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Lavoie-EEG in Major Psychiatric Disorders

Title: Staging model in psychiatry: review of the evolution of electroencephalography abnormalities in major psychiatric disorders

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Abstract

Aim: Clinical staging in psychiatry aims to classify patients according to the severity of their symptoms, from stage 0 (increased risk, asymptomatic) to stage 4 (severe illness), enabling adapted treatment at each stage of the illness. The staging model would gain specificity if one or more quantifiable biological markers could be identified. Several biomarkers reflecting possible causal mechanisms and/or consequences of the pathophysiology are candidates for integration into the clinical staging model of psychiatric illnesses. **Methods:** This review covers the evolution (from stage 0 to stage 4) of the most important brain functioning impairments as measured with electroencephalography (EEG), in psychosis spectrum and in severe mood disorders. **Results:** The present review of the literature demonstrates that it is currently not possible to draw any conclusion with regard to the state or trait character of any of the EEG impairments in both major depressive disorder and bipolar disorder. As for schizophrenia, the most promising markers of the stage of the illness are the pitch mismatch negativity as well as the p300 event-related potentials, as these components seem to deteriorate with increasing severity of the illness. **Conclusions:** Given the complexity of major psychiatric disorders, and that not a single impairment can be observed in all patients, future research should most likely consider combinations of markers in the quest for a better identification of the stages of the psychiatric illnesses.

Key Words: Bipolar Disorder, First episode, High risk, Major Depressive Disorder, Psychosis,

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Introduction

It is widely believed that intervening early in major psychiatric disorders can lead to significantly better clinical and functional outcome for those affected (Bertelsen et al., 2008; Hegelstad et al., 2012; McGorry, Nelson, Goldstone, & Yung, 2010; Norman et al., 2011). Clinical staging in psychiatry aims to classify patients according to their severity of the symptoms, enabling adapted treatment at every stage of the illness. Most particularly, the staging model suggests that more benign treatment can be used in the case of help-seeking individuals presenting with non-specific symptoms, typically observed in the early phases of psychiatric disorders. The clinical staging model for psychotic and severe mood disorders classifies patients according to the severity of their clinical phenotype, from stage 0 (increased risk, asymptomatic) to stage 4 (severe illness; McGorry et al., 2010). However, the use of the staging model in general medicine (e.g., cancer, arthritis) not only relies on the clinical presentation of the patient, but also on measurable biomarkers of their illness. Several biomarkers reflecting causal mechanisms and/or consequences of the pathophysiology are candidates for integration into the clinical staging model of psychiatric illnesses. This review will cover the evolution (from stage 0 to stage 4) of the most important brain functioning impairments, as measured with electroencephalography (EEG) in psychosis spectrum and in severe mood disorders.

EEG measures voltage fluctuations resulting from ionic current flows within the neurons of the brain. Electrodes are used to record the summation of electrical dipoles

along the scalp. EEG has been used to measure the activity of the resting brain during sleep and wakefulness, as well as the brain's response to stimuli. At rest, scalp EEG activity shows oscillations at a variety of frequencies. Several of these oscillations have characteristic frequency ranges and spatial distributions, and are associated with different states of brain functioning. Following the presentation of stimuli, averaging the EEG activity time-locked to the onset of the presentation leads to a stereotyped electrophysiological response called an event-related potential (ERP). ERP waveforms consist of a series of positive and negative voltage deflections, and the amplitude of these waves depends on the strength of the underlying generators. Abnormalities in both resting state EEG and ERPs have been observed in schizophrenia, major depressive disorders (MDD) and bipolar disorder (BD). The aim of this literature review is to provide an overview of the value of various EEG components impairment as markers of major psychiatric illness stages, with the view to help inform treatment.

Methods

Pubmed database searches were conducted using the following criteria: resting EEG [or] gamma-phase synchrony [or] P50 [or] mismatch negativity [or] P300 [and] early stage [or] high risk [or] first episode [and] psychosis [or] schizophrenia [or] bipolar disorder [or] major depressive disorder. If critical literature reviews were available for stages 3 and 4 (recurrence or relapse of symptoms and severe, persistent or unremitting illness) of any of the illnesses, they are presented in the present work. For the early stages, i.e. high risk and first episode, original researches are presented.

The research was conducted in accordance with the Helsinki Declaration.

Resting EEG

For the measurement of resting brain activity, participants are instructed to sit quietly and comfortably for a few minutes with their eyes open, then a few minutes with their eyes closed. The raw EEG data recorded is subsequently Fourier-decomposed into a voltage (power) by frequency spectral graphing. Each defined frequency band, i.e. delta (<4 Hz), theta (4–7 Hz), alpha (8–15 Hz), beta (16–31 Hz) and gamma (>32 Hz) is associated with a variety of physiological functions, and the power calculated for each of these frequency bands is compared between studied groups in research settings.

No single pattern of quantitative EEG abnormalities has been identified in schizophrenia. The most consistent observation obtained from spectral analysis in both medicated and unmedicated patients suffering from schizophrenia is the increased activity in the slow wave bands (delta and theta), mainly in the frontal area (See meta-analyses: Boutros et al., 2008; Galderisi, Mucci, Volpe, & Boutros, 2009), consistent with the decrease in the frontal brain activity observed in schizophrenia. Activity in the delta and theta bands is associated with slow wave sleep (stages 3 and 4) and is potentially pathological in the waking state. It may therefore indicate some brain pathology in schizophrenia (Y. H. Chen et al., 2015). Chronicity has a significant effect on both the delta and theta bands, with the effect size of the difference between patients and controls being much higher in chronic than in first-episode psychosis (FEP) patients and intermediate in mixed samples (Galderisi et al., 2009). EEG spectral power analyses performed in individuals at ultra-high risk (UHR) of psychosis showed no

difference when compared to a control population and did not predict transition to psychosis (S. Lavoie et al., 2012; Ranlund et al., 2014; Zimmermann et al., 2010). The increase in slow wave activity has been associated with more severe negative symptoms in schizophrenia (Gattaz, Mayer, Ziegler, Platz, & Gasser, 1992; Gerez & Tello, 1995; Gross, Joutsiniemi, Rimon, & Appelberg, 2006; Sponheim, Clementz, Iacono, & Beiser, 2000; Venables, Bernat, & Sponheim, 2009) in FEP (Gschwandtner, Zimmermann, Pflueger, Riecher-Rossler, & Fuhr, 2009) and in UHR (S. Lavoie et al., 2012; Zimmermann et al., 2010), making this observation a fairly robust marker of the illness. It is however, not clear what this association means in terms of the staging model, as negative symptoms exist across all stages (Carrion, Correll, Auther, & Cornblatt, 2017). The worsening of negative symptoms with duration of illness and as secondary effect of treatment is likely to make the association more robust in later stages.

Studies have reported large decrease in alpha activity in drug-free BD euthymic patients (Basar et al., 2012; Kano, Nakamura, Matsuoka, Iida, & Nakajima, 1992; Ozerdem, Guntekin, Tunca, & Basar, 2008) compared to healthy controls, whereas in schizophrenia, spontaneous alpha activity is only slightly reduced (Basar et al., 2016). In BP patients with acute hypomania or depression, alpha activity was rather increased (Moeini, Khaleghi, & Mohammadi, 2015) and the authors concluded that the increased alpha power, which corresponds to a decrease in the thalamic metabolism leading to diminished attention, is consistent with BD presentation. Another group demonstrated increased alpha activity in BD patients, however the current state of the patient at the

time of EEG recording was not specified (Narayanan et al., 2014). In this study, all BD patients presented with psychotic features, and their EEG profile (increased delta, theta and alpha) matched that of the schizophrenia group. It could therefore be hypothesized that resting EEG activity is a reflection of the psychotic symptoms rather than a specific marker of psychiatric illness. Indeed, in a heterogeneous BD group with only nine out of 30 patients showing psychotic symptoms, no resting EEG impairment was observed (Venables et al., 2009). In first-episode BP patients with psychotic features, increase low-frequency and alpha power was observed (Clementz, Sponheim, Iacono, & Beiser, 1994), while only the increase in alpha band was reported in first-episode BP patients in acute hypomania or depressive state (Moeini et al., 2015). However, in light of the results available, it could be that the increased slow activity is specific to psychotic symptoms rather than schizophrenia itself.

In patients with MDD, higher alpha power with the eyes closed and greater alpha suppression with the eyes open were observed when compared to healthy controls (for reviews see Olbrich & Arns, 2013; Pollock & Schneider, 1990). An increase in alpha power is thought to reflect a relative decrease in the proportion of local cortical neurons engaged in a particular task performance. Impaired alpha activity is considered an endophenotype for MDD, mediating the pathway between the brain-derived neurotrophic factor BDNF Val66Met polymorphism and depressed mood (Gatt et al., 2008; Zoon et al., 2013). However, the most reproducible resting EEG observation in MDD is the increased frontal alpha asymmetry (See review by Thibodeau, Jorgensen, & Kim, 2006). Indeed, this meta-analytic review demonstrates that studies on resting EEG

in depression show relative right-sided resting frontal alpha asymmetry among adults with MDD, but also in infants of afflicted mothers. While there are conflicting findings, it appears that alpha asymmetry may be a marker for developing a depressive disorder. Indeed, alpha asymmetry indicative of relatively less right than left parieto-temporal activity has been observed in second-generation (Bruder et al., 2005) and third-generation (Bruder, Tenke, Warner, & Weissman, 2007) offspring of parents and/or grand-parents suffering from depression. These results, including data collected in children without a lifetime history of depression, support the hypothesis that right parieto-temporal hypoactivation is an endophenotypic marker of vulnerability to the disease.

Gamma phase synchrony

The synchronous activity of neurons, mediated by oscillations in the gamma-band (30–100 Hz) of the EEG, has been proposed to play an important role in the linking of neurons into cell assemblies that code information in the brain. This synchronisation (phase-locking) has been proposed as a mechanism for the integration, or binding, of activity in distributed neural networks (Peter J. Uhlhaas & Singer, 2006). Research using EEG in both animals and humans have shown that gamma-band synchronisation contributes to variety of cognitive functions including attention and memory (For a review, see Rieder, Rahm, Williams, & Kaiser, 2011). Reduced gamma activity and a lack of lateralisation in response to various stimuli have been repeatedly observed in patients suffering from schizophrenia (For reviews see Lee, Williams, Breakspear, & Gordon, 2003; P. J. Uhlhaas & Singer, 2010). Decreased gamma phase synchrony

relative to a pre-stimulus baseline has also been demonstrated in FEP (Slewa-Younan et al., 2004; Spencer, Salisbury, Shenton, & McCarley, 2008; Symond, Harris, Gordon, & Williams, 2005). In another study with FEP patients, it was shown that the absolute magnitude of gamma synchrony is enhanced, markedly in the left centro-temporal region, when the reference to this baseline period is removed (Flynn et al., 2008). The authors suggested that diminished neural synchronisation to stimuli, regardless of their task relevance, is occurring in an environment of generally excessive synchrony. Tada et al. (2014) investigated the time-course of the auditory gamma-band response in a FEP and in a UHR group and they showed a reduction of early-latency (0–100ms) gamma-band in the FES group and a reduction of late-latency (300–500ms) gamma-band in both UHR and FEP groups. Therefore, the early gamma-band response may be reduced after the onset of psychosis in accordance with the staging model, whereas the late gamma-band response may be impaired before the onset of psychosis and considered an endophenotype. However, these results are not supported by the other gamma-band investigations conducted in UHR to date (Leicht et al., 2016; Perez et al., 2013). In those studies, impairment of early-latency gamma-band was observed in UHR individuals. There is therefore no clear story in respect to staging in schizophrenia and the gamma-band synchrony.

Although the study of gamma-band oscillations in BD has received less attention than in schizophrenia, the same reduced gamma power in response to auditory stimuli has been observed repeatedly (For a review, see Onitsuka, Oribe, & Kanba, 2013).

Therefore, reduced gamma-band activity may not represent an efficient diagnostic tool,

although the mechanisms underpinning this impairment in schizophrenia involves the cortical inhibition by GABA inter-neurons, while this is not the case in BD (Farzan et al., 2010).

In contrast with schizophrenia and BD, MDD individuals displayed an increased gamma-band power sustained during eight seconds following presentation of negative versus neutral words, compared to control participants and to individuals with schizophrenia (Siegle, Condray, Thase, Keshavan, & Steinhauer, 2010). Similarly, in individuals with a first-episode of depression, the gamma-band showed increased cortical activity both at rest and during the performance of an arithmetic counting task and a spatial imagination task (Strelets, Novototsky-Vlasov, & Golikova, 2002).

Event-related potentials

P50

During an auditory dual-click paradigm, a positive polarity on the EEG trace occurs approximately 50ms post-stimulus; this is the so-called P50. The relative decrease of the P50 wave to the second click compared with the first is thought to reflect a sensory gating mechanism, aiming to protect against information overload. The abnormal auditory gating observed in schizophrenia, i.e., a decreased attenuation in the amplitude of the second P50, is a robust candidate endophenotype of the illness (See meta-analyses: Elvira Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004; Patterson et al., 2008). Indeed, a reduced P50 suppression has been linked to several gene loci and was found in healthy relatives of schizophrenia patients (for a review see Turetsky et al.,

2007). A central hypothesis proposed to account for perception and attention deficits in schizophrenia is that these patients cannot inhibit, or “gate,” irrelevant sensory input, leading to an overload of information reaching the brain. Impaired sensory gating has been demonstrated in FEP patients (Devrim-Ucok, Keskin-Ergen, & Ucok, 2008b; Hong et al., 2009), but not by all (de Wilde, Bour, Dingemans, Koelman, & Linszen, 2007; Morales-Munoz et al., 2016). In UHR, the results are also inconsistent with some studies showing impaired P50 (A. Brockhaus-Dumke et al., 2008; Myles-Worsley, Ord, Blailles, Ngiralmu, & Freedman, 2004), while others did not (Cadenhead, Light, Shafer, & Braff, 2005; Hsieh et al., 2012; van Tricht et al., 2015). While P50 reflects pre-attentional gating mechanisms, recent studies have extended the evaluation of sensory gating to later stages, namely N1 and P2, for which deficits have also been observed in UHR, FEP and schizophrenia (A. Brockhaus-Dumke et al., 2008; Morales-Munoz et al., 2016). However, these component, similar to the P50, are rather viewed as endophenotypes of the illness (Hsieh et al., 2012; Morales-Munoz et al., 2016; van Tricht et al., 2015) and are therefore not good candidate as contributors to the staging model in schizophrenia. As a consequence, they are not reviewed any further here.

A recent meta-analysis has shown that sensory gating impairment, as indexed by the decrease in P50 suppression, is present in BP patients and it is likely to worsen with a history of psychosis (Cheng, Chan, Liu, & Hsu, 2016). BP is associated with the decrease in P50 suppression with a high genetic component (Hall, Rijdsdijk, Kalidindi, et al., 2007; Sanchez-Morla et al., 2008) and therefore, P50 suppression impairment is a good candidate for an endophenotype of this mental disease. To our knowledge, only

two studies have looked at the P50 in MDD and they have both demonstrated sensory gating impairment (Kuang, Tian, Yue, & Li, 2016; Y. Wang et al., 2009). Interestingly, impaired P50 sensory gating measured in 40 months old infants was predictive of attention problems and anxious/depressed symptoms three years later (Hutchison et al., 2017), indicative of the neurophysiological dysfunction being present long before the behaviour or symptoms manifestation.

Mismatch negativity

Mismatch negativity (MMN) is a change in the activity of the brain induced by the occurrence of novel stimuli, leading to a switch of attention in the subject (For a review see Naatanen, Kujala, & Winkler, 2011). MMN is thought to reflect the functioning of NMDA receptors (Javitt et al., 1995; Daniel Umbricht, Koller, Vollenweider, & Schmid, 2002). A meta-analysis of 32 studies reports that a decrease in the amplitude of MMN has been consistently replicated in schizophrenia (D. Umbricht & Krljes, 2005). This MMN deficit is a remarkably robust finding, and is one of the most replicable findings in schizophrenia (For a review, see Naatanen, Shiga, Asano, & Yabe, 2015). Impaired MMN has been associated with poor social cognition (Wynn, Sugar, Horan, Kern, & Green, 2010) and poor global functioning (Kawakubo & Kasai, 2006; Light & Braff, 2005a, 2005b; Rasser et al., 2011). Auditory memory encoding deficits in schizophrenia patients could lead to a reduced capacity for short-term storage of verbal information (Kiang et al., 2007). This impairment could in turn interfere not only with abstract thinking, but also with everyday tasks. During a classic Auditory Oddball Paradigm (AOP), MMN is induced by the occurrence of a deviant sound in an otherwise

contiguous stream of events. The most widely used deviant stimuli in schizophrenia research are sounds differing in their duration or pitch frequency.

Frequency MMN (fMMN) illustrates the theoretical concept of the staging model.

Indeed, the Umbricht and Krijes (2005) meta-analysis showed that the effect sizes of fMMN were significantly correlated with the duration of illness, indicating that the fMMN amplitude attenuation could reflect disease progression. While this impairment is well established in chronic schizophrenia and it may be present in FEP (Bodatsch et al., 2011; Oades et al., 2006), most FEP studies show that the fMMN is intact in these patients (Devrim-Ucok, Keskin-Ergen, & Ucok, 2008a; Magno et al., 2008; Mondragon-Maya et al., 2013; D. F. Salisbury, Kuroki, Kasai, Shenton, & McCarley, 2007; Dean F. Salisbury, Shenton, Griggs, Bonner-Jackson, & McCarley, 2002; Todd et al., 2007; D. S. Umbricht, Bates, Lieberman, Kane, & Javitt, 2006; Valkonen-Korhonen et al., 2003). However, a significant decrease in the fMMN amplitude was observed in the same participants in the post-acute phase (Devrim-Ucok et al., 2008a) or one year after their first psychotic episode (D. F. Salisbury et al., 2007). Worsening of the MMN generation has been correlated with the grey matter volume reduction in the primary auditory cortex, a correlation that was also observed in chronic schizophrenia (Rasser et al., 2011). Very few studies have measured fMMN in young individuals presenting with an at-risk mental state, although the amplitude was shown to be intact compared to that seen in controls in three studies (Bodatsch et al., 2011; Anke Brockhaus-Dumke et al., 2005; Mondragon-Maya et al., 2013), while it was decreased in another study (Perez et al., 2014). Finally, the generation of fMMN was shown to be intact in first-degree

relatives (Magno et al., 2008) and in twins of affected patients (Ahveninen et al., 2006), making it a poor contender as a biomarker for the illness. Altogether, it appears that fMMN impairment worsens with deterioration of illness, and this hypothesis has been recently tested using longitudinal study designs. One study supported the hypothesis showing a significant decline in fMMN following transition (S. Lavoie et al., 2018), while the other did not (Atkinson et al., 2017).

As for the amplitude of the MMN in response to a change in the duration of the sound (dMMN), it is equally attenuated in schizophrenia and FEP patients (Atkinson, Michie, & Schall, 2012; Bodatsch et al., 2011; Hermens et al., 2010; Kaur et al., 2011; Oades et al., 2006; Solis-Vivanco et al., 2014), although this was not reported in all studies (Magno et al., 2008; D. S. Umbricht et al., 2006). Almost all studies conducted in UHR individuals showed a decrease in the dMMN amplitude in these individuals compared to controls (Atkinson et al., 2012; Bodatsch et al., 2011; Higuchi et al., 2014; Jahshan, Cadenhead, et al., 2012; Perez et al., 2014; Shaikh et al., 2012; Shin et al., 2009; Solis-Vivanco et al., 2014), apart from two studies (Higuchi et al., 2013; Mondragon-Maya et al., 2013). Most interestingly, studies where UHR individuals who transitioned to psychosis were compared to UHR individuals who did not transition have revealed that the decrease in dMMN amplitude was significant only in those who transitioned (Atkinson et al., 2012; Bodatsch et al., 2011; Higuchi et al., 2014; Higuchi et al., 2013; Perez et al., 2014; Shaikh et al., 2012), and therefore, this impairment could be used as a predictor of the illness.

dMMN deficit seems to be related to the genetic disposition of the patient. Indeed, a modest but significant genetic correlation between the amplitude of dMMN and schizophrenia has been observed, suggesting that it is a potentially valid endophenotype for this disease (Hall, Rijdsdijk, Picchioni, et al., 2007). On the other hand, it was shown that fMMN can be improved by the administration of N-acetylcysteine in schizophrenia patients (Suzie Lavoie et al., 2007), reinforcing its status as a state rather than a trait marker.

MMN has not been extensively studied in both BD and MDD, and most of the studies on this topic have been conducted in stages 3 or 4 of the illnesses. A meta-analysis including seven studies looking at MMN in BD compared to controls showed that BD patients display a significantly reduced frontal MMN of moderate effect size (Chitty, Lagopoulos, Lee, Hickie, & Hermens, 2013). However, close examination of the results obtained from each study included in the meta-analysis reveals highly inconsistent results. Indeed, only three studies showed a significant decrease in MMN amplitude in BD patients compared to controls (Andersson, Barder, Hellvin, Løvdahl, & Malt, 2008; Jahshan, Wynn, et al., 2012; Kaur et al., 2012), while it was not significantly decreased in the four other studies (Catts et al., 1995; Hall et al., 2009; D. F. Salisbury et al., 2007; Daniel Umbricht et al., 2003). A recent comprehensive review of the literature on MMN in BD, also demonstrates that MMN appears to be perturbed in BD but to a lesser degree than that observed in schizophrenia (Hermens, Chitty, & Kaur, 2017). The heterogeneity, not only of the BD population, but also of the methodology followed by the various studies, can possibly explain these discrepancies. For example, while a

great majority of the studies present results from a mix of bipolar I and bipolar II, regardless of the phase they are in, i.e., manic, depressive or euthymic, other studies only state that they have recruited patients with BP. To our knowledge, the MMN impairment in BD has not been rigorously studied in the early stages of the illness.

Similar to BD patients, no real consensus can be reached regarding MMN impairment in MDD patients. In schizophrenia research, the paradigm used to elicit the MMN and the methods used to measure the induced brain activity have become relatively standardised over the years. However, in MDD populations various methodologies have been used, such as visual paradigms instead of auditory paradigms, magnetoencephalography (MEG) instead of EEG, midline electrodes instead of temporal or fronto-central ones, etc. It appears that duration MMN is decreased in MDD when compared to controls (J. Chen et al., 2014; Naismith et al., 2012; Qiao et al., 2013; Takei et al., 2009), while the amplitude of the fMMN remains the same (Daniel Umbricht et al., 2003) or even increases in some MDD patients (He et al., 2010; Kahkonen et al., 2007). At first sight, nothing striking can differentiate the participants in the various studies and it seems like the MNN amplitude is not related to depressive symptoms (He et al., 2010; Takei et al., 2009).

Until recent years, the MMN impairment was thought to be specific to schizophrenia. However, studies conducted in BD and MDD over the last decade or so have been contradicting this hypothesis, therefore threatening the use of the MMN impairment as a diagnostic tool for schizophrenia.

P300

The P300 (P3) waveform has been conceptualised as an index of endogenous cognitive processes appearing on EEG traces as a large positive component peaking around 300ms post-stimulus. The preferred paradigm to elicit the P3 is an active button-press oddball paradigm. A meta-analysis including 46 studies (Elvira Bramon et al., 2004) and another including 104 studies (Jeon & Polich, 2003) showed large pooled effect sizes of 0.85 and 0.89 for P3 amplitude differences between schizophrenia patients and controls at midline electrodes, and the P3 latency was also significantly delayed. Abnormalities in P3 may reflect a failure to allocate attention resources to a stimulus and/or deficits in information processing and cognitive updating. P3 impairments are also consistently observed in neuroleptic-naïve FEP patients (Brown, Gonsalvez, Harris, Williams, & Gordon, 2002; de Wilde et al., 2008; Demiralp et al., 2002; Hermens et al., 2010; Hirayasu et al., 1998; Kaur et al., 2011; McCarley et al., 2002; Ozgurdal et al., 2008; Renoult et al., 2007; van der Stelt, Lieberman, & Belger, 2005; J. Wang et al., 2009; Xiong et al., 2010) and in individuals at clinical high risk for psychosis (E. Bramon et al., 2008; Frommann et al., 2008; Nieman et al., 2014; Ozgurdal et al., 2008; van der Stelt et al., 2005). Interestingly, it was shown that P300 peak amplitude significantly predicted later improvement in negative and general symptoms in high risk individuals who did not transition to psychosis within two years of EEG recording (Kim, Lee, Lee, Kim, & Kwon, 2015). A meta-analysis including 11 studies on P3 amplitudes in unaffected relatives of schizophrenia patients showed that these healthy relatives have reduced P3 amplitudes and increased latency compared to controls (E. Bramon et al., 2005). Its high heritability

and stability makes it a candidate of choice in the research of an endophenotype (For a review see Turetsky et al., 2007). P3 amplitude is indeed a strong contender as a biomarker for psychosis as demonstrated by a study that used Cox regression analysis to estimate the best predictors for transition to psychosis (Nieman et al., 2014). In their Cox model, poor social-personal adjustment and reduced P3 parietal amplitude at midline site predicted transition to a first psychotic episode with a sensitivity of 88.9% and a specificity 82.5%.

In light of these results, it appears that the P3 impairment, although present before the onset of psychosis, worsens with the establishment of the illness, showing better established localisation of the damaged source and slower processes. A study showing a decrease in P3 amplitude in at-risk, FEP and schizophrenia patients compared to controls, revealed a progressive course from prodromal to chronic schizophrenia in terms of P3 amplitude impairment (Ozgurdal et al., 2008). A relationship with illness duration has been established for the P3 latency increase (Mathalon, Ford, Rosenbloom, & Pfefferbaum, 2000; O'Donnell et al., 1995). However, it is important to note that impaired P3 is not specific to schizophrenia, being impaired in other mental or brain disorders, but with less consistency (For a review see Duncan et al., 2009).

P3 is delayed and its amplitude is reduced in BD (Hall et al., 2009; O'Donnell, Vohs, Hetrick, Carroll, & Shekhar, 2004; D. F. Salisbury, Shenton, & McCarley, 1999; Schulze et al., 2008). Unaffected relatives of BD patients also present with the same P3 impairments (Hall et al., 2009; Pierson, Jouvent, Quintin, Perez-Diaz, & Leboyer, 2000;

Schulze et al., 2008). Similar to P50 suppression, impairments in the generation of the P3 should be considered as a potential biological marker of BD.

Findings of deviant P3 are less consistent in depression than in schizophrenia and BD, and they may be related to patient subtypes or to the severity of the disease (For a review see Duncan et al., 2009). For example, the increase in P3 latency seems to be associated with the presence of melancholic symptoms (Bruder et al., 1991; Kemp et al., 2010; Schlegel, Nieber, Herrmann, & Bakauski, 1991) or with cognitive impairments (Vandoolaeghe, van Hunsel, Nuyten, & Maes, 1998). Melancholia was not only associated with an increased P300 latency, but also with an exaggerated P200 (Kemp et al., 2010). Vandoolaeghe et al. (1998), who observed the same profile of impairments, associated the latter to non-responders to antidepressant therapy. Another proposition is that P3 is normal in depressed individuals, although in families with multiple members with schizophrenia, relatives who suffer from MDD may show the same P3 abnormalities as do their relatives with schizophrenia (Blackwood, St Clair, Muir, & Duffy, 1991). However, when the amplitude of P3 was measured in the offspring of parents suffering from depression, a decrease was observed when compared to the P3 amplitude of control subjects without a family history of psychiatric disorders (Zhang, Hauser, Conty, Emrich, & Dietrich, 2007). These inconsistent results regarding ERPs in major depression do not allow us to draw any conclusion. A given impairment might be genetically linked to the disease and/or related to a given symptom or abnormality observed in major depression.

Conclusion

This review attempted to present some the EEG impairment observed in some major psychiatric illnesses in relation to the stage of the illness. Our first observation is that although these impairments have been extensively studied in all stages of schizophrenia, the results remain highly inconsistent in chronic BD and MDD, and almost nonexistent for the early stages of these disorders. The clinical stages of MDD and BD have been defined (Berk et al., 2007; Hetrick et al., 2008), and EEG studies in the early stages of these illnesses are needed in order to obtain a better understanding of the course of the observed impairments. It is currently not possible to draw any conclusion with regard to the state or trait character of any of the EEG impairments reviewed here in both MDD and BD. In schizophrenia, the most promising markers of the stage of the illness are pitch MMN as well as p300, as these components seem to deteriorate with the increasing severity of illness. However, in the current state of the literature, it is not possible to conclude that any brain dysfunction as indexed by impaired EEG components can be used as a marker of stage for any of the major psychiatric illness stage.

Longitudinal studies will be necessary to follow the course of the observed impairments in at-risk individual who, after experiencing a first-episode of psychosis, are later diagnosed with schizophrenia. Most studies are designed with follow-up periods too short to fully appreciate the changes in the brain functioning as indexed by EEG components. Furthermore, many studies follow up at-risk individuals who later transition to a stage 2 disorder, but rare are the studies that follow-up the patients who are later

diagnosed with a stage 3 or 4 disorder. Differential ascertainment across stages of illness in cross-sectional studies can lead to spurious conclusions about staging.

Finally, and most importantly, if these markers are going to be used as diagnostic tools in the establishment of the stage of a psychotic disorder, a quantifying parameter will need be identified as well as normal and pathological ranges.

The main limitation of the current review of the literature is that it does not include all the measurable EEG components available in the literature. Indeed, time-frequency analyses of the ERPs, visual or somato-sensorial ERPs, parameters such as latency, or later components indexing information processing, have not been included in this review. Source localisation, global field power and principal component analyses have also been ignored. It is therefore possible that another EEG marker may be more efficient at identifying stages of illness.

Given the complexity of major psychiatric disorders, and that not a single impairment can be observed in all patients, future research should most likely consider combinations of markers in the quest for a better identification of the stages of the psychiatric illnesses.

Conflict of interest statement

The authors have no conflict of interest to disclose.

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