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Auditory mismatch negativity in bipolar disorder: a focused review

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Abstract: The auditory mismatch negativity, a component of the event-related potential elicited by an unexpected stimulus in a sequence of acoustic stimuli, provides an objective measure of the accuracy of the echoic information processing of the human brain *in vivo*. Auditory mismatch negativity is also a useful probe of cortical glutamatergic N-methyl-D-aspartate receptor activity and disturbance. Notably, auditory mismatch negativity is consistently impaired in schizophrenia. Because of the wide spectrum extending from bipolar affective illness and schizoaffective psychosis to typical schizophrenia, we examined the literature on auditory mismatch negativity in bipolar disorder with the aim to find any neurophysiological dysfunction concerning pre-attentive information processing shared by these clinical conditions. This focused review includes 26 original articles published in peer-reviewed journals and indexed in the National Institutes of Health National Library of Medicine (PubMed) search system. Overall, evidence is consistent with the finding that auditory mismatch negativity is impaired in bipolar disorder with psychotic features, even though to a lesser extent than in schizophrenia. It must be acknowledged that, in a few twin and family studies, mismatch negativity abnormalities were not specifically associated with bipolar disorder. In conclusion, auditory mismatch negativity research supports the involvement of the N-methyl-D-aspartate system in the pathophysiology of bipolar disorder, as previously assessed for schizophrenia, thus creating an intriguing *trait d'union* between these two mental illnesses and stimulating the development of novel

therapeutic agents. With additional replication and validation, auditory mismatch negativity may be further considered as a correlate of a common psychopathology of schizophrenia and bipolar spectrum illnesses.

Keywords: glutamate receptor; neurophysiology; pre-attentive processing; psychosis; translational neuroscience.

Introduction

Bipolar disorder (BD) is a chronic psychiatric illness characterized by changes in mood with recurring episodes of mania, hypomania, depression, and mixed symptoms (Carvalho et al. 2020; Grande et al. 2016; Sekhon and Gupta 2020). BD is one of the main causes of disability in young people, leading to cognitive and functional impairment and increased mortality, particularly by suicide (Carvalho et al. 2020; Grande et al. 2016; Schaffer et al. 2015; Sekhon and Gupta 2020). BD has a lifetime global prevalence ranging from 1 to 3% (Demyttenaere et al. 2004; Moreira et al. 2017), that increases up to 6.4% when sub-threshold cases are included (Judd and Akiskal 2003). Symptoms usually begin at the age of 20 years, being an earlier onset associated with a worse prognosis (Carvalho et al. 2020).

The causes of BD remain unclear; no biomarker has been approved yet for the diagnosis and clinical criteria endure (Vieta and Phillips 2007). Genetic influences are believed to account for 73–93% of the risk of developing BD, indicating a strong hereditary component (Barnett and Smoller 2009). Environmental factors also play a significant role, and individual psychosocial variables may interact with the genetic predisposition (Musci et al. 2019). Less commonly, a bipolar-like disorder may occur because of, or in association with, stroke, traumatic brain injury, human immunodeficiency virus infection, multiple sclerosis, porphyry, temporal lobe epilepsy, or iatrogenic causes (e.g., inappropriate levodopa–carbidopa intake) (Murray et al. 2012; Sablaban and Sivananthan 2019).

Psychotic manifestations often occur in the course of BD, both in the manic and in the depressive phase (Carvalho et al. 2020; Grande et al. 2016; Sekhon and Gupta 2020). Schizophrenia and BD overlap regarding genetic risk, and neuropsychological, clinical, and both structural

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and functional brain changes (Hill et al. 2013; Ivleva et al. 2012; Li et al. 2018; Stahl et al. 2019; Tamminga et al. 2013). In particular, previous studies point out a considerable overlap in genetic susceptibility to schizophrenia and BD, although the influence of early environmental effects is well established in schizophrenia and, to a lesser extent, also in BD (Walker et al. 2002). Structural brain abnormalities of developmental origin, and neuropsychological deficits, have been identified in both schizophrenia and BD. The most plausible explanation is that one or more susceptible genes are shared between schizophrenia and bipolar illness, thus predisposing individuals to psychosis, perhaps by producing a dysregulation of the dopaminergic response to stress (Walker et al. 2002). Additionally, some symptoms, psychosocial functioning, and familial lineage overlap across schizophrenia, schizoaffective disorder, and BD (Tamminga et al. 2013), and all these patients share cognitive deficits (Hill et al. 2013) and similar white and gray matter microstructural alterations, although with some differences (Koshiyama et al. 2020; Maggioni et al. 2016), suggesting that these disorders may exhibit both specific and common features (Maggioni et al. 2016). Accordingly, part of the literature seems to converge on the hypothesis of a continuum extending from BD and bipolar illness with psychotic features to schizoaffective psychosis, up to typical schizophrenia (Kuhne et al. 1988; Tamminga et al. 2013).

In this context, the auditory mismatch negativity (MMN) is a promising tool in psychosis research (Naatanen et al. 2011; Umbricht and Krljes 2005). Auditory MMN (Figure 1) is a component of the event-related potential (ERP) evoked by an unexpected stimulus (deviant) occurring within a sequence of invariant acoustic stimuli (standard), elicited by the divergence between the neuronal model of the physical features of the standard stimulus and the deviant stimulus (Naatanen et al. 1978, 1993). It provides an objective measure of the accuracy of the echoic information processing of the intact human brain or of a dysfunctional brain *in vivo* (Naatanen et al. 2011). Normative data at Fz for the auditory MMN in healthy young adults are 180.5 ± 33.84 ms for latency and -3.2 ± 1.60 μ V for amplitude (Raggi et al. 2013). In addition to the bilateral sources of MMN, located near the primary auditory cortex and predominantly activated in the hemisphere contralaterally to the ear of stimulation, there is also a frontal generator, mainly involving the right hemisphere (Giard et al. 1990; Naatanen and Michie 1979). There seems to be a small delay in the frontal activation compared to that of the auditory cortex (Rinne et al. 2000), supporting the hypothesis that detection of the signal change generated by the auditory cortex may induce the frontal addressing mechanism of attention (Näätänen 1990).

MMN is more evident when the subject ignores the stimuli (Paavilainen et al. 1993) and, therefore, it can be administered, for instance, whereas the participant is watching a video (Raggi et al. 2013). The auditory MMN can occur in response to deviance in pitch, intensity, or duration (Baldeweg et al. 1999; Bardsley et al. 2014), and its elicitation depends on unconscious processes. Therefore, a very small difference in frequency between sinusoidal pure acoustic tones, such as 1,000 Hz for the standard stimuli and 1,020 Hz, 1,050 Hz, or 1,100 Hz for deviant stimuli, are used in common paradigms of clinical settings (Bardsley et al. 2014). To quantify the MMN, which is covered by the brain electrical activity, the evoked response to the standard tone can be subtracted from the corresponding response to the deviant stimulus (Ferri et al. 2003), being this usually more evident on the frontal sites and on the mastoids because of the inversion of the dipole (Alho et al. 1986; Lang et al. 1995).

Auditory MMN is ideal to address whether an impairment of the working memory may be because of premature trace decay using paradigms with a different inter-stimulus interval between tones. In this perspective, there are reports in physiological aging (Raggi et al. 2013), in some neurodegenerative disorders (such as Alzheimer's dementia and Parkinson's diseases) (Pekkonen 2000), and in schizophrenia (Javitt et al. 1998; Umbricht and Krljes 2005). In particular, in schizophrenia MMN is considered as a highly reproducible neurophysiological marker (Javitt 2000; Umbricht et al. 2006) and has shown to follow a progressive course, with reduced MMN amplitude associated with a loss of gray matter in the left superior temporal gyrus (Salisbury et al. 2007). Moreover, MMN deficits index a cortical N-methyl-D-aspartate (NMDA) receptor dysfunction, mostly affecting the memory-trace formation and hence cognition (Gene-Cos et al. 1999; Javitt et al. 1996).

An extensive literature review explains the characteristics of other ERPs (e.g., P3a), some of which have been studied in association with MMN in BD (de Tommaso et al. 2020). ERP components are not seen in raw electroencephalogram (Kavassidis et al. 2012), being detected with averaging (Dawson 1954). The P3a ERP component is a positive scalp-recorded brain potential with a maximum amplitude over the frontal/central electrode sites and a peak latency within the 250–280 ms post-stimulus (Comerchero and Polich 1999). The P3a has been associated with activity related to the engagement of attention (especially orienting and involuntary shifts to changes in the environment) (Friedman et al. 2001) and the processing of novelty (Polich 2007), and the NMDA receptor system is thought to modulate it (Watson et al. 2009). Similar to MMN, P3a is a strongly automatic process (Grillon et al.

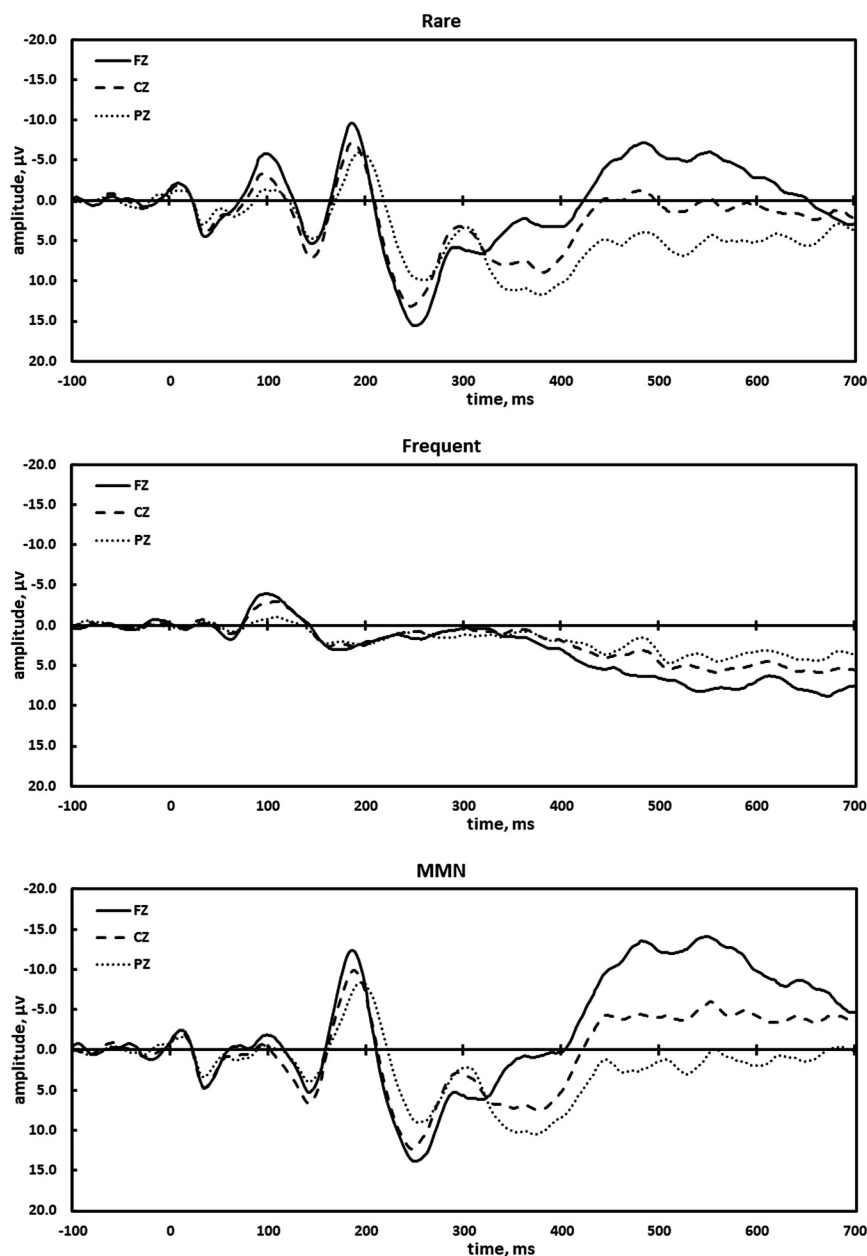


Figure 1: Mismatch negativity (MMN). Example of the response obtained from the midline scalp location Fz, in a healthy subject, after the delivery of deviant or rare (upper panel) and standard or frequent stimuli (middle panel). The difference (deviant–standard) between the two waveforms in the time window of 140–260 ms after stimulus delivery during a passive task condition represents the MMN (bottom panel).

1990) and has been found to be impaired in schizophrenia (Jahshan et al. 2012a; Koshiyama et al. 2020).

The key consideration of our analysis is that psychotic manifestations often occur in the course of BD (Carvalho et al. 2020; Grande et al. 2016; Sekhon and Gupta 2020) and that, as stated, schizophrenia and BD overlap with respect to different domains (Hill et al. 2013; Ivleva et al. 2012; Li et al. 2018; Stahl et al. 2019; Tamminga et al. 2013). Finding alterations in auditory MMN, which has an established usefulness in schizophrenia research (de Tommaso et al. 2020; Gene-Cos et al. 1999; Javitt 2000; Javitt et al. 1998; Salisbury et al. 2007; Umbricht et al. 2006; Umbricht and Krljes 2005), may suggest a potential neurophysiological

marker also in BD with psychosis (Kuhne et al. 1988). Here, we examined the literature on auditory MMN in BD with the aim to find any neurophysiological change concerning pre-attentive information processing shared by these clinical conditions.

Methods

This review focused on all the original articles published in peer-reviewed journals and identified using the National Institutes of Health National Library of Medicine (PubMed) literature search system. Search terms included “bipolar disorder AND mismatch negativity”.

Non-English articles, book chapters, monographs, commentaries, review articles, case studies, dissertations, abstracts, letters to the Editor, and preprints were excluded. Inclusion criteria required that the original research articles included the auditory MMN measure. Titles and abstracts of the retrieved studies were independently reviewed by two authors and faced with inclusion and exclusion criteria. Each full-text article was examined if there were any aspect of the abstracts that was unclear and for the final article selection.

Results

The PubMed-based search produced a total of 39 articles. Seven of them were excluded because they were review papers not dealing with the topic of interest. Six additional articles were excluded because of the following reasons: one because it was about visual MMN; two were not relevant to the topic; three did not include the auditory MMN measure, although focused on the initial stages of information processing.

Therefore, we eventually included 26 studies investigating auditory MMN in BD patients (Andersson et al. 2008; Baldeweg and Hirsch 2015; Braeutigam et al. 2018; Catts et al. 1995; Chitty et al. 2014, 2015a–c; Domjan et al. 2012; Donaldson et al. 2020; Hall et al. 2007, 2009; Jahshan et al. 2012b; Kaur et al. 2011, 2012a,b, 2013, 2019, Kim et al. 2019a,b, 2020; Ogura et al. 1993; Paris et al. 2018; Salisbury et al. 2007; Shimano et al. 2014; Takei et al. 2010), which are listed in Table 1. The main results are summarized in the following paragraphs.

Studies reporting changes in MMN amplitude

Thirteen studies (Andersson et al. 2008; Donaldson et al. 2020; Jahshan et al. 2012b; Kaur et al. 2011, 2012a,b, 2013, Kim et al. 2019a,b, 2020; Ogura et al. 1993; Shimano et al. 2014; Takei et al. 2010) reported an MMN amplitude reduction in BD, suggesting a deficit in pre-attentive auditory processing (Table 1). Among them, four studies observed this reduced MMN amplitude in BD patients compared to healthy controls (Andersson et al. 2008; Ogura et al. 1993; Shimano et al. 2014; Takei et al. 2010), whereas in the other nine studies BD patients were compared to patients with other psychiatric disorders, namely: schizophrenia (Donaldson et al. 2020; Jahshan et al. 2012b; Kaur et al. 2011, 2012a,b, 2013, Kim et al. 2019a,b), schizophrenia-spectrum disorders (Donaldson et al. 2020; Kaur et al. 2011, 2012a), major depressive disorder (Donaldson et al. 2020; Kaur et al. 2011, 2012b; Kim et al. 2020), or other psychotic disorders (Donaldson et al. 2020). None of these studies found

significant differences in MMN amplitude between BD patients and those with other psychiatric disorders. However, except for one study (Donaldson et al. 2020), the other eight found that the reduction was less severe in BD than in schizophrenia (Jahshan et al. 2012b; Kaur et al. 2011, 2012a,b, 2013, Kim et al. 2019a,b, 2020).

Significant correlations were detected between functional outcomes and MMN source activity from the left anterior cingulate cortex, inferior frontal gyrus, and middle frontal gyrus, that was increased in BD compared to major depressive disorder (Kim et al. 2020). Young patients with the most impaired MMN amplitude at baseline showed the most severe levels of disability at follow-up (average of 19 ± 5 months after baseline assessment) (Kaur et al. 2013).

Studies of MMN latency abnormalities

Four articles report an MMN latency prolongation in BD (Andersson et al. 2008; Domjan et al. 2012; Paris et al. 2018; Takei et al. 2010). A magnetoencephalography (MEG) investigation suggested that information processing at the pre-attentive level was impaired in patients with BD, irrespective of clinical symptoms (Takei et al. 2010), whereas increased latency was not influenced by mood variation in another study (Andersson et al. 2008). A delayed MMN latency for the emotional speech processing suggests that vocal emotional cues may not be recognized as salient by BD patients, with possible consequences on social interactions (Paris et al. 2018). Prolonged pitch deviant MMN latency was found in BD with psychotic features (Domjan et al. 2012).

Bipolar twin and family studies

In two articles by the same research group and with very similar samples of monozygotic BD twin pairs (Hall et al. 2007, 2009), unlike P50 suppression ratio (Hall et al. 2007), MMN was not associated with BD. This makes it impossible to define this component of the evoked potential as an endophenotype of psychotic BD.

NMDA and MMN

As mentioned, MMN impairment is viewed as an index of cortical NMDA receptor dysfunction affecting cognition in schizophrenia (Javitt et al. 1996). Interesting findings also come from five studies in BD (Chitty et al. 2014; Chitty et al. 2015a, b, c; Kaur et al. 2019). Abnormal association between hippocampal *in vivo* glutathione concentration,

Table 1: Summary of the relevant data found in bipolar disorder and mismatch negativity component.

Reference	Groups (n)	BD age, years	BD MMN amplitude at Fz (μV)	HC MMN amplitude (μV) at Fz	BD MMN latency (ms) at Fz	HC MMN latency (ms) at Fz	Main findings and significance
Andersson et al. 2008	25 BD II, 28 HC	36.3 ± 13.1	~3	~4	181 ± 16.96	172 ± 13.77	Data may be related to a dysfunction of the frontal-temporal circuitry underlying pre-attentive stimulus change detection
Baldeweg and Hirsch 2015	25 BD, 49 SPR, 15 AD, 49 HC	38.1 ± 10.3	-2.5 ± 1.4 (duration) -3.5 ± 1.5 (frequency)	-2.7 ± 1.4 (duration) -3.3 ± 1.7 (frequency)	N/A	N/A	MMN impairment in SPR, which was not found in BD
Braeutigam et al. 2018	16 BD with psychotic features, 16 SPR, 14 HC	16.8 ± 1.1	~1	~0.8	~160	~180	Dissociable patterns of MMN response in adolescents, suggesting developmentally sensitive, but separate markers for SPR and BD
Catts et al. 1995	11 BD, 22 SPR, 11 HC	36.0, SD N/A (21–53)	-3.23 ± 1.76 (short deviant) -2.46 ± 1.25 (long deviant)	-3.49 ± 1.40 (short deviant) -2.88 ± 2.00 (long deviant)	N/A	N/A	Findings that implicate the auditory cortex in the pathophysiology of SPR but not of BD
Chitty et al. 2014	42 BD, 34 HC	Mean ± SD N/A (16–30)	-4.86 ± 2.2 (BD with low-risk alcohol use) -4.31 ± 2.5 (BD with high-risk alcohol use)	-4.76 ± 2.3 (HC with low-risk alcohol use) -5.04 ± 2.3 (HC with high-risk alcohol use)	N/A	N/A	MMN findings suggesting an additive effect of alcohol on an altered NMDA/glutamatergic system in BD
Chitty et al. 2015	33 BD, 23 HC	23.3 ± 3.5	-4.21 ± 1.8	-5.62 ± 2.3	N/A	N/A	Evidence supporting the role of hippocampal glutamate signaling through the NMDA receptor in temporal MMN
Chitty et al. 2015	28 BD, 22 HC	23.4 ± 3.5	2.15 ± 1.3 (at M1)	2.79 ± 1.5 (at M1)	N/A	N/A	Abnormal association in BD between hippocampal <i>in vivo</i> glutathione concentration and temporal MMN, providing insight into the involvement of hippocampal NMDA in BD
Chitty et al. 2015	46 BD (27 returned for follow-up ~ 18 months later the baseline assessment)	22.2 ± 3.5, (16–30)	-5.52 ± 2.5 (baseline) -5.30 ± 2.5 (follow-up)	N/A	N/A	N/A	Risky alcohol use in BD may further compound pre-existing NMDA receptor abnormalities; reducing alcohol use in the early stages of illness is associated with changes in MMN
Domján et al. 2012	20 BD I with psychotic features, 20 SPR, 21 HC	42.9 ± 9.6	-4.1 ± 4.12 (at Cz, value at Fz N/A)	-6.94 ± 3.04 (at Cz, value at Fz N/A)	186.99 ± 18.85 (at Cz, value at Fz N/A)	163.88 ± 18.5 (at Cz, value at Fz N/A)	Prolonged pitch deviant MMN latency was found to be characteristic of BD

Table 1: (continued)

Reference	Groups (n)	BD age, years	BD MMN amplitude at Fz (μV)	HC MMN amplitude at Fz (μV)	BD MMN latency (ms) at Fz	HC MMN latency (ms) at Fz	Main findings and significance
Donaldson et al. 2020	75 BD + MDD, 116 SPR + SD, 25 OPD, 248 NPD	42 ± 56.0	N/A	N/A	N/A	N/A	Associations of MMN with psychotic symptoms and functioning across psychotic disorders
Hall et al. 2007	10 discordant MZ BD twin pairs, 6 concordant MZ BD twin pairs, 78 HC twin pairs	41.8 ± 13.7 (discordant for BD) 40.3 ± 14.5 (concordant for BD)	-3.30 ± 1.01 (discordant for BD) -2.98 ± 2.00 (concordant for BD)	-3.38 ± 1.46	353.80 ± 26.20 (discordant for BD) 378.17 ± 39.72 (concordant for BD)	347.49 ± 31.55	Unlike P50 suppression, MMN was not associated with the illness
Hall et al. 2009	10 discordant MZ BD twin pairs, six concordant MZ BD twin pairs, six concordant MZ BD twin pairs, 76 HC twin pairs	42.34 ± 11.7	-2.97 ± 1.36	-3.29 ± 1.42	N/A	N/A	MMN was not associated with the illness
Jahshan et al. 2012	52 BD (7 BD I with psychotic features), 30 SPR, 27 HC	45.2 ± 9.8	-1.35 ± 0.87	-2.12 ± 1.22 -1.27 ± 0.81 (BD I) -1.49 ± 0.98 (BD II)	~200	~200	Deficit in pre-attentive auditory processing in BD detected by means of the MMN and the P3a that are less severe than those seen in SPR
Kaur et al. 2011	17 FEP affective-spectrum (BD with psychotic features and MDD with psychotic features), 18 FEP SPR-spectrum (SPR, schizoaffective disorder, schizophreniform disorder), 18 HC	22.8 ± 4.6 (17–36)	-4.4 ± 2.1	-6.4 ± 1.9	N/A	N/A	FEP SPR and FEP affective-spectrum showed reduced frontal-central MMN and central P3a amplitudes compared to HC; FEP subgroups showed poorer cognitive and psychosocial functioning; the combined FEP sample showed significant correlations between frontal-central MMN amplitudes and cognitive measures
Kaur et al. 2012	26 BD (10 with psychotic features; 25% GI, 35% + FMN, 41% + TMMN), 42 SPR-spectrum (55 GI, 35% + FMN, 41% + TMMN), 19 MDD (21% GI, 29% + FMN, 18% + TMMN), 27 HC	Mean ± SD N/A, (16–30)	N/A	-5.9 ± 2.1 -3.6 ± 1.6 (GI) -7.1 ± 1.0 (+FMN) -3.6 ± 2.2 (+TMMN)	N/A	N/A	SPR-spectrum patients tended to show the most global impairments in the neurophysiological complex including MMN
Kaur et al. 2012	20 affective-spectrum (BD I and BD II with or without psychotic features), 20 SPR-spectrum (SPR, schizoaffective disorder, schizophreniform disorder), 20 HC	21.0 ± 4.1 (15–30)	-4.3 ± 1.9	-6.3 ± 2.1	N/A	N/A	Both patient groups showed significantly reduced frontal-central MMN and central P3a amplitudes, performed worse than controls across psychosocial and clinical measures, thus confirming previous findings from the same research group

Table 1: (continued)

Reference	Groups (n)	BD age, years	BD MMN amplitude at Fz (μ V)	HC MMN amplitude at Fz (μ V)	BD MMN latency (ms) at Fz	HC MMN latency (ms) at Fz	Main findings and significance
Kaur et al. 2013	33 affective-spectrum (BD and MDD with or without psychotic features), 27 SPR-spectrum (SPR, schizoaffective disorder, schizophrenia), 30 HC	Mean \pm SD N/A, (16–30)	-4.3 ± 2.3 2.2 ± 1.4 (M 1) 2.3 ± 1.1 (M 2)	-5.2 ± 2.3 2.8 ± 1.3 (M 1) 2.7 ± 1.3 (M 2)	N/A	N/A	Young patients with the most impaired MMN amplitudes at baseline showed the most severe level of disability at follow-up
Kaur et al. 2019	47 BD (37 with psychotic features), 13 SPR, lack of a HC group	23.5 ± 4.2 (16–33)	-4.7 ± 1.9	N/A	N/A	N/A	Proton magnetic resonance spectroscopy and ERPs provides <i>in vivo</i> evidence that glutamatergic processes may underlie MMN generation in early-stage SPR but not in the early-stage BD, suggesting differences in the MMN mechanism in these groups
Kim et al. 2019a, b	37 BD, 38 SPR, 32 HC	41.00 ± 13.06 (20–63)	-1.95 ± 1.25	-2.73 ± 1.53	N/A	N/A	Moderate impairment of pre-attentive processing in BD exhibited intermediate MMN amplitude among SPR and HC groups; average MMN significantly correlated with the cortical thickness of the left anterior cingulate cortex and the right superior temporal gyrus
Kim et al. 2019a, b	30 BD, 27 SPR, 25 HC	39.70 ± 12.61 (20–63)	-2.12 ± 1.38	-3.33 ± 1.76	N/A	N/A	Moderate impairment of pre-attentive processing in fact BD sufferers exhibited intermediate MMN amplitude among SPR and HC groups
Kim et al. 2020	29 BD, 27 MDD, 33 HC	33.86 ± 14.71	-2.72 ± 0.97	-3.81 ± 1.57	~ 220	~ 210	Deficient pre-attentive processing in BD; a significant correlation between functional outcomes and MMN activity, that seems to be a candidate evaluation tool for functional outcomes in mood disorders
Ogura et al. 1993	8 BD, 12 DSE, 16 DRE, 36 HC	36.5 ± 5.8 (18–65)	-0.2 ± 2.8	-1.5 ± 2.3	N/A	N/A	The MMN latency of the two groups did not differ, whereas the MMN of patients was reduced in amplitude; thus, these subjects may have an alteration in the fully automatic cerebral mismatch related to MMN
Paris et al. 2018	14 BD, 14 HC	32.77 ± 6.92	-3.05 ± 1.85 (Happy Vocal)	-2.33 ± 0.87 (Happy Vocal)	170.62 ± 29.17 (Happy vocal)	131.51 ± 22.2 (Happy vocal)	Delayed MMN latency for emotional speech processing suggesting vocal

Table 1: (continued)

Reference	Groups (n)	BD age, years	BD MMN amplitude at Fz (μV)	HC MMN amplitude (μV) at Fz	BD MMN latency (ms) at Fz	HC MMN latency (ms) at Fz	Main findings and significance
Salisbury et al. 2007	17 BD with psychotic features (13 retested), 16 SPR, 20 HG	21.8 ± 5.0	-2.94 ± 1.65 (Sad Vocal) -3.04 ± 1.20 (time 1) -3.08 ± 0.93 (time 2)	-2.18 ± 1.32 (Sad Vocal) -4.09 ± 1.86 (time 1) -4.47 ± 1.44 (time 2)	194.47 ± 18.50 (Sad Vocal) N/A	163.92 ± 39.23 (Sad vocal) N/A	emotional cues may not be recognized as salient by subjects with BD SPR patients, who initially showed normal mean MMN, at longitudinal retesting showed a significant reduction in MMN, suggesting a post-onset reduction (imaging and MMN amplitude) in SPR but not BD
Shimano et al. 2014	22 BD, 22 HC	39.60 ± 10.90 (21–60)	~14	~19	~150	~140	BD may exhibit pre-attentive auditory dysfunction indexed by reduced pitch magnetic MMN responses. Pitch magnetic MMN could be a trait marker reflecting global BD severity
Takei et al. 2010	10 BD, 20 HC	45.5 ± 11.4 (29–64)	N/A (attenuated)	N/A	N/A (prolonged)	N/A	MEG investigation suggesting that information processing at the pre-attentive level is impaired in BD, irrespective of the clinical symptoms

Data are shown as mean ± standard deviation. AD, Alzheimer's disease; BD, bipolar disorder; DRE, depression with recurrent episodes; DSE, depression with a single episode; ERP, event-related potential; FEP, first-episode psychosis; GI, globally impaired; HC, healthy control; MDD, major depressive disorder; MMN, mismatch negativity; MZ, monozygotic; NPD, no psychotic disorder; MEG, magnetoencephalography; MRI, magnetic resonance imaging; NMDA, N-methyl-D-aspartate; OPD, other psychotic disorder; SD, schizoaffective disorder; SPR, schizophrenia; +MMN, largest frontal mismatch negativity; +TMMN, largest temporal mismatch negativity. All missing data in the cells were not available.

measured via proton magnetic resonance spectroscopy, and temporal MMN provides insights into the hippocampal NMDA disturbance implicated in BD (Chitty et al. 2015a, b). Moreover, NMDA receptors are inhibited by acute ethanol administration and undergo brain region-specific adaptations after chronic alcohol exposure (Siggins et al. 2003; Zamudio et al. 2020). This might imply the increased likelihood of alcohol-related disorder in BD compared to the general population (Di Florio et al. 2014). MMN findings also suggest an additive effect of alcohol on the altered NMDA/glutamatergic system in BD (Chitty et al. 2014).

A survey aimed to examine the NMDA receptor activity in BD adolescents and young adults in relation to changes in alcohol use (Chitty et al. 2015c). The authors found that a reduction in risky drinking patterns was associated with increased temporal MMN and decreased frontal-central MMN, whereas larger temporal MMN at baseline was a significant predictor of greater alcohol use at follow-up (Chitty et al. 2015c). Thus, risky alcohol use in BD may further compound pre-existing NMDA receptor abnormalities. Reducing alcohol use in the early stages of the disorder was associated with changes in MMN (Chitty et al. 2015c), thus attributing to this ERP a crucial role in the clinical and neurophysiological follow-up.

MMN and P3a

Some findings suggest that, in emerging psychiatric disorders, there are distinct MMN/P3a profiles of patient subgroups, independently of their current symptomatology (Kaur et al. 2012b). However, aiming to investigate

pre-attentive auditory information processing in BD with a comprehensive approach, we have included six studies in this review involving the measure of both MMN and P3a (Andersson et al. 2008; Jahshan et al. 2012b; Kaur et al. 2011, 2012a, b; Paris et al. 2018).

Table 2 summarizes the findings of amplitude and latency: despite the two different levels of pre-attentive information processing (Friedman et al. 2001; Näätänen 1990; Rinne et al. 2000), there is a similar response pattern in the amplitude alteration, with a concordance of its reduction in four out of six reports, and totally in five out of six studies.

Discussion

From a pure neurophysiological perspective, MMN is consistently impaired in schizophrenia (de Tommaso et al. 2020; Gene-Cos et al. 1999; Javitt 2000; Javitt et al. 1998; Salisbury et al. 2007; Umbricht et al. 2006; Umbricht and Krljes 2005). This new appraisal of the literature, despite some weakness in relation to family studies, emphasizes that MMN abnormalities occur mainly in BD with psychotic features. This finding supports the intriguing model of the so-called “unitary psychosis”, which refers to the hypothesis that psychotic symptoms in different clinical conditions may refer to a single underlying disease process (Berrios and Beer 1994), although this model still remains uncertain and not shared by all clinicians and researchers. As further support, an earlier study found an association between MMN and psychotic symptoms (Hall et al. 2007). Taken together, these findings lead to the need for a better comprehension of the nature of MMN in psychotic BD, to fully understand its potential as a biological marker and therapeutic target.

It is worth noting that half of the studies reviewed here did not report a significant difference in MMN amplitude between BD patients and healthy controls or between BD and schizophrenia (Baldeweg and Hirsch 2015; Braeutigam et al. 2018; Catts et al. 1995; Chitty et al. 2014, 2015a–c; Domjan et al. 2012; Hall et al. 2007, 2009; Kaur et al. 2019; Paris et al. 2018; Salisbury et al. 2007). However, all the patients included in these studies, except for two (Braeutigam et al. 2018; Salisbury et al. 2007), were affected by BD without psychosis. In particular, in the study by Salisbury et al. (Salisbury et al. 2007), schizophrenia, BD with psychosis, and controls did not differ in MMN amplitude at baseline; conversely, at the longitudinal testing, the schizophrenia group showed MMN amplitude reduction. In the other more recent study, MEG was used to examine the neuronal auditory response elicited by a roving MMN

Table 2: Studies of the mismatch negativity (MMN) and the P3a in patients with bipolar disorder compared to healthy controls.

References	MMN amplitude	MMN latency	P3a amplitude	P3a latency
Andersson et al. 2008	↓	↑	=	↑ (Only female patients)
Jahshan et al. 2012	↓	=	↓	=
Kaur et al. 2011	↓	=	↓	=
Kaur et al. 2012a	↓	=	↓	=
Kaur et al. 2012b	↓	=	↓	=
Paris et al. 2018	=	↑	↓	=

↑, increased; ↓, decreased; =, unchanged.

paradigm in adolescents with schizophrenia, in those with BD and psychosis, and in typically developing individuals (Braeutigam et al. 2018). The authors found a significantly reduced MMN latency in BD compared to the other groups, whereas the amplitude was significantly decreased only in patients with schizophrenia (Braeutigam et al. 2018).

It should be mentioned that a review published in 2017 has summarized the literature on MMN in BD, although undertaken in the context of a clinical focus on schizophrenia (Hermens et al. 2018). Despite the concept of a schizophrenia-related specificity of MMN (Baldeweg and Hirsch 2015), there is mounting evidence supporting the possibility of MMN in BD as a neurophysiological marker of intermediate effect, as confirmed by two earlier meta-analyses revealing moderate effect sizes for MMN impairment in BD (Chitty et al. 2013; Erickson et al. 2016). However, a closer inspection of the studies indicates that there may be subgroups of BD patients with an MMN impairment comparable to schizophrenia (Hermens et al. 2018), suggesting the effect of severity and/or chronicity of illness (Salisbury et al. 2007). Notably, in 2017 there was still a paucity of MMN studies directly comparing schizophrenia and BD, which have been now included in the present review (Braeutigam et al. 2018; Kaur et al. 2019; Kim et al. 2019a, b), along with the results of MMN changes across both psychotic (Donaldson et al. 2020) and affective disorders (Kim et al. 2020). Finally, another recent study reviewed here has assessed the role of MMN in emotional speech processing deficits in BD (Paris et al. 2018).

Compared to the previous review on this topic (Hermens et al. 2018), therefore, here we provide a more comprehensive update of the literature and, more importantly, support the role of MMN as a biomarker also in BD with psychotic features. This might answer the question related to the extent to which this neurophysiological change is unique or overlap across BD and schizophrenia (Thaker 2008). Nevertheless, as it is challenging for a single marker to be pathognomonic for such complex diseases (Clementz et al. 2016), in future studies MMN needs to be integrated with multivariate constructs (e.g., neuroimaging, psychopathological, and other electrophysiological findings, such as MEG or transcranial magnetic stimulation) (Faro et al. 2010), which are more likely to be superior, in terms of effect sizes, in distinguishing subgroups of patients.

Several animal and human studies have shown that administration of the NMDA receptor antagonists attenuates MMN amplitude, thus providing convincing support for the specific role of NMDA receptor in MMN generation (Kenemans and Kahkonen 2011). On the contrary, dopaminergic (Umbricht et al. 1998; Umbricht et al. 1999) and serotonergic receptor agents (Leung et al. 2010; Umbricht

et al. 2002) do not modulate MMN. In this review, we have identified five studies on the relationship between MMN and NMDA receptor expression in BD (Chitty et al. 2014; Chitty et al. 2015a, b, c; Kaur et al. 2019). In two of them (Chitty et al. 2015b; Kaur et al. 2019), the combination of electroencephalogram and proton magnetic resonance spectroscopy has allowed the quantification of some key neurometabolite concentrations *in vivo*, thereby providing a more integrated understanding of the glutamatergic system underlying MMN generation (Ramadan et al. 2013).

In a study of both T1-weighted structural magnetic resonance imaging and auditory MMN, a reduced average MMN amplitude in BD was associated with cortical thinning in the left anterior cingulate cortex and in the right superior temporal gyrus (Kim et al. 2019a). These results support that MMN alterations in BD might be associated with structural changes in the regions serving MMN generators (Jemel et al. 2002; Rinne et al. 2000). Moreover, the mentioned surveys about auditory MMN suggest an additive effect of alcohol on a perturbed NMDA/glutamatergic system in BD (Chitty et al. 2014, 2015c).

Overall, MMN research supports the involvement of the NMDA system in the pathophysiology of BD, as previously assessed for schizophrenia (Javitt et al. 1996), thus creating a *trait d'union* between these illnesses. It springs from this the possibility to explore the development of novel therapeutic agents modulating this receptor, such as ketamine, memantine, AZD6765, traxoprodil, MK-0657, GLYX-13, NRX-1047, D-cycloserine, and sarcosine, being all of them targeting this system (Dang et al. 2014; Iadarola et al. 2015).

It appears also evident from the present review the utility of investigating pre-attentive information processing in BD by assessing both MMN and P3a, based on the good concordance of their amplitude reduction found in some studies (Table 2). These two ERPs probe different levels of pre-attentive information processing and do not share the same generators (Friedman et al. 2001; Näätänen 1990; Rinne et al. 2000), being both dependent on an automatic process. In a clinical setting, it is of pivotal importance to use simple paradigms, like a three-tone (standard, deviant, novel) auditory oddball paradigm (Raggi et al. 2013). Moreover, ERPs do not use radiation, are practical and quite inexpensive, thus being useful for both clinical evaluation and research purposes. Lastly, given the heritable component of BD (Barnett and Smoller 2009; Stahl et al. 2019), more familial and twin studies are warranted to understand whether MMN parameters might be reproducible across families and provide putative endophenotypes of psychotic BD (Hall et al. 2007, 2009).

Conclusion

The neural mechanisms underlying BD are still under investigation. Auditory MMN, which is considered to be a biomarker for schizophrenia, might represent a useful tool also in the clinical and research approach to BD with psychotic features, particularly in follow-up evaluations and in the design of novel therapeutic agents modulating the NMDA receptor activity. With additional replication and validation, MMN may be further considered as a correlate of common psychopathology of schizophrenia and bipolar spectrum illnesses.

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References

- Alho, K., Paavilainen, P., Reinikainen, K., Sams, M., and Naatanen, R. (1986). Separability of different negative components of the event-related potential associated with auditory stimulus processing. *Psychophysiology* 23: 613–623.
- Andersson, S., Barder, H.E., Hellvin, T., Lovdahl, H., and Malt, U.F. (2008). Neuropsychological and electrophysiological indices of neurocognitive dysfunction in bipolar II disorder. *Bipolar Disord.* 10: 888–899.
- Baldeweg, T. and Hirsch, S.R. (2015). Mismatch negativity indexes illness-specific impairments of cortical plasticity in schizophrenia: a comparison with bipolar disorder and Alzheimer's disease. *Int. J. Psychophysiol.* 95: 145–155.
- Baldeweg, T., Richardson, A., Watkins, S., Foale, C., and Gruzeli, J. (1999). Impaired auditory frequency discrimination in dyslexia detected with mismatch evoked potentials. *Ann. Neurol.* 45: 495–503.
- Bardsley, B., Parker, D., and Lockton, E. (2014). Implementation of integrated mismatch negativity in differentiating children with specific language impairment. *Neuropediatrics* 45: 10–15.
- Barnett, J.H. and Smoller, J.W. (2009). The genetics of bipolar disorder. *Neuroscience* 164: 331–343.
- Berrios, G.E. and Beer, D. (1994). The notion of a unitary psychosis: a conceptual history. *Hist. Psychiatry* 5: 13–36.
- Braeutigam, S., Dima, D., Frangou, S., and James, A. (2018). Dissociable auditory mismatch response and connectivity patterns in adolescents with schizophrenia and adolescents with bipolar disorder with psychosis: a magnetoencephalography study. *Schizophr. Res.* 193: 313–318.
- Carvalho, A.F., Firth, J., and Vieta, E. (2020). Bipolar disorder. *N. Engl. J. Med.* 383: 58–66.
- Catts, S.V., Shelley, A.M., Ward, P.B., Liebert, B., McConaghy, N., Andrews, S., and Michie, P.T. (1995). Brain potential evidence for an auditory sensory memory deficit in schizophrenia. *Am. J. Psychiatry* 152: 213–219.
- Chitty, K.M., Kaur, M., Lagopoulos, J., Hickie, I.B., and Hermens, D.F. (2014). Risky alcohol use predicts temporal mismatch negativity impairments in young people with bipolar disorder. *Biol. Psychol.* 99: 60–68.
- Chitty, K.M., Lagopoulos, J., Hickie, I.B., and Hermens, D.F. (2015a). Hippocampal glutamatergic/NMDA receptor functioning in bipolar disorder: a study combining mismatch negativity and proton magnetic resonance spectroscopy. *Psychiatry Res.* 233: 88–94.
- Chitty, K.M., Lagopoulos, J., Hickie, I.B., and Hermens, D.F. (2015b). Investigating the role of glutathione in mismatch negativity: an insight into NMDA receptor disturbances in bipolar disorder. *Clin. Neurophysiol.* 126: 1178–1184.
- Chitty, K.M., Lagopoulos, J., Kaur, M., Hickie, I.B., and Hermens, D.F. (2015c). The N-methyl-D-aspartate receptor as a neurobiological intersection between bipolar disorder and alcohol use: a longitudinal mismatch negativity study. *Int. J. Neuropsychopharmacol.* 18. <https://doi.org/10.1093/ijnp/pyu113>.
- Chitty, K.M., Lagopoulos, J., Lee, R.S., Hickie, I.B., and Hermens, D.F. (2013). A systematic review and meta-analysis of proton magnetic resonance spectroscopy and mismatch negativity in bipolar disorder. *Eur. Neuropsychopharmacol.* 23: 1348–1363.
- Clementz, B.A., Sweeney, J.A., Hamm, J.P., Ivleva, E.I., Ethridge, L.E., Pearlson, G.D., Keshavan, M.S., and Tamminga, C.A. (2016). Identification of distinct psychosis biotypes using brain-based biomarkers. *Am. J. Psychiatry* 173: 373–384.
- Comerchero, M.D. and Polich, J. (1999). P3a and P3b from typical auditory and visual stimuli. *Clin. Neurophysiol.* 110: 24–30.
- Dang, Y.H., Ma, X.C., Zhang, J.C., Ren, Q., Wu, J., Gao, C.G., and Hashimoto, K. (2014). Targeting of NMDA receptors in the treatment of major depression. *Curr. Pharm. Des.* 20: 5151–5159.
- Dawson, G.D. (1954). A summation technique for the detection of small evoked potentials. *Electroencephalogr. Clin. Neurophysiol.* 6: 65–84.
- de Tommaso, M., Betti, V., Bocci, T., Bolognini, N., Di Russo, F., Fattapposta, F., Ferri, R., Invitto, S., Koch, G., and Miniussi, C., et al. (2020). Pearls and pitfalls in brain functional analysis by event-related potentials: a narrative review by the Italian Psychophysiology and Cognitive Neuroscience Society on methodological limits and clinical reliability-part I. *Neurol. Sci.* 41: 2711–2735.
- Demyttenaere, K., Bruffaerts, R., Posada-Villa, J., Gasquet, I., Kovess, V., Lepine, J.P., et al. (2004). Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World mental Health surveys. *J. Am. Med. Assoc.* 291: 2581–2590.
- Di Florio, A., Craddock, N., and van den Bree, M. (2014). Alcohol misuse in bipolar disorder. A systematic review and meta-analysis of comorbidity rates. *Eur. Psychiatry* 29: 117–124.
- Domjan, N., Csifcsak, G., Drotos, G., Janka, Z., and Szendi, I. (2012). Different patterns of auditory information processing deficits in chronic schizophrenia and bipolar disorder with psychotic features. *Schizophr. Res.* 139: 253–259.
- Donaldson, K.R., Novak, K.D., Foti, D., Marder, M., Perlman, G., Kotov, R., and Mohanty, A. (2020). Associations of mismatch negativity with psychotic symptoms and functioning

- transdiagnostically across psychotic disorders. *J. Abnorm. Psychol.* 129: 570–580.
- Erickson, M.A., Ruffle, A., and Gold, J.M. (2016). A meta-analysis of mismatch negativity in schizophrenia: from clinical risk to disease specificity and progression. *Biol Psychiatry* 79: 980–987.
- Faro, A., Giordano, D., Kavasidis, I., Pino, C., Spampinato, C., Cantone, M.G., Lanza, G., and Pennisi, M. (2010). An interactive tool for customizing clinical Transcranial Magnetic Stimulation (TMS) experiments. In: Bamidis, P.D., and Pallikarakis, N. (Eds.), *XII Mediterranean conference on medical and biological engineering and computing 2010. IFMBE proceedings*, Vol. 29. Springer, Berlin, pp. 200–203.
- Ferri, R., Elia, M., Agarwal, N., Lanuzza, B., Musumeci, S.A., and Pennisi, G. (2003). The mismatch negativity and the P3a components of the auditory event-related potentials in autistic low-functioning subjects. *Clin. Neurophysiol.* 114: 1671–1680.
- Friedman, D., Cycowicz, Y.M., and Gaeta, H. (2001). The novelty P3: an event-related brain potential (ERP) sign of the brain's evaluation of novelty. *Neurosci. Biobehav. Rev.* 25: 355–373.
- Gene-Cos, N., Ring, H.A., Pottinger, R.C., and Barrett, G. (1999). Possible roles for mismatch negativity in neuropsychiatry. *Neuropsychiatry Neuropsychol. Behav. Neurol.* 12: 17–27.
- Giard, M.H., Perrin, F., Pernier, J., and Bouchet, P. (1990). Brain generators implicated in the processing of auditory stimulus deviance: a topographic event-related potential study. *Psychophysiology* 27: 627–640.
- Grande, I., Berk, M., Birmaher, B., and Vieta, E. (2016). Bipolar disorder. *Lancet* 387: 1561–1572.
- Grillon, C., Courchesne, E., Ameli, R., Geyer, M.A., and Braff, D.L. (1990). Increased distractibility in schizophrenic patients. Electrophysiologic and behavioral evidence. *Arch. Gen. Psychiatry* 47: 171–179.
- Hall, M.H., Rijdsdijk, F., Kalidindi, S., Schulze, K., Kravariti, E., Kane, F., Sham, P., Bramon, E., and Murray, R.M. (2007). Genetic overlap between bipolar illness and event-related potentials. *Psychol. Med.* 37: 667–678.
- Hall, M.H., Schulze, K., Rijdsdijk, F., Kalidindi, S., McDonald, C., Bramon, E., Murray, R.M., and Sham, P. (2009). Are auditory P300 and duration MMN heritable and putative endophenotypes of psychotic bipolar disorder? A Maudsley Bipolar Twin and Family Study. *Psychol. Med.* 39: 1277–1287.
- Hermens, D.F., Chitty, K.M., and Kaur, M. (2018). Mismatch negativity in bipolar disorder: a neurophysiological biomarker of intermediate effect?. *Schizophr. Res.* 191: 132–139.
- Hill, S.K., Reilly, J.L., Keefe, R.S., Gold, J.M., Bishop, J.R., Gershon, E.S., Tamminga, C.A., Pearlson, G.D., Keshavan, M.S., and Sweeney, J.A. (2013). Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. *Am. J. Psychiatry* 170: 1275–1284.
- Iadarola, N.D., Niciu, M.J., Richards, E.M., Vande Voort, J.L., Ballard, E.D., Lundin, N.B., Lundin, N.B., Nugent, A.C., Machado-Vieira, R., and Zarate, C.A., Jr. (2015). Ketamine and other N-methyl-D-aspartate receptor antagonists in the treatment of depression: a perspective review. *Ther. Adv. Chronic Dis.* 6: 97–114.
- Ivleva, E.I., Bidesi, A.S., Thomas, B.P., Meda, S.A., Francis, A., Moates, A.F., Witte, B., Keshavan, M.S., and Tamminga, C.A. (2012). Brain gray matter phenotypes across the psychosis dimension. *Psychiatry Res.* 204: 13–24.
- Jahshan, C., Cadenhead, K.S., Rissling, A.J., Kirihaara, K., Braff, D.L., and Light, G.A. (2012a). Automatic sensory information processing abnormalities across the illness course of schizophrenia. *Psychol. Med.* 42: 85–97.
- Jahshan, C., Wynn, J.K., Mathis, K.I., Altshuler, L.L., Glahn, D.C., and Green, M.F. (2012b). Cross-diagnostic comparison of duration mismatch negativity and P3a in bipolar disorder and schizophrenia. *Bipolar Disord.* 14: 239–248.
- Javitt, D.C. (2000). Intracortical mechanisms of mismatch negativity dysfunction in schizophrenia. *Audiol. Neuro. Otol.* 5: 207–215.
- Javitt, D.C., Grochowski, S., Shelley, A.M., and Ritter, W. (1998). Impaired mismatch negativity (MMN) generation in schizophrenia as a function of stimulus deviance, probability, and interstimulus/interdeviant interval. *Electroencephalogr. Clin. Neurophysiol.* 108: 143–153.
- Javitt, D.C., Steinschneider, M., Schroeder, C.E., and Arezzo, J.C. (1996). Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. *Proc. Natl. Acad. Sci. U.S.A.* 93: 11962–11967.
- Jemel, B., Achenbach, C., Muller, B.W., Ropcke, B., and Oades, R.D. (2002). Mismatch negativity results from bilateral asymmetric dipole sources in the frontal and temporal lobes. *Brain Topogr.* 15: 13–27.
- Judd, L.L. and Akiskal, H.S. (2003). The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *J. Affect. Disord.* 73: 123–131.
- Kaur, M., Battisti, R.A., Lagopoulos, J., Ward, P.B., Hickie, I.B., and Hermens, D.F. (2012a). Neurophysiological biomarkers support bipolar-spectrum disorders within psychosis cluster. *J. Psychiatry Neurosci.* 37: 313–321.
- Kaur, M., Battisti, R.A., Ward, P.B., Ahmed, A., Hickie, I.B., and Hermens, D.F. (2011). MMN/P3a deficits in first episode psychosis: comparing schizophrenia-spectrum and affective-spectrum subgroups. *Schizophr. Res.* 130: 203–209.
- Kaur, M., Chitty, K.M., Lagopoulos, J., Hickie, I.B., Duffy, S.L., and Hermens, D.F. (2019). Elucidating the glutamatergic processes underlying mismatch negativity deficits in early stage bipolar disorder and schizophrenia: a combined ¹H-MRS and EEG study. *J. Psychiatr. Res.* 113: 83–89.
- Kaur, M., Lagopoulos, J., Lee, R.S., Ward, P.B., Naismith, S.L., Hickie, I.B., and Hermens, D.F. (2013). Longitudinal associations between mismatch negativity and disability in early schizophrenia- and affective-spectrum disorders. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 46: 161–169.
- Kaur, M., Lagopoulos, J., Ward, P.B., Watson, T.L., Naismith, S.L., Hickie, I.B., Hermens, D.F. (2012b). Mismatch negativity/P3a complex in young people with psychiatric disorders: a cluster analysis. *PLoS One* 7: e51871.
- Kavasidis, I., Pino, C., Spampinato, C., Maiorana, F., and Lanza, G. (2012). Performance evaluation of classifiers in distinguishing mental tasks from EEG signals. *Proceedings of the 9th IASTED International Conference on Biomedical Engineering, BioMed*, pp. 171–177.
- Kenemans, J.L. and Kahkonen, S. (2011). How human electrophysiology informs psychopharmacology: from bottom-up driven processing to top-down control. *Neuropsychopharmacology* 36: 26–51.

- Kim, S., Baek, J.H., Shim, S.H., Kwon, Y.J., Lee, H.Y., Yoo, J.H., and Kim, J.S. (2020). Mismatch negativity indices and functional outcomes in unipolar and bipolar depression. *Sci. Rep.* 10: 12831.
- Kim, S., Jeon, H., Jang, K.I., Kim, Y.W., Im, C.H., and Lee, S.H. (2019a). Mismatch negativity and cortical thickness in patients with schizophrenia and bipolar disorder. *Schizophr. Bull.* 45: 425–435.
- Kim, Y., Kwon, A., Min, D., Kim, S., Jin, M.J., and Lee, S.H. (2019b). Neurophysiological and psychological predictors of social functioning in patients with schizophrenia and bipolar disorder. *Psychiatry Investig* 16: 718–727.
- Koshiyama, D., Miura, K., Nemoto, K., Okada, N., Matsumoto, J., Fukunaga, M., and Hashimoto, R. (2020). Neuroimaging studies within cognitive genetics collaborative research Organization aiming to replicate and extend works of ENIGMA. *Hum. Brain Mapp.*, doi:<https://doi.org/10.1002/hbm.25040>.
- Kuhne, G.E., Morgner, J., and Koselowski, G. (1988). The model of unitary psychosis as a basis for understanding affective processes in psychoses. *Psychopathology* 21: 89–94.
- Lang, A.H., Eerola, O., Korpilahti, P., Holopainen, I., Salo, S., and Aaltonen, O. (1995). Practical issues in the clinical application of mismatch negativity. *Ear Hear.* 16: 118–130.
- Leung, S., Croft, R.J., Guille, V., Scholes, K., O'Neill, B.V., Phan, K.L., and Nathan, P.J. (2010). Acute dopamine and/or serotonin depletion does not modulate mismatch negativity (MMN) in healthy human participants. *Psychopharmacology (Berlin)* 208: 233–244.
- Li, J., Tang, Y., Womer, F., Fan, G., Zhou, Q., Sun, W., Xu, K., and Wang, F. (2018). Two patterns of anterior insular cortex functional connectivity in bipolar disorder and schizophrenia. *World J. Biol. Psychiatry* 19: S115–S123.
- Maggioni, E., Bellani, M., Altamura, A.C., and Brambilla, P. (2016). Neuroanatomical voxel-based profile of schizophrenia and bipolar disorder. *Epidemiol. Psychiatr. Sci.* 25: 312–316.
- Moreira, A.L.R., Van Meter, A., Genzlinger, J., and Youngstrom, E.A. (2017). Review and meta-analysis of epidemiologic studies of adult bipolar disorder. *J. Clin. Psychiatry* 78: e1259–e1269.
- Murray, E.D., Buttner, N., and Price, B.H. (2012). Depression and psychosis in neurological practice. In: Bradley, W.G., Daroff, R.B., Fenichel, G.M., and Jankovic, J. (Eds.). *Neurology in clinical practice*, 6th ed. London: Butterworth Heinemann.
- Musci, R.J., Augustinavicius, J.L., and Volk, H. (2019). Gene-environment interactions in Psychiatry: recent evidence and clinical implications. *Curr Psychiatry Rep.* 21: 81.
- Näätänen, R. (1990). The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. *Behav. Brain Sci.* 13: 201–233.
- Naatanen, R., Gaillard, A.W., and Mantysalo, S. (1978). Early selective-attention effect on evoked potential reinterpreted. *Acta Psychol.* 42: 313–329.
- Naatanen, R., Kujala, T., Kreegipuu, K., Carlson, S., Escera, C., Baldeweg, T., and Ponton, C. (2011). The mismatch negativity: an index of cognitive decline in neuropsychiatric and neurological diseases and in ageing. *Brain* 134: 3435–3453.
- Naatanen, R. and Michie, P.T. (1979). Early selective-attention effects on the evoked potential: a critical review and reinterpretation. *Biol. Psychol.* 8: 81–136.
- Naatanen, R., Paavilainen, P., Tiitinen, H., Jiang, D., and Alho, K. (1993). Attention and mismatch negativity. *Psychophysiology* 30: 436–450.
- Ogura, C., Nageishi, Y., Omura, F., Fukao, K., Ohta, H., Kishimoto, A., and Matsubayashi, M. (1993). N200 component of event-related potentials in depression. *Biol Psychiatry* 33: 720–726.
- Paavilainen, P., Tiitinen, H., Alho, K., and Naatanen, R. (1993). Mismatch negativity to slight pitch changes outside strong attentional focus. *Biol. Psychol.* 37: 23–41.
- Paris, M., Mahajan, Y., Kim, J., and Meade, T. (2018). Emotional speech processing deficits in bipolar disorder: the role of mismatch negativity and P3a. *J. Affect. Disord.* 234: 261–269.
- Pekkonen, E. (2000). Mismatch negativity in aging and in Alzheimer's and Parkinson's diseases. *Audiol. Neuro. Otol.* 5: 216–224.
- Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clin. Neurophysiol.* 118: 2128–2148.
- Raggi, A., Tasca, D., Rundo, F., and Ferri, R. (2013). Stability of auditory discrimination and novelty processing in physiological aging. *Behav. Neurol.* 27: 193–200.
- Ramadan, S., Lin, A., and Stanwell, P. (2013). Glutamate and glutamine: a review of in vivo MRS in the human brain. *NMR Biomed.* 26: 1630–1646.
- Rinne, T., Alho, K., Ilmoniemi, R.J., Virtanen, J., and Naatanen, R. (2000). Separate time behaviors of the temporal and frontal mismatch negativity sources. *Neuroimage* 12: 14–19.
- Sablabin, I.M. and Sivananthan, M. (2019). A man made manic: levodopa-carbidopa-induced mania in traumatic brain injury. *Prim. Care Companion CNS Disord.* 21. <https://doi.org/10.4088/pcc.18br02379>.
- Salisbury, D.F., Kuroki, N., Kasai, K., Shenton, M.E., and McCarley, R.W. (2007). Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. *Arch. Gen. Psychiatry* 64: 521–529.
- Schaffer, A., Isometsa, E.T., Tondo, L., D, H.M., Turecki, G., Reis, C., Cassidy, F., Sinyor, M., Azorin, J.M., and Kessing, L.V., et al. (2015). International Society for Bipolar Disorders Task Force on Suicide: meta-analyses and meta-regression of correlates of suicide attempts and suicide deaths in bipolar disorder. *Bipolar Disord.* 17: 1–16.
- Sekhon, S. and Gupta, V. (2020). Mood disorder. In: *StatPearls*. Florida: Treasure Island.
- Shimano, S., Onitsuka, T., Oribe, N., Maekawa, T., Tsuchimoto, R., Hirano, S., Ueno, T., Hirano, Y., Miura, T., and Kanba, S. (2014). Preattentive dysfunction in patients with bipolar disorder as revealed by the pitch-mismatch negativity: a magnetoencephalography (MEG) study. *Bipolar Disord.* 16: 592–599.
- Siggins, G.R., Martin, G., Roberto, M., Nie, Z., Madamba, S., and De Lecea, L. (2003). Glutamatergic transmission in opiate and alcohol dependence. *Ann. N.Y. Acad. Sci.* 1003: 196–211.
- Stahl, E.A., Breen, G., Forstner, A.J., McQuillin, A., Ripke, S., Trubetskoy, V., Mattheisen, M., Wang, Y., Coleman, J.R.I., and Gaspar, H.A., et al, Bipolar Disorder Working Group of the Psychiatric Genomics Consortium (2019). Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat. Genet.* 51: 793–803.
- Takei, Y., Kumano, S., Maki, Y., Hattori, S., Kawakubo, Y., Kasai, K., Fukuda, M., and Mikuni, M. (2010). Preattentive dysfunction in bipolar disorder: a MEG study using auditory mismatch negativity. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 34: 903–912.
- Tamminga, C.A., Ivleva, E.I., Keshavan, M.S., Pearlson, G.D., Clementz, B.A., Witte, B., Morris, D.W., Bishop, J., Thaker, G.K., and Sweeney, J.A. (2013). Clinical phenotypes of psychosis in the

- bipolar-schizophrenia network on intermediate phenotypes (B-SNIP). *Am. J. Psychiatry* 170: 1263–1274.
- Thaker, G.K. (2008). Neurophysiological endophenotypes across bipolar and schizophrenia psychosis. *Schizophr. Bull.* 34: 760–773.
- Umbricht, D.S., Bates, J.A., Lieberman, J.A., Kane, J.M., and Javitt, D.C. (2006). Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia. *Biol. Psychiatry* 59: 762–772.
- Umbricht, D., Javitt, D., Novak, G., Bates, J., Pollack, S., Lieberman, J., and Kane, J. (1998). Effects of clozapine on auditory event-related potentials in schizophrenia. *Biol. Psychiatry* 44: 716–725.
- Umbricht, D., Javitt, D., Novak, G., Bates, J., Pollack, S., Lieberman, J., and Kane, J. (1999). Effects of risperidone on auditory event-related potentials in schizophrenia. *Int. J. Neuropsychopharmacol.* 2: 299–304.
- Umbricht, D., Koller, R., Vollenweider, F.X., and Schmid, L. (2002). Mismatch negativity predicts psychotic experiences induced by NMDA receptor antagonist in healthy volunteers. *Biol. Psychiatry* 51: 400–406.
- Umbricht, D. and Krljes, S. (2005). Mismatch negativity in schizophrenia: a meta-analysis. *Schizophr. Res.* 76: 1–23.
- Vieta, E. and Phillips, M.L. (2007). Deconstructing bipolar disorder: a critical review of its diagnostic validity and a proposal for DSM-V and ICD-11. *Schizophr. Bull.* 33: 886–892.
- Walker, J., Curtis, V., and Murray, R.M. (2002). Schizophrenia and bipolar disorder: similarities in pathogenic mechanisms but differences in neurodevelopment. *Int. Clin. Psychopharmacol.* 17: S11–S19.
- Watson, T.D., Petrakis, I.L., Edgecombe, J., Perrino, A., Krystal, J.H., and Mathalon, D.H. (2009). Modulation of the cortical processing of novel and target stimuli by drugs affecting glutamate and GABA neurotransmission. *Int. J. Neuropsychopharmacol.* 12: 357–370.
- Zamudio, P.A., Gioia, D.A., Lopez, M., Homanics, G.E., and Woodward, J.J. (2020). The escalation in ethanol consumption following chronic intermittent ethanol exposure is blunted in mice expressing ethanol-resistant GluN1 or GluN2A NMDA receptor subunits. *Psychopharmacology (Berlin)*, <https://doi.org/10.1007/s00213-020-05680-z>.

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