Progress in Neuro-Psychopharmacology & Biological Psychiatry 46 (2013) 161–169

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Longitudinal associations between mismatch negativity and disability in early schizophrenia- and affective-spectrum disorders

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ARTICLE INFO

Article history:
Received 9 April 2013
Received in revised form 1 July 2013
Accepted 3 July 2013
Available online 11 July 2013

Keywords:
Bipolar
Disability
Longitudinal
Mismatch negativity
P3a
Schizophrenia

ABSTRACT

Background: Impaired mismatch negativity (MMN) is a robust finding in schizophrenia and, more recently, similar impairments have been reported in other psychotic- and affective-disorders (including at early stages of illness). Although cross-sectional studies have been numerous, there are few longitudinal studies that have explored the predictive value of this event-related potential in relation to clinical/functional outcomes. This study assessed changes in MMN (and the concomitant P3a) amplitude over time and aimed to determine the longitudinal relationship between MMN/P3a and functional outcomes in patients recruited during the early stage of a schizophrenia- or affective-spectrum disorder.

Methods: Sixty young patients with schizophrenia- and affective-spectrum disorders and 30 healthy controls underwent clinical, neuropsychological and neurophysiological assessment at baseline. Thirty-one patients returned for clinical and neuropsychological follow-up 12–30 months later, with 28 of these patients also repeating neurophysiological assessment. On both occasions, MMN/P3a was elicited using a two-tone passive auditory paradigm with duration deviants.

Results: Compared with controls, patients showed significantly impaired temporal MMN amplitudes and trend-level deficits in central MMN/P3a amplitudes at baseline. There were no significant differences for MMN measures between the diagnostic groups, whilst the schizophrenia-spectrum group showed reduced P3a amplitudes compared to those with affective-spectrum disorders. For those patients who returned for follow-up, reduced temporal MMN amplitude at baseline was significantly associated with greater levels of occupational disability, and showed trend-level associations with general and social disability at follow-up. Paired t-tests revealed that MMN amplitudes recorded at the central-midline site were significantly reduced in patients over time. Interestingly, those patients who did not return for follow-up showed reduced frontal MMN and fronto-central P3a amplitudes compared to their peers who did return for repeat assessment.

Conclusions: This study provides some evidence of the predictive utility of MMN at the early stages of schizophrenia- and affective-spectrum disorders and demonstrated that MMN impairments in such patients may worsen over time. Specifically, we found that young patients with the most impaired MMN amplitudes at baseline showed the most severe levels of disability at follow-up. Furthermore, in the subset of patients with repeat neurophysiological testing, central MMN was further impaired suggestive of neurodegenerative effects. MMN may serve as a neurophysiological biomarker to more accurately predict functional outcomes and prognosis, particularly at the early stages of illness.

1. Introduction

Mismatch negativity (MMN) is an event-related potential (ERP) that indexes fundamental and pre-attentive sensory processes such as echoic memory and attentional switching (Javitt, 2000; Naatanen, 1990). For more than twenty years, MMN has been extensively studied in schizophrenia with reductions in its amplitude being one of the most replicable and robust findings in the psychophysiological literature (Michie, 2001; Naatanen et al., 2007; Naatanen et al., 2012). Another ERP, the 'P300' or 'P3' has also been shown to be a biomarker

Abbreviations: MMN, mismatch negativity; ERP, event-related potential; EEG, electroencephalography; EOG, electro-oculogram; HDRS, Hamilton depressive rating scale; BPRS, brief psychiatric rating scale; SOFAS, social and occupational functioning scale; TMT, trails making test; RAVLT, Rey auditory verbal learning test; WHO DAS-II, World Health Organisation disability assessment schedule; ANOVA, analysis of variance; FUP, patients who returned for follow-up; non-FUP, patients who did not return for follow-up.

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http://dx.doi.org/10.1016/j.pnpbp.2013.07.002

for schizophrenia (Javitt et al., 2008; Turetsky et al., 2009), as has its variant, the 'P3a' (Fisher et al., 2010; Turetsky et al., 2009). P3a purportedly reflects fronto-central orienting processes (Friedman et al., 2001; Lagopoulos et al., 1998; Polich, 2007) in response to a novel or deviant stimuli and, thus, it typically follows MMN in deviance detection paradigms. In combination, these biomarkers have been described as the 'MMN/P3a' complex (Hermens et al., 2010; Kaur et al., 2011; Kaur et al., 2012a; Kaur et al., 2012b; Light et al., 2007).

Initial investigations of MMN and P3a in schizophrenia examined chronic patients (Catts et al., 1995; Fisher et al., 2010; Michie, 2001; Shelley et al., 1991; Turetsky et al., 2009), however, more recently, research has expanded to show impairments in younger patient groups at early stages of psychosis (Atkinson et al., 2012; Bodatsch et al., 2011; Brockhaus-Dumke et al., 2005; Hermens et al., 2010; Mondragón-Maya et al., 2013; Shin et al., 2009). In our own work, we have demonstrated that MMN/P3a is similarly impaired in early stage schizophrenia- and affective-spectrum psychotic disorders (Kaur et al., 2011) as well as in early stage bipolar disorders (Kaur et al., 2012a). We have also reported on MMN impairments in late-life depression (Naismith et al., 2012) and mild cognitive impairment (Mowszowski et al., 2012). Likewise, several other studies have now found MMN and P3a impairments in depressed children (Lepisto et al., 2004), adults with depression (Takei et al., 2009), more chronic stages of bipolar disorder (Jahshan et al., 2012b; Takei et al., 2010) and schizotypal personality disorder (Niznikiewicz et al., 2009). Taken together, the recent literature suggests that impairments in the MMN/P3a complex may not be as diagnostically specific as previously proposed, but may instead index common underlying pathophysiological processes in younger patients with psychotic (and related) disorders.

Although there are numerous studies that have examined MMN in psychiatric samples using cross-sectional designs, few have employed longitudinal designs. One such study found that individuals at ultra high-risk for psychosis who converted to first-episode psychosis at 24-month follow-up had the greatest reductions in MMN at baseline (Bodatsch et al., 2011), thus underscoring the potential of MMN in estimating the conversion risk of an individual. Another longitudinal study by Salisbury et al. (2007) found no differences in MMN on group comparisons among first-hospitalised schizophrenia, first-hospitalised psychotic bipolar disorder and the control group. However, in schizophrenia, MMN was strongly associated with left hemisphere Heschl gyrus grey matter volume. At follow-up (an average of 18-months later), both MMN amplitudes and left hemisphere Heschl gyrus grey matter volumes were reduced and shown to be tightly coupled in patients with schizophrenia suggesting that MMN may be an index of progressive cortical volume reduction. Importantly, this research identified a highly significant longitudinal relationship between MMN and structural brain changes. In two studies, Light and Braff (2005b) and Light et al. (2012) showed that in chronic schizophrenia patients, impaired frontal MMN remained stable over 12–24 months in their first study and over 12 months in their recent study. Despite this, they proposed that investigations into earlier stages of the illness are warranted to determine when MMN amplitude attenuates and how it may change over time. Overall, these findings suggest that MMN may index progressive changes that occur more rapidly early on in the course of illness but remain stable, in an attenuated form, at later stages. Other research has determined that MMN amplitudes assessed in the acute and post-acute phases of schizophrenia were equally attenuated at frontal sites at both time points (with the inter-test interval ranging between 1 and 13 months) indicating a trait- rather than state-dependent nature (Shinozaki et al., 2002). In contrast, this study also showed that MMN recorded at the mastoids was significantly reduced in the acute phase as compared with the post-acute phase suggesting that MMN recorded at temporal sites may be more state-dependent. As such, this finding highlights the value of assessing both frontal and temporal MMN amplitudes. In a three year follow-up study examining clozapine treatment response in schizophrenia, Schall et al. (1999) found that 'intact' MMN was associated with good treatment response and concluded that MMN may have capacity in predicting therapeutic outcome. Overall, the aforementioned findings demonstrate the utility of MMN in predicting illness trajectory, both clinically and neurobiologically, as well as probable treatment response. The longitudinal utility of MMN in young, early-stage patients requires further investigation.

The aim of the current study was to determine: firstly, the longitudinal stability of MMN/P3a and corresponding clinical, functional and cognitive characteristics in a group of patients at the early stages of a schizophrenia- or affective-spectrum disorder and, secondly, the predictive utility of MMN/P3a by examining its relationship with functional outcomes. Specifically, the Social and Occupational Functioning Scale (SOFAS) (Goldman et al., 1992) and the World Health Organisation Disability Assessment Scale II (WHO DAS-II) (Chwastiak and Von Korff, 2003) was used to measure functional outcome where the former is a measure general/global functioning and the latter is a measure of general disability as well as six component factors (understanding and communicating; getting around; self-care; getting along with people; household; and work and participation in society). In the current study, we have included both schizophrenia- and affective-spectrum patients in our overall patient group, in keeping with our previous findings that MMN/P3a is similarly impaired at the early stages of illness in patients meeting criteria for both diagnostic spectra (Jahshan et al., 2012b; Kaur et al., 2011; Kaur et al., 2012a). We hypothesised that at the early stages of illness, impairments in MMN/P3a will worsen after 12–24 months and that the MMN/P3a recorded at baseline will be associated with poorer functional measures at follow-up.

2. Methods

The current study was approved by the University of Sydney Human Research Ethics Committee. All participants gave written informed consent prior to participation in the study and were determined by their referring psychiatrist to have the mental and intellectual capacity to do so.

2.1. Procedure

Sixty young outpatients (see details below) underwent a baseline clinical, neuropsychological and neurophysiological assessment and consented to being contacted in the future (i.e. after at least 12 months had elapsed) for follow-up assessments as part of our longitudinal neurobiological study (Hermens et al., 2011; Lee et al., 2013; Scott et al., 2013). As described in our previous neurophysiological studies (Chitty et al., 2011; Hermens et al., 2010; Kaur et al., 2011; Kaur et al., 2012a; Kaur et al., 2012b; Pesa et al., 2012), patients were recruited from specialised referral services for the assessment and early intervention of mental health problems (Scott et al., 2009; Scott et al., 2012). Twenty-two per cent (13/60) of the patients assessed at baseline could not be contacted at follow-up, for the following reasons: changed contact details ($n = 8$) or, did not respond to phone calls or emails ($n = 5$). Of the 78% (47/60) who were contacted, 27% (16/60) declined follow-up participation on the following grounds: refused to participate ($n = 7$), were unavailable due to work/study ($n = 2$), moved away ($n = 1$), were too unwell ($n = 4$) or did not attend scheduled appointments ($n = 2$). Just over half of the original patient sample (i.e. 52%; 31/60) did return for follow-up assessment. Three of these patients underwent clinical and neuropsychological assessments, however, neurophysiological testing was not conducted.