EEG biomarkers in major depressive disorder: Discriminative power and prediction of treatment response

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Abstract

Major depressive disorder (MDD) has high population prevalence and is associated with substantial impact on quality of life, not least due to an unsatisfactory time span of sometimes several weeks from initiation of treatment to clinical response. Therefore extensive research focused on the identification of cost-effective and widely available electroencephalogram (EEG)-based biomarkers that not only allow distinguishing between patients and healthy controls but also have predictive value for treatment response for a variety of treatments. In this comprehensive overview on EEG research on MDD, biomarkers that are either assessed at baseline or during the early course of treatment and are helpful in discriminating patients from healthy controls and assist in predicting treatment outcome are reviewed, covering recent decades up to now. Reviewed markers include quantitative EEG (QEEG) measures, connectivity measures, EEG vigilance-based measures, sleep-EEG-related measures and event-related potentials (ERPs). Further, the value and limitations of these different markers are discussed. Finally, the need for integrated models of brain function and the necessity for standardized procedures in EEG biomarker research are highlighted to enhance future research in this field.

Introduction

Major depressive disorder (MDD) is associated with high lifetime prevalence, estimated between 13.2–16.5% (Volkert et al., 2013). Its social and economic burden and, more importantly, its impact on quality of life and individual suffering of patients has triggered efforts for identification of biomarkers that might help to better predict treatment response in MDD to various treatments. According to the definition, a biomarker should be assessable objectively and provide information about physiological or pathological processes or responses to treatment interventions (Atkinson et al., 2001). They can be measured in order to help diagnose and stage a disorder, to give a prognostic outline or to predict treatment outcome (prognosis).

In recent years, several anatomical, metabolic and physiological aberrations in MDD have been reported; for example, decreased cortical volumes in prefrontal brain areas such as the dorsolateral prefrontal cortex or the subgenual gyrus (e.g. Chang, C. C. et al., 2011), altered connectivity and activity in frontal and anterior cingulate cortex (ACC) networks (Fox et al., 2012; Pizzagalli, 2011) or altered inflammatory cytokine and growth factor levels (Schmidt et al., 2011). Still, none of these findings have made their way into routine prognostic use, in part due to the unavailability of the measures in clinical everyday work, low specificity and also due to the heterogeneity of findings. The electroencephalogram (EEG), which is already used in many clinics for routine diagnostic purposes, does meet several of the requirements for biomarker research, for example wide availability and cost-effectiveness. Since the very beginning of EEG research after the first descriptions of human scalp recordings of neuronal activity (Berger, 1933), the possible usage in neuropsychiatric disorders has been emphasized, and is underpinned by recent findings of the EEG as one of the most heritable biomarkers (De Gennaro et al., 2008), particularly alpha peak frequency (APF), alpha activity and the event-related potential (ERP) P300 (Van Beijsterveldt & van Baal, 2002). Further, the EEG provides a temporal resolution in a time scale of milliseconds, which is the time-frame at which neuronal activity, and especially cognition, takes place. The EEG does not assess a surrogate marker of neuronal activity, for example glucose utilization or blood oxygenation, but directly captures on-going electric activity from the brain that makes this technique a valuable complementary brain imaging method.
Therefore the EEG provides an excellent basis for the development of biomarkers, although heterogeneous findings of EEG parameters in MDD, not least due to different methodologies and a lack of standardization, accompanied sometimes by over-interpretation of findings, have blunted the value of EEG-based measures. Further, the assumption of a homogeneous biological pathway in MDD, and thus one characteristic neurophysiological signature, is misleading. Instead, the clinical diagnosis of MDD reflects a cluster of observable behavioural and reported affective alterations with many possible underlying biological pathways. To improve and guide future research, the aim of this work is to give a descriptive and comprehensive overview of EEG-based research in MDD.

Methods

A literature search was performed in the PubMed database using the following Keywords: ‘depression’ or ‘major depressive disorder’ and ‘EEG’, ‘QEEG’, ‘electroencephalogram’. From the obtained results the title and abstract were screened and it was decided whether they contributed to the field of EEG biomarker research in MDD or not. Due to the immense body of literature in this field, this review is not intended as a systematic review; rather, it provides a comprehensive overview of EEG-based findings on the road towards more powerful electrophysiological biomarkers in MDD.

Results

A first description relating EEG patterns to affective capacity has already been given by Lemere (1936), only 5 years after Berger’s first description of the human EEG (Berger, 1933). Since then, different measures have emerged and have been quantified to distinguish between patients with MDD and healthy subjects. The first part of this review is dedicated to these EEG biomarkers that discriminate between MDD and healthy subjects. Because of the known delayed onset of clinical effect of most antidepressants and their limited efficacy, it is also desirable to find parameters that help to separate responders from non-responders before or soon after treatment initiation. Hence, the second part of this review covers biomarkers that are assessed either at baseline and/or at the early stages of treatment (referred to as ‘treatment emergent’ biomarkers) and provide a predictive value for clinical outcome of treatment. Table 1 gives a brief overview of the most important measures for discrimination between patients with MDD and healthy subjects and for treatment prediction in MDD.

Quantitative EEG. EEG data comprises information about neural activity from different brain sites at different frequencies. Time series analysis methods, especially, such as fast Fourier transformation, for example, allow quantification of cortical activity to be assessed via the EEG and to reliably separate different components such as the power of the main frequency bands, delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), and beta (13–25 Hz). Elevated EEG alpha activity during rest in depressed patients, especially, has been one of the main and most consistent findings from studies of recent decades, in line with the first observation from Lemere (1936): ‘The ability to produce “good” alpha waves seems to be a neurophysiological characteristic which is related in some way to the affective capacity of the individual.’ While Begić et al. (2011), Jaworska et al. (2012a), Roemer et al. (1992) and von Knorring et al. (1983) reported elevated absolute alpha power, others described increases in relative power (John et al., 1988; Prichep & John, 1992). Increases were mainly located to parietal and frontal (e.g. Grin-Yatsenko et al., 2009; Jaworska et al., 2012a) or occipital sites (Bruder et al., 2008). Recently, Grin-Yatsenko (2010) replicated these findings in a large sample with increased alpha (and theta power) in patients in early stages of depression. Other studies failed to find alpha power differences between patients and healthy controls (Flor-Henry et al., 1979; Knott & Lapierre, 1987) or reported decreased (relative) alpha activity in patients with MDD in comparison to other patient groups (Poszi et al., 1995) or in treatment-resistant patients with MDD (Price et al., 2008). As will be reported later, excess alpha is also associated with a favourable response to antidepressive treatments (Ulrich et al., 1984) and antidepressants decrease alpha power (Itil, 1983), further supporting a functional role of this rhythm in at least a subgroup of MDD patients.

It has been proposed that the effects of the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism on trait depression were mediated by EEG alpha power in a study of 305 healthy controls (HCs) (Gatt et al., 2008), which was recently replicated in MDD patients (Zoon et al., 2013), where the BDNF MetMet polymorphism in MDD seems to be associated with low-voltage alpha EEG.

Besides alpha power measures, increased slow wave activity in MDD has also been reported (Kwon et al., 1996; Lieber & Prichep, 1988; Nyström et al., 1986; Roemer et al., 1992). Interestingly, several prognostic studies have reported the excess theta group in MDD to be related to non-response to antidepressant treatments (Iosifescu et al., 2009; Knott...
Table 1. Listing of EEG-based methods for discrimination between patients with major depressive disorder (MDD) and healthy controls, and for prediction of treatment outcome.

<table>
<thead>
<tr>
<th>Method</th>
<th>Measures</th>
<th>Usage</th>
<th>Main findings in MDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>qEEG</td>
<td>E.g. EEG power via FFT</td>
<td>Quantification of EEG power at different EEG frequency bands</td>
<td>Increased EEG alpha activity at especially occipital sites in MDD; frontal widespread increases of slow activity are associated with non-response</td>
</tr>
<tr>
<td>EEG source estimates, e.g. LORETA</td>
<td>Current source FFT density</td>
<td>Estimation of the intracortical generators of scalp EEG activity</td>
<td>Local increases of theta activity within the anterior cingulate cortex are associated with good treatment response</td>
</tr>
<tr>
<td>Alpha asymmetry</td>
<td>Left/right hemispheric alpha power</td>
<td>Computation of EEG power differences between, e.g. hemispheres</td>
<td>Decreased right prefrontal alpha activity and an increased left prefrontal alpha activity in MDD have been discussed controversially</td>
</tr>
<tr>
<td>EEG connectivity, (non-linear and linear) coherence</td>
<td>Quantified coupling of two EEG time series</td>
<td>Assessment of (phase and/or amplitude) synchronization of neural activity between brain areas</td>
<td>Altered connectivity patterns have been reported in MDD; further characterization is needed</td>
</tr>
<tr>
<td>EEG vigilance</td>
<td>Different vigilance stages from wakefulness to sleep onset</td>
<td>Assessment of declines of vigilance, i.e. tonic brain arousal during eyes-closed resting condition</td>
<td>A hyper-stable regulation with fewer declines to lower EEG vigilance stages is found in MDD</td>
</tr>
<tr>
<td>EEG cordance</td>
<td>A complex measure that comprises absolute and relative power values</td>
<td>Assessment of EEG activity that is related to brain perfusion</td>
<td>Decrease of theta cordance at prefrontal sites after treatment initiation is associated with response</td>
</tr>
<tr>
<td>ERPs</td>
<td>Amplitude, latency and scalp distribution of averaged, stimulus-induced EEG waves</td>
<td>Assessment of time-locked responses to external stimuli</td>
<td>Several potentials have been found to have a diagnostic or predictive value</td>
</tr>
<tr>
<td>LDAEP</td>
<td>Difference between N1-P2 amplitude in response to increased stimulus intensities</td>
<td>Assessment of the serotonergic function</td>
<td>A strong pre-treatment LDAEP predicts favourable treatment response</td>
</tr>
<tr>
<td>+ P50</td>
<td>Positive deflection after approximately 50 ms</td>
<td>Assessment of sensory ‘gating’ and filtering of incoming information</td>
<td>Increased amplitudes in patients with MDD or bipolar disorder</td>
</tr>
<tr>
<td>+ P300</td>
<td>Positive deflection after approximately 300 ms</td>
<td>Assessment of attentional aspects and processing of incoming information</td>
<td>Decreased amplitude and increased latencies are found in MDD</td>
</tr>
<tr>
<td>Sleep EEG</td>
<td>Neurophysiologically defined sleep stages</td>
<td>Assessment of neurophysiological sleep properties</td>
<td>Disturbed sleep patterns in MDD</td>
</tr>
<tr>
<td>+ REM sleep</td>
<td>Latency and density of REM episodes</td>
<td>Characterization of REM sleep episodes</td>
<td>Increased REM sleep density and decreased REM sleep latency in MDD</td>
</tr>
<tr>
<td>+ SWA</td>
<td>E.g. DSR</td>
<td>Quantification of slow EEG activity during different sleep stages</td>
<td>Association between SWA and treatment response</td>
</tr>
</tbody>
</table>

DSR, delta sleep ratio; ERPs, event-related potentials; FFT, fast Fourier transformation; LDAEP, loudness-dependent auditory evoked potential; LORETA, low resolution electromagnetic tomography; MDD, major depressive disorder; qEEG, quantitative electroencephalogram; SWA, slow wave activity.
ET al., 1996; Arns et al., 2012). Within the fast frequencies, some evidence exists of increased beta range activity in depressed patients (Knott et al., 2001; Lieber & Prichep, 1988).

To overcome often-cited limitations of comparisons between topographic EEG study due to different references or montages, some studies used estimates of intracortical EEG sources such as, for example, low resolution brain electromagnetic tomography (LORETA). This approach has resulted in the most consistent finding with an altered theta activity in frontal areas, most specifically the ACC (Jaworska et al., 2012a; Korb et al., 2008; Mientus et al., 2002).

**Alpha asymmetry**

A large body of literature has been dedicated to lateralized frontal activity in MDD, often referred to as frontal asymmetry. Following the assumption that increased alpha activity reflects a resting, non-active state, and a decreased alpha activity is associated with an increased activity, it is assumed the MDD is characterized by a hyperactive right prefrontal cortex (lower alpha), and a hypoactive left prefrontal cortex (higher alpha). In 1983 a group led by Davidson started publishing their work on frontal alpha asymmetry in depression. They reported a relative hyperactivation of the right frontal cortex, which was not found for the parietal cortex (Schaffer et al., 1983). Henriques and Davidson (1990) laid a further foundation for the concept of frontal alpha asymmetry in depression, where they consider ‘approach’ and ‘withdrawal’ as the essential basis for this asymmetry. The approach system facilitates appetitive behavior and generates certain forms of positive affect. The withdrawal system facilitates the withdrawal of an organism from sources of aversive stimulation and generates certain forms of negative affect’ (Davidson, 1998, page 608). These two systems have been conceptualized as relatively orthogonal. They interpreted the decreased left-sided frontal activation as a deficit in the approach system, and hence subjects with this condition are more prone to certain negative affective states and depressive disorders, given a certain level of environmental stress. On the other hand, they suggested that the right-sided frontal activation is related to withdrawal-related emotion and psychopathology such as anxiety disorders (Henriques & Davidson, 1990).

In line with this hypothesis, a decreased alpha power at right frontal sites relative to the left side has been reported (Chang et al., 2012; Flor-Henry, 1976; Henriques & Davidson, 1991; Schaffer et al., 1983). Besides the findings from Saletu et al. (2005), who reported increased right frontal activity in postmenopausal depressed women via LORETA, no study confirmed the asymmetry differences based on intracortical source estimates thus far. However, many studies have failed to replicate the findings of alpha asymmetry in MDD (Carvalho et al., 2011; Gold et al., 2013; Price et al., 2008; Reid et al., 1998; Segreave et al., 2011).

By taking a closer look at the often cited Henriques and Davidson (1991) data, these researchers used data from 15 MDD and 13 HC. They reported significant differences in alpha asymmetry between depressive patients and controls on the group level, however, they reported that only two out of 13 HCs (15%) deviated significantly from depressive asymmetry scores and only one out of 15 depressives (7%) deviated significantly from normal asymmetry scores. Therefore, there is more overlap between groups than there are true differences. This clearly demonstrates, along with the above-mentioned failures to replicate these findings, that this measure has no value for diagnostic purposes, which is also acknowledged by Davidson (1998).

Furthermore, measures of frontal alpha asymmetry in MDD are only moderately stable over time (Debener et al., 2000; Tomarken et al., 1992), have low heritability (Anokhin et al., 2006; Smit et al., 2007), and are influenced by differences in cranial and brain parenchymal asymmetries in bone thickness (Myslobodsky et al., 1989) and differences in EEG montages (Hagemann et al., 1998, 2001; Reid et al., 1998), making this a very problematic EEG measure to reliably and consistently differentiate MDD from HC. Two studies from the same group investigated the prognostic value of alpha asymmetry and found conflicting results (Bruder et al., 2001, 2008), which makes the prognostic value of this measure questionable.

**EEG vigilance**

In the resting state after closing the eyes a transition takes place from wakefulness to sleep onset, paralleled by temporal and spatial changes of EEG activity (EEG vigilance stages). These changes of frequency over time and space yield important information that might be relevant for discrimination between MDD and healthy controls or even treatment prediction. Recently Hegerl & Hensch (2012) reinvigorated a framework that associates a tonically hyperaroused central nervous system (CNS) in affective disorders, reflected by a lack of a decline of EEG-based vigilance during rest with clinical symptoms of MDD such as social withdrawal and sensation avoidance (Bente, 1964). Earlier, Ulrich & Fürstenberg (1999) already demonstrated that different subtypes of depression could be separated, with the ‘organic subtype’ yielding a hyperstable or rigid EEG vigilance in comparison to HCs. This was further confirmed by
Hegerl et al. (2011) and Olbrich et al. (2012), who demonstrated that patients with MDD exhibited an increased tonic vigilance level quantified via EEG as compared to HCs. Although more studies are needed to confirm the validity of the EEG vigilance measure, this approach seems promising since it links clinical symptoms of MDD at the behavioural level, underlying pathomechanisms and electrophysiological findings. Furthermore, from a conceptual level these findings tend to be in line with the often reported excess alpha which is consistently found in MDD relative to controls, albeit this EEG vigilance model adds a theoretical explanation relating EEG activity to behaviour; for review also see (Hegerl & Hensch, 2012). Interestingly, Zoon et al. (2013) found an indirect linkage of the BDNF Val66Met polymorphism and depression severity via absolute EEG alpha power in 107 MDD patients. In this study, a decreased EEG alpha power during the resting state, possibly related to altered EEG vigilance stages, was associated with more severe depression ratings while Val66Met polymorphism was related to lower EEG alpha power.

Event-related potential

Event-related potentials are averaged responses to stimuli of various sensory modalities that are recorded via EEG. The amplitude, latency and scalp distribution of different potential waveforms (Fig. 1) allows analysis and quantification of the processing of external stimuli at a high temporal resolution.

The loudness-dependent auditory evoked potential (LDAEP) is a measure reflecting the difference between N1-P2 amplitude in response to increased stimulus intensities. It has been demonstrated that high basal levels of serotonin in the CNS are related to a suppression of AEP responsiveness (Hegerl & Juckel, 1993). Conversely, low serotonin levels are reflected in the facilitation of response curves. However, most studies failed to find alterations of LDAEP in MDD in comparison to HCs (Jaworska et al., 2012b; Linka et al., 2007; Park et al., 2010).

Another ERP measure is the P300 that is generated after presentation of rare or infrequent stimuli in a so-called oddball paradigm. It is thought to reflect attentional aspects or processing of incoming information and has been reported to be smaller in amplitude in MDD by the majority of studies (e.g. Blackwood et al., 1987; Diner et al., 1985; Roth et al., 1981). Bruder et al. (2002) compared the P300 amplitude between patients with depression only, anxiety only, a co-morbid group, and a control group, and demonstrated that as compared to the healthy control group the ‘anxiety group’ specifically exhibited an increased P300 amplitude, the MDD-only group a reduced P300 amplitude, and the MDD group with co-morbid anxiety showed no differences in P300 amplitude, demonstrating the need to take co-morbidities such as anxiety into account when assessing P300 amplitudes.

Generally, larger reductions in P300 amplitude are reported in melancholic depression, psychotic depression and depression with suicidal features. Furthermore, a prolonged P300 latency is often found in depression (Bruder et al., 2009; Vandoolaege et al., 1998) but seems not to be influenced by the depressive state, and can hence be seen as a trait rather than a state marker (Kalayam & Alexopoulos, 1999; Taylor et al., 2006).

Also, the early potential P50, a measure for sensory gating and early distinction between relevant and irrelevant stimuli has been found to be altered in MDD. Baker et al. (1990) reported of impaired sensory gating in depressive and manic patients, and Sánchez-Morla et al. (2008) repeated these findings with increased P50 amplitudes as markers for impaired suppression of irrelevant stimuli in bipolar patients. Further, Wang et al. (2009) reported increases in patients with MDD in comparison to HCs without a predictive value.

Although no differences of the N400, a potential associated with semantic processing, have been revealed between patients with MDD and healthy subjects in different studies (Deldin et al. 2006; Klumpp et al. 2010), Ryau et al. (2012) reported differences between manic patients and patients with schizophrenia. Findings of other ERP components from different paradigms, e.g. altered mismatch negativity with decreased amplitudes in MDD (Chang, Y. et al., 2011; Naismith et al. 2012), further highlight the possibilities of these markers as potential

![Fig. 1. Schematic event-related potential (ERP) wave of an auditory oddball paradigm showing the typical designation of components.](image-url)
biomarkers in depression, although some studies failed to find ERP correlates of behavioural differences between MDD and HCs (Quinn et al., 2012).

EEG connectivity measures

The working brain is not only defined via the location and magnitude of activation clusters but also through the interaction of neural activity between different areas. The EEG provides information about the coupling between distinct cortical areas with non-linear (phase synchronization) and linear (amplitude) properties of the time series that allow analysis of relevant network activity in EEG data. Some early studies report differences of one of the first EEG connectivity measures, namely the EEG coherence between patients with MDD and HCs (Lieber, 1988; O’Connor et al., 1979). Since then, different measures (e.g. partial directed coherence, Granger causality, structural synchrony index, phase synchrony index) have emerged that might help to assess alteration of EEG-based connectivity in MDD. Many investigators (Knott et al., 2001; Lee et al., 2011; Park et al., 2007; Sun et al., 2008) report of decreased EEG coherence measures in MDD. In contrast, other research groups found an increased EEG connectivity in MDD, most consistently in the alpha band (Fingelkurts et al., 2007; Jeong et al., 2013; Leuchter et al., 2012). To clarify the meaning of contrary direction of alterations (i.e. decrease or increase of connectivity measures), critical discussions about the impact of EEG amplitude and volume conduction on the different connectivity measures are needed. Then EEG connectivity-based measures could probably serve as reliable and valid biomarkers.

Sleep research

MDD is often accompanied by sleep disturbances (Benca et al., 1992). Therefore it is not surprising that quite robust findings of EEG research in MDD stem from sleep research. Consistent results from several decades of sleep research report a disturbed sleep architecture comprising an increased rapid eye movement (REM) density (Goetz et al., 1991; Lauer et al., 1991), a shortened REM sleep latency (Reynolds et al., 1985; Rotenberg et al., 2002) and altered slow wave sleep (SWS) in MDD (Hoffmann et al., 2000; Lopes et al., 2007), though, others found no REM sleep increases in a study of 67 male MDD patients (Hubain et al., 2006). However, the first non-REM sleep phase especially seems to have a diagnostic value: Armitage et al. (2001) reported that amplitude differences of delta power within the first REM period differentiated between MDD and HCs, and Hoffmann et al. (2000) showed that slow wave activity was lower during the first REM period in MDD.

Further, decreased SWS, decreased sleep efficiency and delayed sleep onset were found to predict recurrence of depressive symptoms (Emslie et al., 2001; Hatzinger et al., 2004; Jindal et al., 2002) while long REM latency and decreased REM density were predictive for the development of depression in high risk subjects (Rao et al., 2009).

While some of these features of sleep EEG have been reported to diminish after treatment with antidepressants (Jindal et al., 2003; Kluge et al., 2007; Quera Salva et al., 2007), there is evidence that increased REM density and decreased REM latency (Friess et al., 2008; Modell et al., 2005; Rao et al., 2009) are markers of vulnerability in subjects with high risk for MDD and could thus be considered ‘trait’ markers.

EEG biomarkers and treatment prediction

In the above overview, QEEG and EEG markers that can differentiate between MDD and healthy subjects have been discussed in more detail. In the following section we will further explore which measures also hold prognostic value in predicting treatment outcome to various antidepressant treatments.

Baseline markers

Quantitative EEG and LORETA. In 1997 Mayberg et al. reported that increased pre-treatment resting metabolism of the rostral anterior cingulate (BA 24a/b) predicted favourable treatment response to antidepressants. Since then, this has sparked a huge research interest into the link between the ACC and treatment response in depression, and to date this is the most investigated finding in treatment prediction in depression. In order to integrate all these results recently a meta-analysis was performed (Pizzagalli, 2011), including 23 studies. A total of 19 studies reported that responders to antidepressant treatment (medication, electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS) or sleep deprivation (SD)) demonstrated increased ACC activity pre-treatment, whereas the remaining four studies found the opposite. The overall effect size (ES) was large (ES = 0.918). The relationship between increased ACC activity and favourable antidepressant response was found consistently across treatments (selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), ketamine, rTMS and SD), imaging modalities (EEG-LORETA, fMRI and SPECT) and did not depend on medication status at baseline. No clear relationship between activity in the anterior cingulate and specific neurotransmitter systems has been reported (Mulert et al., 2007) and treatment-resistant depressive patients have also been shown to respond to deep
brain stimulation of ACC areas (see Hamani et al., 2011 for a review) suggesting that ACC activity reflects a reliable biomarker for antidepressant treatment response in general.

Increased theta in the ACC imaged with LORETA has been shown to reflect increased metabolism in the ACC (Pizzagalli et al., 2003) and is thus a reliable predictor for a favourable treatment outcome. Furthermore, ACC theta activity also often shows up as frontal midline theta, thus excess theta at electrode sites Fz or FCz has been found to be associated with a favourable treatment outcome (Spronk et al., 2011). This frontal midline theta should not be confused with wide-spread frontal theta, which is more often a reflection of drowsiness, or as discussed above, a sign of low vigilance. This widespread frontal excess theta has often been found to be associated with non-response to antidepressant treatments, also see below for further details.

In QEEG research, various pre-treatment differences in EEG measures have been reported to be associated with improved antidepressant treatment outcomes. Biomarkers associated with poor antidepressant response which have at least been replicated once include:

1. Increased slow EEG power at baseline. Increased theta (rTMS: Arns et al., 2012; TCA: Knott et al., 1996), increased relative theta (SSRI & serotonin–norepinephrine reuptake inhibitors (SNRI): Iosifescu et al., 2009) and increased delta power (SSRI: Knott et al., 2000; TCA-trend: Knott et al., 1996). However, Cook et al. (1999) found no differences in theta for responders and non-responders to fluoxetine.

2. A slow individual alpha peak frequency (iAPF) for antidepressant medication (Ulrich et al., 1984) and rTMS treatment (Arns et al., 2010, 2012; Conca et al., 2000).

Event-related potentials

Also from the field of evoked potentials, some promising measures that correlate with treatment response have been published. A strong pre-treatment LDAEP as a function of stimulus intensity that indicates low serotonergic function has been demonstrated to predict a larger decrease of depressive symptoms after treatment with SSRIs (Gallinat et al., 2000; Juckel et al., 2007; Lee et al., 2005; Mulert et al., 2002). In contrast to the hypothesis of a normalized serotonergic transmission after treatment, a retest after 4 weeks did not show a change of the LDAEP (Gallinat et al., 2000).

Also, a reduced P300 amplitude has been reported to be associated with a poor treatment outcome to antidepressant medication (Bruder et al., 1995, 2001) and ECT (Ancy et al., 1996; Gangadhar et al., 1993). Furthermore, a prolonged P300 latency has been found to be associated with a poor treatment outcome (Ionta et al., 2012; Kalayam & Alexopoulos, 1999; Vandoolaeghe et al., 1998). Several authors have suggested that these non-responders to antidepressant medication can be regarded as a subgroup with 'pre-frontal dysfunction' (Dunkin et al., 2000; Kalayam & Alexopoulos, 1999; Vandoolaeghe et al., 1998).

Taylor et al. (2006) reported that SSRI non-responders were characterized by more psychomotor slowing as compared to responders, and interpreted this to be related to reduced dopaminergic neurotransmission. In this respect the P300 latency might also be seen as an electrophysiological measure of psychomotor speed, hence suggesting that a combination of a slow P300 latency and a slowed reaction time points to an underlying dopaminergic rather than serotonergic problem. This was underlined by a reported association between P300 amplitude and latencies and dopamine D2/D3 receptor status (Pogarell et al., 2011) in MDD, and might explain why this subgroup of patients is less responsive to antidepressant medication. On the other hand, a recent study failed to find a relationship between the P300 and dopaminergic genes (Spronk et al., 2013) suggesting the association with dopamine and the P300 is not that straightforward.

Other ERP measures such as increased amplitude of somatosensory-evoked potentials after infusion of ketamine in responders (Cornwell et al., 2012) or an increased N100 amplitude (Danos et al. 1994) have also been reported to have some value in the prediction of treatment.

Sleep EEG

In sleep research, the slow wave activity (SWA) seems to play an important role for treatment prediction. Luthringer et al. (1995) reported increased relative delta power in sleep EEG recordings in responders to antidepressant treatment, although others failed to find power differences between responders and non-responders to psychotherapy and antidepressant
EEG biomarkers in major depressive disorder

 treatment (Buysse et al., 2001) or sleep deprivation (Nissen et al., 2001). Still, the latter reported of decreasing SWA in responders for consecutive nonREM episodes of one night, expressed in a high delta sleep ratio (DSR), a finding that could not be repeated by Argyropulos et al. (2009). The amount of selective suppression of frontal SWA through acoustic stimuli was also found to correlate with improvements from baseline depression severity (Landsnuss et al., 2011). In contrast, a low DSR predicting treatment response was found recently by Duncan et al. (2013) in otherwise treatment-resistant patients with MDD after infusion of ketamine. At first glance these heterogeneous findings probably reflect the impact of treatment methods on the predictive value of EEG biomarkers. Besides classical sleep EEG parameters, a decreased coherence within the beta, delta and theta band in sleep EEG also predicted non-response in adolescents and the occurrence of depressive episodes (Morehouse et al., 2002).

Treatment emergent markers

**EEG cordance.** Within the last decade it was found that not only baseline measurements might help to predict favourable treatment outcome but also the assessment of changes of EEG activity after treatment onset. For the EEG cordance, a complex measure that reflects the association between relative and absolute EEG power and has been associated with brain perfusion (Leuchter et al., 1999), it was reported by Leuchter et al. (1997) and Rabinoff et al. (2011) that 48 h to 1 week after treatment initiation, patients with MDD who later showed a clinical response yielded a decrease of theta cordance at prefrontal sites in comparison to baseline (also Bares et al., 2007, 2008; Cook et al., 2002, 2005; Leuchter et al., 2002). This was not the case in non-responders or patients treated with placebo (Leuchter et al., 2002). Hunter et al. (2010) also report a decrease of midline and right frontal cordance after 48 h of antidepressant treatment in patients with suicidal ideations.

**Antidepressant treatment response index**

A further marker of treatment response worth mentioning is the antidepressant treatment response (ATR) index, a measure that combines relative and absolute alpha power from different montages. Developed by the same research group as the cordance measure, it has been found to be predictive for remission or response in a large trial with n = 376 (Leuchter et al., 2009). The prediction of response was later confirmed in a small placebo controlled trial (Hunter et al., 2011). The question whether ATR or cordance performs better in predicting treatment response has not been addressed so far (Kuo & Tsai, 2010).

**Discussion**

From the first observations of altered EEG related to affective capacity in 1938 (Lemere, 1936) to more controlled research in MDD now, is a long way from the mere ‘qualitative’ description of altered alpha activity to complex ‘quantitative’ measures such as cordance and P300. Steady research has tried to sharpen the tools for discriminating patients with MDD from healthy controls and to identify possible EEG-based markers for treatment prediction to shorten treatment paths and improve efficacy of treatment.

In the field of MDD, especially, differences in the EEG alpha and theta frequency range during rest have been reported consistently, and both these measures have also been differentially associated with treatment outcome. Still, the interpretation of these measures remains vague. On one hand EEG alpha power has been associated with an idling function that reflects disengagement of cortical areas from active information processing and hence increased alpha power at occipital or frontal areas has been interpreted as a subvigil brain state in MDD. On the other hand, increased EEG alpha power during rest has been associated with increased EEG vigilance in MDD and altered decline towards decreased vigilance states with elevated theta and delta activity. Also, the results from sleep research show diminished drops toward deep sleep stages with decreased SWA during sleep in MDD and altered REM sleep profiles. Thus, EEG-based biomarkers of MDD in general might reflect a rigid and less flexible CNS (to externally and internally forced changes of brain function) that leads to impaired behavioural adaptation of the whole organism to the requirements of its environment in major depression.

However, discrepancies of findings from all EEG-based measures remain and surely reflect different underlying mechanisms and subgroups that are not represented within diagnostic systems such as DSM-IV and ICD-10. Still, some of the divergent findings could possibly be resolved if changes of neurophysiologically assessed brain function would be interpreted in a more generalized manner rather than trying to trace them down to specific cognitive functions or barely interpretable terms. Different interpretations of findings (e.g. alpha activity as a marker for generalized hyperstable vigilance or as a sign of less vigilant focal brain areas), reveal the lack of commonly accepted models about the meaning of EEG-based markers. Thus, integrated frameworks such as the EEG vigilance model that combine neurophysiological findings with clinical symptoms are urgently
needed to refine and better understand widely accepted biomarkers. By showing an indirect linkage between the BDNF Val66Met polymorphism and symptom severity of MDD that is mediated through (possibly vigilance-dependent) resting state EEG alpha power, Zoon et al. (2013) also substantially contribute to a holistic understanding of neurophysiological biomarkers in MDD.

The first steps towards an integration of concepts also requires taking into account different aspects of brain activity. Comparisons with findings from other neuroimaging modalities are necessary and can be achieved via studies that do not rely on montage and reference-dependent measures, but instead use current density maps or estimated sources of scalp EEG. For example, the increased frontal midline theta activity in MDD has been traced to the rostral ACC, reflective of increased metabolic activity, and confirmed with other imaging techniques such as fMRI, PET and SPECT imaging as reviewed in a meta-analysis from Pizzagalli (2011). This replication from other imaging modalities enhances the interpretation of findings and strengthens the generation of hypothesis about possible biomarkers. Further, region of interest (ROI) based analysis of EEG source estimates could increase the statistical power for research on EEG biomarkers. More work is also needed to add information of cortical neurotransmitters, e.g. glutamate and gamma-aminobutyric acid, and excitation – inhibition balance, measured via MRI spectroscopy or paired-pulse TMS protocols (Tremblay et al., 2013) to models of altered EEG-profiles in MDD. The integration of concepts might further benefit from biomarkers of neuronal interaction such as EEG-based coherence and related markers. These measures provide insight into the coupling of distant brain areas and allow the analysis of altered network function. Especially within fMRI research, connectivity analysis is a rapidly growing field. It should be in the focus of EEG research to identify neurophysiological correlates of altered fMRI brain connectivity because the EEG would allow the translation of these findings into clinical relevant biomarkers.

ERP-based approaches for identification of biomarkers might also be of value due to the reported association of different potentials to neurotransmitter function. Although the LDAEP has failed to distinguish between patients and controls in general, its function at different neurotransmitter receptors, ERP measures might be of particular use for guiding the clinical decision for a special antidepressant agent.

From the clinical point of view, EEG-based biomarkers for differentiation between patients and healthy subjects are only of limited value because the diagnosis is derived from clinical criteria. Although these biomarkers can help to understand the multiple patho-mechanisms that lead to MDD, the main focus of EEG biomarker research has shifted to the prognosis of the course of illness during treatment. And indeed, remarkable progress has been made with several biomarkers that have shown a consistently predictive value. As a baseline marker, especially rACC theta, the LDAEP, the iAPF, the P300 and frontal theta activity have been found to predict treatment response to specific agents such as SSRIs or SNRIs, while cordon measures as well as the ATR show notable success as treatment-emergent biomarkers and predicting treatment response in the early course of treatment.

However, several issues, especially standardized procedures of recording condition, pre-processing and analysis of data should be on the agenda on the way towards valid and clinically useful biomarkers for treatment prediction to prevent this field of research from the blunting incomparability of studies:

- Length of recording and length of used EEG epochs for analysis should be unified
- The order in which EEG is collected (i.e. is the eyes open EEG or the eyes closed EEG recorded as the first task, or after 30–60 min of neuropsychological tests?)
- Used channels and channel numbers, and especially how ROIs are defined (voxel-based, sphere, etc.) should be unified, especially for the use of source estimation techniques due to the dependency of these tools to channel distribution
- The condition (resting, trying or not trying to fall asleep, interfere or not interfere when vigilance declines) and the environment (light, noise, temperature) should be kept constant
- Pre-processing procedures (e.g. correction or removal of artefact segments) and the choice of segments (whole EEG record with artefact minimization or analysis of selected artefact-free epochs) should be clarified
- Measures used should be similar or at least comparable throughout different studies
- Due to the impact of circadian rhythms on EEG profiles (e.g. via vigilance changes), time of recording should be standardized and further be comparable to the working schedule in clinical EEG laboratories, e.g. during the morning or early afternoon

It should be noticed that the International Pharmacoe EEG Society (IPEG) recently released guidelines (Jobert et al., 2012; 2013) that help to make
obtained results from different recording sites and study centres comparable; for ERP studies the International Federation of Clinical Neurophysiology has released a guideline for event-related potentials in clinical research (Duncan et al. 2009). The value of upcoming works on EEG-based biomarkers in MDD should also be judged by the comparability with other studies and by the accordance with standardized procedures.

Besides the standardization of EEG biomarker research, there are other aspects that could further enhance the value and validity of EEG biomarker research. At first, most of the studies up to now included only a limited number of subjects and there is a clear lack of multi-centre studies in EEG research, a fact that is a clear deficiency of EEG research in comparison to biomarker research in other fields of medicine. It should be a future goal to enrol large, hypothesis-driven cohort studies to test the validity of already existing biomarkers, such as the multi-centre international Study to Predict Optimized Treatment (iSPOT) (Williams et al., 2011). These studies should not necessarily focus on one measure but should compare combinations of markers for their discriminative and predictive power, i.e. integrative neuroscience (Kuo & Tsai, 2010; Spronk et al., 2011). The search for predictive biomarkers could also benefit from approaches that incorporate combinations of EEG-based and non-EEG markers as demonstrated by Spronk et al. (2011). Furthermore, used measures should not be too complex since simple description of the underlying mechanisms that lead to neurophysiologically assessable biomarkers would greatly enhance its acceptance by clinicians and help to justify the usage of these biomarkers for therapeutic interventions in patients.

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EEG biomarkers in major depressive disorder 613
EEG biomarkers in major depressive disorder


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