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# 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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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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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.

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