Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Mismatch negativity in bipolar disorder: A neurophysiological biomarker of intermediate effect?

Daniel F. Hermens [a,*], Kate M. Chitty [b], Manreena Kaur [c]

[a] Youth Mental Health Team, Brain and Mind Centre, The University of Sydney, Camperdown, NSW, Australia
[b] Translational Australian Clinical Toxicology (TACT) Research Group, Discipline of Pharmacology, Sydney Medical School, The University of Sydney, NSW, Australia
[c] Monash Alfred Psychiatry Research Centre, The Alfred and Monash University Central Clinical School, VIC, Australia

ARTICLE INFO

Article history:
Received 2 February 2017
Received in revised form 11 April 2017
Accepted 13 April 2017
Available online xxxx

Keywords:
Mismatch negativity
Bipolar disorder
Glutamate
NMDA receptor
Neurophysiological biomarker
Schizophrenia

ABSTRACT

The event-related potential, mismatch negativity (MMN), has been touted as a robust and specific neurophysiological biomarker of schizophrenia. Earlier studies often included bipolar disorder (BD) as a clinical comparator and reported that MMN was significantly impaired only in schizophrenia. However, with the increasing number of MMN studies of BD (with larger sample sizes), the literature is now providing somewhat consistent evidence of this biomarker also being perturbed in BD, albeit to a lesser degree than that observed in schizophrenia. Indeed, two meta-analyses have now shown that the effect sizes in BD samples suggest a moderate impairment in MMN, compared to the large effect sizes shown in schizophrenia. Pharmacologically, MMN is an extremely useful non-invasive probe of glutamatergic (more specifically, *N*-methyl-D-aspartate [NMDA] receptor) disturbances and this system has been implicated in the pathophysiology of both schizophrenia and BD. Therefore, it may be best to conceptualize/utilize MMN as an index of a psychopathology that is shared across psychotic and related disorders, rather than being a diagnosis-specific biomarker. More research is needed, particularly longitudinal designs including studies that assess MMN over an individual's life course and then examine NMDA receptor expression/binding post-mortem. At this point and despite a disproportionate amount of research, the current evidence suggests that with respect to BD, MMN is a neurophysiological biomarker of intermediate effect. With replication and validation of this effect, MMN may prove to be an important indicator of a common psychopathology shared by a significant proportion of individuals with schizophrenia and bipolar spectrum illnesses.

1. Introduction

Affecting about 60 million people worldwide, bipolar disorder (BD) is a major mental illness responsible for the loss of more disability-adjusted life-years than all forms of cancer due to its early onset and subsequent chronicity (Merikangas et al., 2011). Characterized by fluctuating mood symptoms, BD is typically expressed by the cycling from major depressive states to hypomanic or manic episodes, which in severe cases are accompanied by psychosis. Early symptoms of BD usually emerge during adolescence and young adulthood (Kim-Cohen et al., 2003; Paus et al., 2008), and if not identified and treated appropriately advance to a chronic state associated with more severe symptoms, greater mood episode frequency and shorter inter-episode intervals (Post, 2007). In this regard BD has been described as a 'neuroprogressive' illness (Berk, 2009; Kapczinski et al., 2008; Post, 2007), although the pathophysiology of BD remains poorly understood given its complex and multifactorial nature (Sigitova et al., 2016). In the light of this, there is a need to establish robust biological markers or 'biomarkers' of BD to improve diagnostic accuracy and to facilitate preventative strategies (Frey et al., 2013).

Recently, the International Society for Bipolar Disorders (ISBD) Biomarkers Network Task Force proposed some potential candidate biomarkers for BD, with a focus on in three main areas of research: neuroimaging, peripheral biomarkers and genetics (Frey et al., 2013). Specifically, grey matter in cortical-cognitive brain networks, activation in ventral limbic regions and in vivo glutamate levels as indexed by magnetic resonance spectroscopy (MRS) were highlighted as neuroimaging biomarker targets. With regards to peripheral biomarkers: oxidative stress, inflammation and neurotrophins were identified as crucial areas of interest. Finally, genes linked to alterations in calcium metabolism, circadian rhythm, neuronal development as well as brain connectivity were flagged as potential genetic biomarkers of BD. Despite the range and apparent validity of the biomarkers presented, the Task Force noted that there are key unanswered questions relating to the utility of these biomarkers both in terms of predicting outcome (particularly at early stages) and in guiding treatment decisions (Frey et al., 2013).

* Corresponding author at: Brain and Mind Centre, University of Sydney, 100 Mallett Street, Camperdown, NSW 2050, Australia.
E-mail address: daniel.hermens@sydney.edu.au (D.F. Hermens).

http://dx.doi.org/10.1016/j.schres.2017.04.026
0920-9964/

Thus, it is worth reflecting on the utility of biomarkers in general. As highlighted by Mayeux (2004), while biomarkers often aid in understanding the prediction, cause, diagnosis, progression, regression, or outcome of treatment of disease, their utility "has grown out of the need to have more direct measurement of exposures in the causal pathway of disease" and, while some represent direct steps in the causal pathway of a disease, others are related in some indirect way (Mayeux, 2004). However, Lenzenweger (2013) claims that a biomarker may not be specifically embedded in the causal chain for the disease, but simply reflects "some measurable deviation in the organism, reflective of either internal factors operating in either health/illness or the impact of an external agent". For Mayeux (2004), there are two major types: biomarkers of exposure (i.e. for risk prediction; indices of the 'internal dose' of exposure), and biomarkers of disease (for screening/diagnosis and monitoring progression). Furthermore, biomarkers are often conceptualized as being either trait or state markers, which is particularly pertinent to BD whereby the latter could be useful in the differentiation of mood states or may be applicable only within a specific mood episode (Frey et al., 2013).

Event-related potentials (ERPs), extracted from the electroencephalogram and time-locked to discrete perceptual and/or cognitive events, are commonly utilized as ('neurophysiological') biomarkers. In the context of psychiatric disorders, ERPs have been described as particularly important biomarkers (Domjan et al., 2012). One neurophysiological biomarker, mismatch negativity (MMN), has been identified as a 'breakthrough' in terms of the understanding and treatment of psychotic disorders (Light and Naatanen, 2013); there are a significant number of studies showing this ERP to be consistently impaired in schizophrenia, with large effect sizes (Erickson et al., 2016; Umbricht and Krljes, 2005). Indeed, with the accumulating evidence (i.e. replication of MMN impairment in schizophrenia samples) there was also an interest in understanding the specificity of this purported biomarker and the natural clinical comparator was often BD. In the sections below, we summarize the literature on MMN in BD (often undertaken in the context of a clinical focus on schizophrenia) and then discuss potential explanations for MMN impairment in BD as reported in recent meta-analyses (albeit to a lesser degree than that observed in schizophrenia) (Chitty et al., 2013; Erickson et al., 2016). First, however, it is important to consider what MMN represents and its underlying mechanism. This is essential as it may be best to conceptualize/utilize MMN within the Research Domain Criteria (RDoC) framework (Insel et al., 2010), whereby it serves as an index of a psychopathology that is shared across psychotic and related disorders, rather than being a diagnosis-specific biomarker (Erickson et al., 2016).

1.1. Mismatch negativity (MMN): A neurophysiological biomarker

The presentation of a deviant stimulus within a stream of repeated standard stimuli elicits an automatic change detection mechanism, and this can be quantified by measuring the negative going ERP known as MMN (Naatanen, 1990; Naatanen et al., 2007). Accordingly, MMN has also been interpreted as an index of the brain's ability to extract relevant information from an irrelevant background (Hermens et al., 2010). Impairments in deviance detection phenomena, even at the early stages of processing, may induce significant disturbances in higher-order cognitive functioning; hence the importance of such indices in psychiatry and neuroscience (Schmidt et al., 2013). Indeed impairments of MMN have been shown to be significantly associated with functional impairments, in a range of psychiatric samples (Baldeweg and Hirsch, 2015; Hermens et al., 2010; Kaur et al., 2013; Light and Braff, 2005a, 2005b; Light et al., 2007).

Pharmacologically, MMN is an extremely useful, non-invasive probe of glutamatergic (more specifically, *N*-methyl-D-aspartate [NMDA] receptor) disturbances due to its reliable attenuation by antagonism at this receptor across animals and humans (Ehrlichman et al., 2008; Heekeren et al., 2008; Javitt et al., 1996; Kreitschmann-Andermahr et al., 2001; Pang and Fowler, 1999; Umbricht et al., 2000). The mechanism explaining the role of the NMDA receptor in MMN has been investigated using dynamic causal modeling, with evidence consistent with the predictive coding hypothesis (Schmidt et al., 2013). That is, the synaptic plasticity necessary for the development of the sensory memory trace is disrupted by NMDA receptor antagonism and therefore MMN is diminished. These findings align with the well-known principal role of the NMDA receptor in regulation of synaptic plasticity within the brain (Bennett, 2000; Bliss and Collingridge, 1993). While there is documented evidence for the roles of dopamine, serotonin (5HT) and gamma-aminobutyric acid (GABA), nicotinic and muscarinic receptors in MMN it is generally accepted that the roles of these agents are less robust and likely exert less regulatory effects (Garrido et al., 2009). A large body of research has shown that antipsychotics tend not modulate MMN (Korostenskaja et al., 2005; Leung et al., 2007; Leung et al., 2010; Pekkonen et al., 2002; Schall et al., 1998; Umbricht et al., 1998; Umbricht et al., 1999) although there is some evidence of an increase in MMN amplitude with antipsychotic treatment (Kahkonen et al., 2001; Zhou et al., 2013). By comparison, the number of studies investigating the effects of other psychotropic medication is scant. In terms of serotonergic modulation, while there is purportedly no change in MMN after 5HT depletion (Leung et al., 2010) or psilocybin (Umbricht et al., 2002), however, the administration of high-dose escitalopram (Wienberg et al., 2010) and tryptophan depletion (Kahkonen et al., 2005) has been shown to increase MMN amplitudes. Studies also have found that MMN does not change with the mood stabilizers, lamotrigine (Vayisoglu et al., 2013) and lithium (Jahshan et al., 2012), nor with anxiolytics and hypnotics (Kasai et al., 2002), benzodiazepines (Murakami et al., 2002), and methylphenidate (Korostenskaja et al., 2008). However, as these findings have not been reproduced, they should be treated with caution.

Disturbances of the NMDA receptor and the neurometabolites involved in its regulation and modulation have been implicated in the pathophysiology of BD (Chitty et al., 2015a; Chitty et al., 2013; Ghasemi et al., 2014; Sanacora et al., 2008). Post-mortem studies showing perturbed NMDA receptor expression, binding, stoichiometry and functioning in BD are commonly detected in the temporal region (Beneyto et al., 2007; Law and Deakin, 2001; McCullumsmith et al., 2007; Nudmamud-Thanoi and Reynolds, 2004; Scarr et al., 2003) and the prefrontal cortex (Beneyto and Meador-Woodruff, 2008; Rao et al., 2010; Rao et al., 2012; Woo et al., 2004). It is noteworthy that many of these findings seem to be specific to NMDA receptors, with no corresponding abnormalities found in other glutamatergic receptors (i.e. AMPA or kainate) (Beneyto et al., 2007; Scarr et al., 2003). Documented success of NMDA receptor antagonists in treating BD also implicates the receptor in the pathophysiology of the disorder. For example, memantine and ketamine, amantadine, D-cycloserine, magnesium and zinc have all shown therapeutic action in BD, and in many cases have shown efficacy in treatment resistant patients (for review see (Ghasemi et al., 2014)).

The earlier studies investigating MMN impairments across clinical groups claimed that MMN impairments are exclusive to patients with schizophrenia; and specifically suggest that it is not impaired in patients with BD (Catts et al., 1995; Hall et al., 2009; Salisbury et al., 2007; Umbricht et al., 2003). On closer inspection of these studies, however, methodological aspects of the respective study designs may warrant caution as the BD samples tended to be smaller in number, rated lower on symptom severity and/or were remitted for longer periods of time compared to the schizophrenia samples (Catts et al., 1995; Hall et al., 2009; Umbricht et al., 2003). In contrast, more recent research has shown that in BD, MMN amplitudes are attenuated and/or have increased latencies (Andersson et al., 2008; Jahshan et al., 2012; Takei et al., 2010). It is interesting to note that in the decade following the null findings reported by the first study of MMN in BD (Catts et al., 1995), there were very few investigations into MMN in BD, despite numerous published studies of MMN in schizophrenia-spectrum subjects. In the

Please cite this article as: Hermens, D.F., et al., Mismatch negativity in bipolar disorder: A neurophysiological biomarker of intermediate effect?, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.04.026