controls (88.9 ± 5.1; $p < 0.001$).

The average evoked potentials measured at Fz for both controls and UHR following the presentation of the standard and frequency-deviant sounds, as well as the standard-minus-frequency-deviant difference wave, are illustrated in Fig. 1A. Fig. 1B shows the mean ERP amplitudes between 130 ms and 200 ms in the two groups. The inferential analyses of the mean amplitude data revealed a main effect of stimulus-type, $F(1,69) = 218.36$, $p < 0.001$, 95% CI[7.53, 9.88], $\eta_P^2 = 0.76$, indicating an overall MMN effect averaged across groups. There was no main effect of group, $F < 1$.

The interaction contrast showed that the difference between the standard- and the frequency-deviant-evoked wave (i.e., fMMN magnitude) of the UHR group was smaller than that of controls at baseline, $F(1,69) = 4.86$, $p = 0.03$, 95% CI[0.12, 2.47], $\eta_P^2 = 0.07$. There were no significant differences between the groups when the frequency-deviant sounds were considered in isolation, $F < 1$, but there was a non-significant trend towards the standard sounds giving a larger voltage in the control group than in the UHR group, $F(1,69) = 3.85$, $p = 0.05$, 95% CI[−0.01, 1.48], $\eta_P^2 = 0.05$.

3.2. fMMN response deteriorates with the transition to psychosis

Of the 27 UHR individuals who attended two EEG sessions, six participants transitioned to psychosis by 12-month follow-up (the UHR-T group) and 21 participants did not (the UHR-NT group). The transition-to-psychosis rate in this group was therefore 22.2%. Of the 15 UHR participants who did not attend the follow-up session, only two transitioned to psychosis at 12-month follow-up (13.3%). See Table 1 for participants' characteristics at baseline. At follow-up, SOFAS scores were significantly higher in UHR-NT (66.7) compared to UHR-T (55.0; $p = 0.03$).

The magnitude of the fMMN response for both groups (Fig. 2A and B) was analyzed using an ANOVA. The main effect of group (UHR-T, UHR-NT) was not significant, $F < 1$. However, group significantly interacted with measurement occasion, $F(1,24) = 4.77$, $p = 0.04$, 95% CI[0.10, 3.43], $\eta_P^2 = 0.17$. Simple effect analyses were conducted to further investigate this interaction. In the six UHR-T individuals there was a significant decline in MMN magnitude over the study period of 1.14 μV (unweighted units), $F(1,4) = 8.12$, $p = 0.046$, 95% CI[0.03, 2.25], $\eta_P^2 = 0.67$, whereas UHR-NT individuals showed a non-significant, numeric increase in MMN magnitude of 0.60 μV between measurements, $F(1,19) = 2.09$, $p = 0.16$, 95% CI[−0.27, 1.47], $\eta_P^2 = 0.10$.

Of the six UHR-T participants, three were allocated to the ω-3 PUFAs, whereas three were in the placebo group. Of the 21 UHR-NT participants, 13 took ω-3 PUFAs over the first 6-months of the study, whereas eight took placebo. Given the potential confound between treatment and transition status, a secondary analysis was conducted with treatment condition (PUFAs vs. placebo) as a co-variate. This analysis confirmed that the significant interaction held; $F(1,23) = 5.61$, $p = 0.03$, 95% CI[0.24, 3.52], $\eta_P^2 = 0.20$.

As there appeared to be a difference between UHR-NT and UHR-T at baseline, a simple effect contrast examined any differences between groups; no significant differences were found, $F(1,25) = 1.61$, $p = 0.21$, 95% CI[−0.75, 3.17], $\eta_P^2 = 0.06$.

To summarize, those individuals who transitioned to psychosis showed a significant decline in MMN magnitude from baseline (i.e., before they exhibited psychotic symptoms) to immediately after exhibiting psychotic symptoms, whereas the UHR-NT group did not show a change in MMN magnitude over the six-month study period.

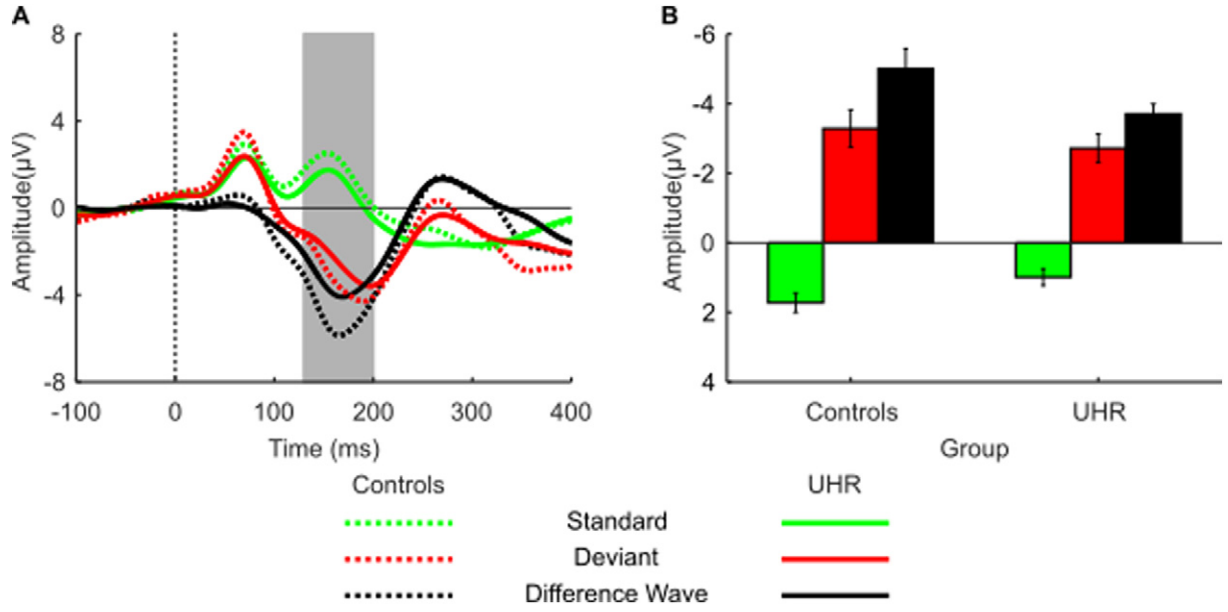

Fig. 1. A) The average evoked potentials measured at Fz for both controls and UHR following the presentation of the standard and frequency-deviant sounds, and the difference wave between standard-evoked ERP and deviant-evoked ERP. The grey area designate the time interval during which the peak MMN amplitude was measured. B) Mean standard-evoked ERP amplitude, deviant-evoked ERP amplitude, and difference between both ERPs in controls and UHR. Error bars refer to standard error of the mean.

3.3. Supplementary data: the relationship between exposure to ω-3 PUFAs and fMMN

Of the 27 UHR individuals who provided two EEG measurements (i.e., baseline and post-transition or 6-month follow-up), 16 were assigned to the ω-3 PUFA group and 11 were assigned to the placebo group. Four people transitioned before the treatment period was completed (i.e., within six months of baseline) and were thus omitted from these analyses as they did not provide a post-treatment measure. Three of these people were in the ω-3 PUFA group and one was in the placebo group.

As the present study was underpowered to detect between-group differences, we have not performed inferential statistical analyses on this data. However, in case they may be of interest to the readers, the summary statistics for the fMMN data (mean, standard error, and 95% confidence intervals), as well as the demographics and clinical characteristics of the participants in the two treatment groups are presented in Table 2. The effect size of the between-group difference in fMMN difference score (i.e., fMMN post- minus pre-treatment) was $d = 0.57$. The raw data are available from the authors upon request for use in any future meta-analytic studies exploring the clinical utility of ω-3 PUFAs in UHR individuals.

Table 1
Characteristics of UHR participants who did not transition to psychosis (UHR-NT) and of those who transitioned to psychosis (UHR-T) within 12 months of study entry.

Characteristics	UHR-NT (n = 21)	UHR-T (n = 6)	*p*-Value
Gender, nb females (%)	14 (66.7)	3 (50.0)	0.638[b]
Age (years), mean ± SD	17.9 ± 2.9	16.7 ± 1.3	0.334[a]
SOFAS score	55.8 ± 9.3	57.3 ± 11.6	0.733[a]
At-risk for psychosis group, nb (%)			0.416[b]
Attenuated symptoms	16 (76.2)	6 (100)	
Trait risk factor	2 (9.5)	0 (0.0)	
BLIPS	0 (0.0)	0 (0.0)	
Attenuated symptoms + trait	3 (14.3)	0 (0.0)	
Delay between baseline and follow-up EEG (days)	190.0 (17.4)	192.3 (130.3)	0.966[a]

[a] Student's *t*-test.
[b] Chi Square.

4. Discussion

The current study presents two interesting observations. First, fMMN amplitude was significantly impaired in our UHR cohort relative to healthy controls. Second, individuals who transitioned to psychosis showed a significant fMMN deterioration, whereas UHR individuals who did not transition exhibited a relatively stable fMMN. However, the small sample sizes in the second analysis, particularly in the UHR-T group, means that this finding should be interpreted with caution until it can be replicated.

Of the previous studies investigating fMMN in UHR (Atkinson et al., 2017; Bodatsch et al., 2011; Koshiyama et al., 2017; Mondragon-Maya et al., 2013; Nagai et al., 2013), to the best of our knowledge only one has shown decreased fMMN in UHR (Perez et al., 2014), consistent with the results of the present study. These studies in UHR have used either the CAARMS or the Structured Interview for Prodromal Symptoms (SIPS; Miller et al., 2002) to determine the eligibility of participants. The present study recruited at-risk samples who exhibited either reduced functioning, or chronically low functioning, as measured with the SOFAS. Given that reduced functioning is reliably correlated with reduced MMN amplitude in psychosis (Hermens et al., 2010; Jahshan et al., 2012; Kaur et al., 2013; Kawakubo and Kasai, 2006; Light and Braff, 2005a, 2005b; Rasser et al., 2011), the additional specification of low functioning as an UHR criterion may be responsible for the lower mean fMMN amplitude observed.

Our results show that UHR-T individuals presented with a significant decline in fMMN magnitude from baseline to immediately after exhibiting psychotic symptoms, whereas the UHR-NT group did not show a change in fMMN magnitude over the follow-up period. The longitudinal aspect to our study is crucial because if we had only compared the UHR-T group to the UHR-NT cross-sectionally, no significant difference would have been observed and we would have missed the critical decline in the fMMN amplitude.

The present data are consistent with the hypothesis that fMMN may be a state marker for psychosis. Indeed, the fMMN appears to illustrate the theoretical concept of the staging model (McGorry et al., 2014), in that impairment in fMMN worsens with increased symptomatology. The Umbricht and Krljes (2005) meta-analysis showed that the effect sizes of fMMN were significantly correlated with the duration of illness, indicating that fMMN amplitude attenuation could reflect disease

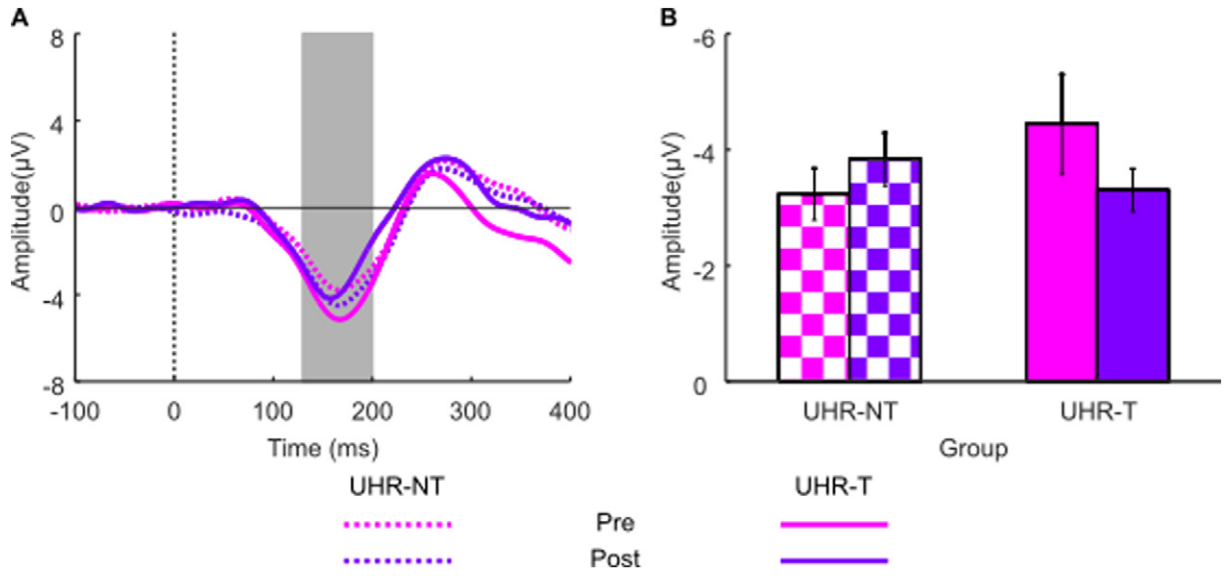

Fig. 2. A) Difference wave between standard-evoked ERP and deviant-evoked ERP for the UHR-NT and the UHR-T groups. The grey area designate the time interval during which the peak MMN amplitude was measured. B) Mean MMN magnitudes (standard—deviant; μV) in UHR-NT and in UHR-T. Error bars refer to standard error of the mean.

progression. It was also shown that fMMN can be improved by the administration of *N*-acetyl-cysteine in schizophrenia patients (Lavoie et al., 2007), reinforcing its status as a state marker of the illness rather than a trait marker. The present observation of a decline in fMMN around the time of transition to psychosis also supports this hypothesis. To the best of our knowledge, only one other study has looked at the longitudinal changes in the fMMN following transition to psychosis, and their results showed no change in fMMN amplitude over time (Atkinson et al., 2017). Similar to the present report, their UHR-T group constituted of six individuals and, therefore, the statistical power for both studies is low. Replicating these results with a longitudinal design in a larger UHR cohort would be a worthwhile endeavor.

There are a number of limitations that apply to the present study. The sample size for the UHR-T group was very small ($n = 6$), which limits the statistical power of analyses and restricts the generalizability of the results. Recruitment in the UHR population remains challenging and future studies may benefit from data-pooling. A second and related issue concerns the time-bound criterion for conversion to psychosis employed in this study, which defined 'conversion' as the development of psychosis within 12 months of UHR assessment. Given that transition risk generally remains elevated two to three years from baseline assessment of UHR status (Fusar-Poli et al., 2012; Nelson et al., 2013), it is possible that this relatively strict criterion captured only a subset of the true sample of UHR converters in the present study.

Table 2
Characteristics of UHR participants randomized to the ω-3 PUFA group and the placebo group.

Characteristics	Placebo (n = 10)	ω-3 PUFA (n = 13)	*p*-Value
Gender, nb females (%)	8 (80.0)	8 (61.5)	0.405[b]
Age (years), mean ± SD	17.2 ± 2.7	17.9 ± 3.0	0.575[a]
SOFAS score	57.7 ± 12.9	55.1 ± 7.3	0.705[a]
At-risk for psychosis group, nb (%)			0.372[b]
Attenuated symptoms	9 (90.0)	9 (69.2)	
Trait risk factor	0 (0.0)	2 (15.4)	
BLIPS	0 (0.0)	0 (0.0)	
Attenuated symptoms + trait	1 (10.0)	2 (15.4)	
Baseline fMMN, mean ± SD	3.26 ± 2.34	3.67 ± 1.95	N/A
Baseline 95% CI	1.88, 4.65	2.81, 5.47	
Post-treatment fMMN, mean ± SD	4.14 ± 2.25	3.43 ± 1.61	N/A
Post-treatment 95% CI	2.71, 4.62	2.65, 4.22	

[a] Student's *t*-test.
[b] Chi Square.

5. Conclusion

The current study has shown that fMMN amplitude was significantly impaired relative to healthy controls in a UHR cohort presenting with relatively low functioning. Furthermore, UHR individuals who subsequently transitioned to psychosis showed a significant deterioration in fMMN following the worsening of their positive symptomatology, while UHR individuals who did not transition exhibited stable fMMN. While these results are consistent with the hypothesis that fMMN is a state marker of psychotic symptoms, it should be treated with caution until it can be replicated in a larger sample.

Role of the funding source
This work was supported by a grant from the University of Melbourne (601947) (SL) and a NARSAD grant (17537; TW). The Neurapro study was supported by the Stanley Medical Research Institute (07TGF-1102), the NHMRC Australia Program (566529) and the Colonial Foundation. BN was supported by a NARSAD Independent Investigator Grant from the Brain & Behavior Research Foundation (23199), OG was supported by an Australian Research Council (ARC) grant (DE150100667), and TW is supported by a Career Development Fellowship from the NHMRC1 (APP1090507) and Discovery Projects from the ARC (DP140104394; DP170103094).

Contributors
SL designed the study and drafted the manuscript. BJ and OG processed the data and drafted the Results section. AA performed the EEG recordings. All authors critically reviewed the manuscript.

Acknowledgements
We thank all of the participants and their families.

Conflict of interest
The authors have no conflict of interest to declare.

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