

Personalized Medicine in ADHD and Depression: Use of Pharmaco-EEG

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Abstract This chapter summarises recent developments on personalised medicine in psychiatry with a focus on ADHD and depression and their associated biomarkers and phenotypes. Several neurophysiological subtypes in ADHD and depression and their relation to treatment outcome are reviewed. The first important subgroup consists of the ‘impaired vigilance’ subgroup with often-reported excess frontal theta or alpha activity. This EEG subtype explains ADHD symptoms well based on the EEG Vigilance model, and these ADHD patients responds well to stimulant medication. In depression this subtype might be unresponsive to antidepressant treatments, and some studies suggest these depressive patients might respond better to stimulant medication. Further research should investigate whether sleep problems underlie this impaired vigilance subgroup, thereby perhaps providing a route to more specific treatments for this subgroup. Finally, a slow individual alpha peak frequency is an endophenotype associated with treatment resistance in ADHD and depression. Future studies should incorporate this endophenotype in clinical trials to investigate further the efficacy of new treatments in this substantial subgroup of patients.

Keywords ADHD · Depression · QEEG · Personalised medicine · Phenotype · Biomarker

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1 Introduction

The landscape in psychiatry recently underwent a dramatic change. Large-scale studies investigating the effects of conventional treatments for ADHD and depression in clinical practise have demonstrated, at the group-level, limited efficacy of antidepressant medication and cognitive behavioural therapy in depression (STAR*D: Rush et al. 2006), an overestimation of the effects of cognitive behavioural therapy for depression as a result of publication bias (Cuijpers et al. 2010) and limited long-term effects of stimulant medication, multicomponent behaviour therapy and multimodal treatment in ADHD (NIMH-MTA trial: Molina et al. 2009), although latent class analysis reported a subgroup consisting of children who demonstrated sustained effects of treatment at 2 years follow-up (Swanson et al. 2007). Furthermore, several large pharmaceutical companies announced that they would ‘...pull the plug on drug discovery in some areas of neuroscience...’ (Miller 2010). This can be considered a worrying development, since there is still much to improve in treatments for psychiatric disorders. The conclusions about limitations in efficacy and long-term effects are all based on the interpretation of group-averaged data, but also demonstrate that there is a percentage of patients responding to antidepressants (Rush et al. 2006) and there is a subgroup of patients demonstrating long-term effects (Swanson et al. 2007). Therefore, a move beyond data regarding the average effectiveness of treatments to identify the best treatment for any individual (Simon and Perlis 2010) or personalised medicine is crucial.

The fact that only subgroups of patients respond to treatment raises important questions about the underlying assumptions of neurobiological homogeneity within psychiatric disorders, and is rather suggestive of neurobiological heterogeneity. Therefore, a move beyond data regarding the average effectiveness of treatments, to identify the best treatment for a given individual (Simon and Perlis 2010) or personalised medicine is highly relevant. In personalised medicine it is the goal to prescribe the right treatment, for the right person at the right time as opposed to the current ‘trial-and-error’ approach, by using biomarkers of endophenotypes.

From the point of view that biomarkers should be cost-effective, easy applicable and implemented within the routine diagnostic procedure, the quantitative EEG (QEEG) seems to be appropriate. Still the question is whether it should be considered a diagnostic or prognostic technique? Although several EEG-biomarkers have shown robust discriminative power regarding neuropsychiatric conditions (for depression also see: Olbrich and Arns 2013) it seems not within reach that biomarkers will replace the clinical diagnosis (Savitz et al. 2013). As another illustration, consider any psychiatric disorder as defined according to the DSM-IV or DSM-V (DSM). Besides a list of behavioural symptoms, there is always the final criterion that the complaints result in ‘impairments in daily life’. Specifically, this criterion makes it almost impossible to devise any neurobiological test to replace diagnosis based on the DSM, since for one person the same level of impulsivity and inattention is considered a blessing (i.e. artist or CEO), whereas for another person the same levels of impulsivity and inattention is considered a curse, and hence results in a diagnosis only for the latter subject.

Given the recent development of personalised medicine (in line with the NIMH Strategic Plan on Research Domain Criteria or RdoC, and termed Precision Medicine) and the above limitations of current psychiatric diagnosis and treatments, in this chapter we will focus on the prognostic use of QEEG in psychiatry.

This prognostic use of EEG or QEEG has a long history. For example, Satterfield et al. (1971, 1973) were the first to investigate the potential use of EEG in predicting treatment outcome to stimulant medication (main results outlined further on). In 1957 both Fink, Kahn and Oaks (Fink and Kahn 1957) and Roth et al. (1957) investigated EEG predictors to ECT in depression. Fink recently summarised these findings eloquently as: ‘*Slowing of EEG rhythms was necessary for clinical improvement in ECT*’ (Fink 2010).

2 Personalised Medicine: Biomarkers and Endophenotypes

Personalised medicine aims to provide the right treatment to the right person at the right time as opposed to the current ‘trial-and-error’ approach. Genotypic and phenotypic information (or ‘biomarkers’) lie at the basis of this approach. However, 2011 marked the 10th year anniversary of the completion of the Human

Genome project, which has sparked numerous large-scale Genome Wide Association studies (GWA) and other genotyping studies in psychiatric disorders, only accounting for a few percent of the genetic variance (Lander 2011). This suggests that a strictly genetic approach to personalised medicine for psychiatry will not be as promising as initially expected. The notion of personalised medicine suggests *heterogeneity* within a given DSM-IV disorder, rather than *homogeneity*, at least from a brain-function-based perspective. Therefore, a variety of ‘endophenotypes’ or ‘biomarkers’ are expected within a single DSM-IV disorder to require a different treatment.

The National Institutes of Health declared a biomarker as ‘A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention’ (De Gruttola et al. 2001). However, the idea behind an endophenotype is that it is the intermediate step between genotype and behaviour and thus is more closely related to genotype than behaviour alone. Therefore, endophenotypes can be investigated to yield more information on the underlying genotype. Given the interest in the last couple of years for genetic linkage studies, this term has become more topical again. In parallel, there have also been many studies using the term biological marker, trait, biomarker etc. Here it is important that, in line with Gottesman and Gould (2003), an ‘endophenotype’ refers to a marker when also certain heritability indicators are fulfilled, whereas a ‘biomarker’ simply refers to differences between patient groups, which do not necessarily have a hereditary basis.

Older studies attempting to aid the prescription process with more objective knowledge have studied biological (e.g. neurotransmitter metabolites), psychometric (personality questionnaires), neuropsychological (cognitive function) and psychophysiological (EEG, ERP) techniques (Joyce and Paykel 1989). Biological techniques (such as neurotransmitter metabolites) have to date shown little promise as reliable predictors of treatment response and are not yet recommended for routine clinical practise (Joyce and Paykel 1989; Bruder et al. 1999). Similarly, the clinical utility of ‘behavioural phenotypes’ remains poor and, at this moment, none of these predictors have clinical use in predicting treatment outcome to various anti-depressive treatments (Simon and Perlis 2010; Cuijpers et al. 2012; Bagby et al. 2002).

However, there has been renewed interest in the use of other measures such as pharmacogenomics (Frieling and Tadić 2013) and pharmacometabolomics (Hefner et al. 2013), which are speculated to show promise in the use of personalised medicine. However to date pharmacogenomics have not shown promising results in predicting treatment outcome in psychiatric disorders (Johnson and Gonzalez 2012; Ji et al. 2011; Menke 2013) and pharmacometabolomics is considered potentially promising at most at this moment, with few reports on its role in personalised medicine (Johnson and Gonzalez 2012; Quinones and Kaddurah-Daouk 2009).

Recent studies suggest that more direct measures of brain function, such as psychophysiology and neuropsychology, may be more reliable in predicting treatment response in depression (Olbrich and Arns 2013). The underlying idea

behind this concept is that for example neurophysiological data from EEG capture ongoing neuronal activity at the timescale it takes place, outpacing any other modality such as neuroimaging techniques like fMRI or PET. Further, the EEG is not a surrogate marker of neuronal activity (such as the blood desoxygenation level dependent signal in fMRI or the glucose utilisation in PET) but gives insight into the actual cortical activity. Therefore, the EEG can help to define stable endophenotypes incorporating both the effects of nature and nurture. This potentially makes the EEG an ideal candidate biomarker, which has the potential to predict treatment outcome.

3 EEG as an Endophenotype?

Many studies have investigated the heritability of the EEG in twin studies and family studies (Vogel 1970), and found that many aspects of the EEG are heritable. In a meta-analysis van Beijsterveldt and van Baal (2002) demonstrated high heritability for measures such as the alpha peak frequency (81 %), alpha EEG power (79 %), P300 amplitude (60 %) and P300 latency (51 %), all suggesting that EEG and ERP parameters fulfil the definition of an endophenotype. Below two examples of EEG Phenotypes are discussed in more detail.

3.1 Low-Voltage (Alpha) EEG (LVA) and Alpha Power

LVA is the most well-described EEG phenotype to date and was first described by Adrian and Matthews (1934). The latter author exhibited an EEG in which alpha rhythm ‘...*may not appear at all at the beginning of an examination, and seldom persists for long without intermission...*’. The LVA EEG has been known to be heritable (autosomal dominant) and the heritability of alpha power is estimated at 79–93 % (Smit et al. 2005, 2010; Anokhin et al. 1992). Low-voltage EEG is a well-described endophenotype in anxiety and alcoholism (Enoch et al. 2003; Ehlers et al. 1999; Bierut et al. 2002). Alpha power and LVA have been successfully associated with a few chromosome loci (Ehlers et al. 1999; Enoch et al. 2008) but also with single genes: a serotonin receptor gene (HTR3B) (Ducci et al. 2009), corticotrophin-releasing binding hormone CRH-BP (Enoch et al. 2008), a gamma-amino butyric acid (GABA)-B receptor gene (Winterer et al. 2003) and with the BDNF Val66Met polymorphism (Gatt et al. 2008; Zoon et al. 2013).

3.2 Alpha Peak Frequency (APF)

The APF has been shown to be the most reproducible and heritable EEG characteristic (van Beijsterveldt and van Baal 2002; Smit et al. 2005; Posthuma et al. 2001) and has been associated with the COMT gene, with the Val/Val genotype

marked by a 1.4 Hz slower APF as compared to the Met/Met group (Bodenmann et al. 2009) which could not be replicated in two large independent samples in our lab (Veth et al. submitted), casting doubt on this specific linkage and requiring further studies to unravel the genetic underpinnings of this measure.

In summary, the EEG has a long history in identifying biomarkers or endophenotypes aiding the prediction of treatment outcome and the EEG can be considered a stable, reproducible measure of brain activity with high heritability.

4 ADHD

Considerable research has been carried out for investigating the neurophysiology of ADHD. The first report describing EEG findings in ‘behavior problem children’ stems from 1938 (Jasper et al. 1938) when the authors described a distinct EEG pattern: ‘...*There were occasionally two or three waves also in the central or frontal regions at frequencies below what is considered the normal alpha range, that is, at frequencies of 5–6/s...*’ (Jasper et al. 1938, p. 644), which we now know to be frontal theta, although the term theta was not introduced until 1944 by Walter and Dovey (1944). In this group of ‘behavior problem children’ they described a ‘Class 1’ as ‘hyperactive, impulsive and highly variable’ which closely resembles the current diagnosis of ADHD. The most predominant features in this group were the occurrence of slow waves above one or more regions and an ‘abnormal EEG’ in 83 % of the cases. Within ‘Class 1’ they also reported a subgroup which they termed as ‘sub-alpha rhythm’ with slow frontal regular activity which occurred in a similar way as the posterior alpha (*‘...In other cases a 5–6/s rhythm would predominate in the anterior head regions simultaneous with an 8–10/s rhythm from the posterior regions...’*), thus already hinting at the heterogeneity of EEG findings that has continued to date and will be explained further below. Satterfield and colleagues (1971, 1973) were the first to investigate the potential use of EEG in predicting treatment outcome to stimulant medication. They found that children with excess slow wave activity and large amplitude evoked potentials were more likely to respond to stimulant medication (Satterfield et al. 1971) or, more generally, that abnormal EEG findings could be considered as predictor for positive treatment outcome (Satterfield et al. 1973). Below, the literature on ADHD will be reviewed in more detail focusing on some main subtypes for which at least replication studies have been published.

4.1 ‘Excess Theta’ and ‘Theta/Beta Ratio’: Impaired Vigilance Regulation

The most consistent findings reported in the literature on ADHD since the introduction of quantitative EEG are those of increased absolute power in theta and increased theta/beta ratio (TBR). The clearest demonstration of the ‘diagnostic

utility' of this measure is from Monastra et al. (1999), who showed in a multi-centre study of 482 subjects that using a single electrode location (Cz) they could classify with an accuracy of 88 % children with ADHD based on the TBR. Note that most of these studies focused on the EEG as a diagnostic tool for ADHD, which is not automatically compatible with the notion of using the EEG for predictive purposes (as part of personalised medicine) as these two aims have conflicting implications, where the diagnostic use of EEG assumes homogeneity among patients with ADHD, while the predictive approach assumes heterogeneity ('A predictive biomarker is a baseline characteristic that categorises patients by their likelihood for response to a particular treatment' (Savitz et al. 2013)).

Three meta-analyses have investigated the diagnostic value of theta power and the TBR in ADHD compared to healthy controls. Boutros and colleagues (2005) concluded that increased theta power in ADHD is a sufficiently robust finding to warrant further development as a diagnostic test for ADHD, with data suggesting that relative theta power is an even stronger discriminator than absolute theta power. In 2006, Snyder and Hall conducted a meta-analysis specifically investigating the TBR, theta and beta and concluded that an elevated TBR is '*...a commonly observed trait in ADHD relative to controls... by statistical extrapolation, the effect size of 3.08 predicts a sensitivity and specificity of 94 %...*' (Snyder and Hall 2006, p. 453)). However, there is a problem with this extrapolation from an effect sizes (ES) to a sensitivity and specificity measure [see: (Arns et al. 2013a, b) for details] and hence these extrapolated values from Snyder and Hall (2006) should not be considered accurate. A recent meta-analysis incorporating more recent studies refines these findings further and shows a clear 'time effect' of studies, where earlier studies demonstrated the largest ES and more recent studies found the lowest ES between ADHD and non-ADHD groups (Arns et al. 2013a). This chronological effect in the findings was mostly related to the TBR being increased in the non-ADHD control groups which was interpreted by the authors as possibly being related to a decreasing sleep duration observed for non-ADHD children over time (Arns et al. 2013a, b; Iglowstein et al. 2003; Dollman et al. 2007) also found in a meta-analysis covering the last 100 years (Matricciani et al. 2011). Reduced sleep duration can result in prolonged sleep restriction, which results in increased fatigue and increased theta [see Arns and Kenemans (2012) for a review]. However, it was concluded that a substantial subgroup of ADHD patients (estimated between 26–38 %) are characterised by an increased TBR, even in recent studies (Arns et al. 2013a, b). Excess theta and elevated TBR are also favourable predictors for treatment outcome to stimulant medication (Arns et al. 2008; Clarke et al. 2002; Suffin and Emory 1995) and neurofeedback (Arns et al. 2012a; Monastra et al. 2002), thereby demonstrating the predictive value of this measure.

Conceptually, the EEG subtype with excess theta and/or enhanced TBR in ADHD are consistent with the EEG Vigilance model originally developed by Bente (1964) and further developed by Hegerl et al. (2012), which also overlaps with what is sometimes referred to as 'underarousal' and also with the EEG cluster described as 'cortical hypoarousal' (Clarke et al. 2011).

The EEG Vigilance framework can be regarded as an extension of the sleep stage model with a focus on eyes-closed resting period with transitions from relaxed wakefulness through drowsiness to sleep onset, which is seen in stage N2. The EEG allows classifying different functional brain stages at a time scale of, e.g. 1-s epochs, which reflect decreasing levels of vigilance from W to A1, A2, A3, B1, B2 and B3. W stage reflects a desynchronized low amplitude EEG which occurs, e.g. during arithmetic. The three A stages reflect stages where alpha activity is dominant posteriorly (A1), equally distributed (A2), followed by alpha anteriorisation (A3), whereas B stages are reflective of the lowest vigilance stages, which are characterised by an alpha drop-out or low-voltage EEG with slow horizontal eye movements (B1) followed by increased frontal theta and delta activity (B2/3). These vigilance stages are followed by sleep onset with the occurrence of K-complexes and sleep spindles, which mark the transition to stage C in the vigilance model, or classically to stage N2 sleep.

The sequence of EEG vigilance stages that can be assessed in an individual reflect the ability of relaxing or falling asleep. Due to its high temporal resolution of 1-s epochs it is sensitive to short drops of vigilance in contrast to traditional sleep medicine measures. Using a clustering method, three types of EEG vigilance regulation have been defined in a group of healthy subjects: a stable type, a slowly declining type and an unstable type (Olbrich et al. 2012). A stable or rigid EEG Vigilance regulation means that an individual remains in higher vigilance stages for an extended time and does not exhibit lower vigilance stages. This would be seen as rigid parietal/occipital alpha (stage A1), which is often seen in depression (Olbrich et al. 2012; Ulrich et al. 1990; Hegerl et al. 2012). On the other hand, unstable EEG Vigilance regulation suggests that an individual very quickly drops to lower EEG Vigilance stages, displaying the characteristic drowsiness EEG patterns such as frontal theta (stage B2/3), and they switch more often between EEG Vigilance stages. This labile or unstable pattern is often seen in ADHD (Sander et al. 2010). The often-reported 'excess theta' in ADHD mentioned above should thus be viewed as a predominance of the low B2/3 vigilance stages.

A summary of this model is depicted in Fig. 1. An unstable vigilance regulation explains the cognitive deficits that characterise ADHD and Attention Deficit Disorder (ADD), such as impaired sustained attention. Vigilance stabilisation behaviour explains the hyperactivity aspect of ADHD as an attempt to upregulate vigilance.

To summarise, in the majority of ADHD patients an EEG pattern is observed illustrative of a reduced and unstable vigilance regulation (i.e. the same EEG signature a healthy, but fatigued person would possibly demonstrate at the end of the day). The interpretation of increased theta activity as patterns of decreased tonic arousal suggests that the hyperactive behaviour of ADHD patients can be seen as a counter mechanism to auto-stabilisation via externalising behaviour that increases vigilance by riskful and sensation-seeking behaviour. Further, a decreased vigilance in a subgroup of patients with ADHD explains the positive effects of stimulant medication: vigilance is shifted to a high and stable level without the need for externalising behaviour. Interestingly, a similar pattern of

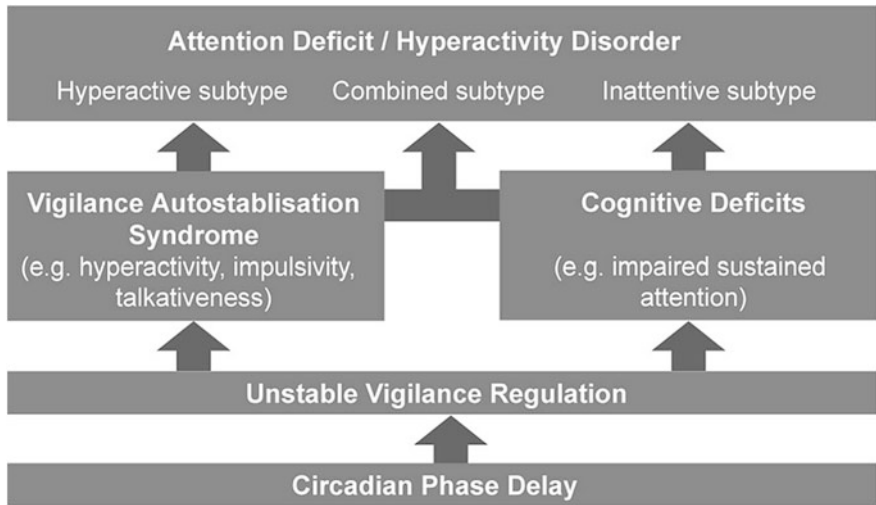


Fig. 1 Overview of the relation between an unstable vigilance regulation and behavioural symptoms of ADHD. Circadian phase delay can be considered one cause for the unstable vigilance regulation, but more in general sleep disorders are known to result in unstable vigilance regulation

reduced EEG vigilance can be found in manic patients, which sometimes also show patterns of reduced vigilance (Small et al. 1997) along with sensation-seeking behaviour. Again, this subtype with reduced vigilance seems responsive to stimulant medication (Schoenknecht et al. 2010).

Recent reviews are increasingly focusing on the role of sleep problems as the underlying aetiology of ADHD, in at least a subgroup of patients (Arns and Kenemans 2012; Miano et al. 2012). A majority of ADHD patients can be characterised by sleep onset insomnia, caused by a delayed circadian phase (van der Heijden et al. 2005; Van Veen et al. 2010). Although this cannot be considered a full-blown sleep disorder, chronic sleep onset insomnia can result in chronic sleep restriction which is known to result in impaired vigilance, attention and cognition (Van Dongen et al. 2003; Axelsson et al. 2008; Belenky et al. 2003). This is further evidenced by a recent meta-analysis incorporating data from 35,936 healthy children, reporting that sleep duration is positively correlated with school performance, executive function, and negatively correlated with internalising and externalising behaviour problems (Astill et al. 2012). Furthermore, it is known that symptoms associated with ADHD can be induced in healthy children by sleep restriction (Fallone et al. 2001; Golan et al. 2004), which also resulted in increased theta EEG power after a week of sleep restriction (effect size=0.53; Beebe et al. 2010). These studies demonstrate that sustained sleep restriction results in impaired vigilance regulation (excess theta) as well as impaired attention, suggesting an overlap between ADHD symptoms and sleep disruptions. Chronobiological treatments normalising this delayed circadian phase, e.g. early morning

bright light (Rybak et al. 2006) and sustained melatonin treatment (Hoebert et al. 2009) have been shown to normalise this sleep onset insomnia and also result in clinical improvement on ADHD symptoms. Therefore, this subgroup of ADHD patients with excess theta and elevated TBR is considered a group with impaired vigilance regulation caused by a delayed circadian phase (also see Fig. 1 and Arns and Kenemans (2012) for a review and Arns et al. (2013a, b)). Thereby it is understandable that vigilance stabilising treatments such as stimulant medication have been shown to be particularly effective in this subgroup (Arns et al. 2008; Clarke et al. 2002; Suffin and Emory 1995), whereas chronobiological treatments with sustained treatment (resulting in long-term normalisation) as well as neuro-feedback treatment are also expected to be efficacious (Arns and Kenemans 2012).

Thus, conceptually, this excess theta subgroup can be interpreted as a subgroup with impaired vigilance regulation, likely caused by sleep restriction and/or other factors systematically influencing sleep duration.

4.2 The ‘Slow Individual Alpha Peak Frequency’ Subgroup

As pointed out above from the old Jasper et al. (1938) study in behavioural problem children, a cluster was identified which most closely resembles what we would now refer to as ADHD. In this ‘Class 1’ cluster they also reported an additional subgroup, which they termed a ‘sub-alpha rhythm’ with slow frontal regular activity, which occurred in a similar way as the posterior alpha (*‘...In other cases a 5–6/s rhythm would predominate in the anterior head regions simultaneous with an 8–10/s rhythm from the posterior regions...’*). Nowadays, we would consider this a slowed Alpha Peak Frequency or slowed APF. Interestingly since the introduction of quantitative EEG in the 1960s, almost no studies have reported on the APF in ADHD whereas older studies have consistently reported on this measure (Arns 2012). Since it has been shown that ADHD children with a slow APF do not respond well to stimulant medication (Arns et al. 2008), whereas ADHD children with excess theta do (Clarke et al. 2002; Suffin and Emory 1995), it is crucial to dissociate these two different EEG subtypes, which tend to overlap in the EEG frequency domain. As pointed out by Arns et al. (2008) and further demonstrated in Lansbergen et al. (2011), the often-reported increased TBR in ADHD actually combines both the excess frontal theta group (interpreted as the ‘impaired vigilance regulation subgroup’) as well as a slow APF subgroup, due to the alpha frequency slowing to such a degree that it overlaps with the theta frequency band (4–8 Hz). Therefore, in addition to the limited validity of TBR presented above, this is a further reason why the TBR is probably not a specific measure since it incorporates different subtypes of ADHD. From a personalised medicine perspective this is not optimal, since these subtypes respond differentially to medication and are hypothesised to have a different underlying pathophysiology.

Several studies have now demonstrated that a slow APF is associated with non-response to several treatments such as stimulant medication in ADHD (Arns et al. 2008), rTMS in depression (Arns et al. 2010; Arns 2012), antidepressant medication (Ulrich et al. 1984), comorbid depressive symptoms in ADHD after neurofeedback (Arns et al. 2012a) and antipsychotic medication (Itil et al. 1975). Since alpha peak frequency is associated with a heritability of 81 % (van Beijsterveldt and van Baal 2002), this suggests that a slow APF might be considered a non-specific predictor or even endophenotype for non-response to treatments across a range of disorders. This subgroup comprises a substantial proportion of patients (28 % in ADHD: Arns et al. (2008), 17 % in depression: Arns et al. (2012b)) for whom currently no known treatment exists [see: Arns (2012) for a review].

4.3 Paroxysmal EEG Abnormalities and Epileptiform Discharges

Older studies preceding the era of quantitative EEG have mainly employed visual inspection of the EEG such as identification of epileptiform or paroxysmal activity, estimating the incidences of paroxysmal patterns in ADHD (or former diagnostic classes of ADHD) to be from between 12–15 % (Satterfield et al. 1973; Capute et al. 1968; Hemmer et al. 2001) to approximately 30 % (Hughes et al. 2000), which is high compared to 1–2 % in normal populations (Goodwin 1947; Richter et al. 1971). Note that these individuals did not present with convulsions and thus did not have a clinical diagnosis of epilepsy, but simply exhibited a paroxysmal EEG without a history of seizures. In autism, a prevalence of 46–86 % for paroxysmal EEG activity or epileptiform EEG abnormalities has been reported (Parmeggiani et al. 2010; Yasuhara 2010), hence the findings in the old research on ‘abnormal’ EEG might have been partly confounded by a subgroup with autism, since autism was not included as a diagnostic entity in the DSM until 1980 when the DSM-III was released.

The exact implications of this paroxysmal and epileptiform EEG activity in subjects without a history of clinical signs of seizures are not very well understood and it is good clinical practise not to treat these subjects with anticonvulsive medication (*‘Treat the patient, not the EEG’*). In a very large study among healthy jet fighter pilots, Lennox-Buchthal et al. (1960) classified 6.4 % as ‘marked and paroxysmally abnormal’. Moreover, they found that pilots with such EEGs were three times more likely to be involved in a plane crash due to pilot error, indicating that even though these people are not ‘epileptic’ their brains are ‘not normal’ and hence the presence of paroxysmal EEG continues to be an exclusion criterion for becoming a pilot to this day. It is interesting to note that several studies found that ADHD patients (Itil and Rizzo 1967; Davids et al. 2006; Silva et al. 1996) and patients with autism (Yasuhara 2010) do respond to anticonvulsant medication. The reported effect size for carbamazepine in the treatment of ADHD was 1.01,

which is quite similar to the effect size for stimulant medication (Wood et al. 2007). Furthermore, some studies have demonstrated that interictal and/or sub-clinical spike activity has detrimental effects on neuropsychological, neurobehavioural, neurodevelopmental, learning and/or autonomic functions and some of these children with subclinical spike patterns do respond to anticonvulsant medication both with a reduction of spikes measured in the EEG and with improvements on memory and attention (Mintz et al. 2009). Like in other psychiatric disorders such as panic disorders (Adamaszek et al. 2011) these findings suggest the existence of a subgroup with paroxysmal EEG, who might better respond to anticonvulsant medication; however further research is required to substantiate this.

4.4 Excess Beta Subgroup

There is clear evidence for a subgroup of ADHD patients that are characterised by excess beta or beta-spindles, and make up 13–20 % (Chabot and Serfontein 1996; Clarke et al. 2001a). Several studies demonstrated that these patients do respond to stimulant medication (Clarke et al. 2003; Chabot et al. 1999; Hermens et al. 2005). Relatively little is known about this excess beta group and about the occurrence of beta-spindles. The latter are generally observed as a grapho-element that indicate sleep onset (AASM Manual) and can also be found in patients with mania (Small et al. 1997). Further, they occur as medication effect due to vigilance decreasing agents like benzodiazepines (Blume 2006) or barbiturates (Schwartz et al. 1971). Furthermore, Clarke et al. (2001b) reported this ADHD subgroup was more prone to moody behaviour and temper tantrums and Barry et al. (2009) reported that the ERP's of this subgroup differed substantially from ADHD children without excess beta, suggesting a different dysfunctional network explaining their complaints. Interestingly the ERP's of the excess beta subgroup appear more normal than those of the ADHD subgroup without excess beta.

Originally Gibbs & Gibbs in 1950 (see: Niedermeyer and Lopes da Silva 1993) distinguished two types of predominantly fast EEG, a moderate increased beta, which they termed 'F1' and a marked increased beta, which they termed 'F2'. Records of the F1 type were initially considered as 'abnormal' until the 1940s, whereas since that time Gibbs & Gibbs only considered the F2 type as 'abnormal'. However, currently electroencephalographers have shown a more lenient philosophy towards the interpretation of fast tracings (Niedermeyer and Lopes da Silva 1993, p. 161). At this moment, the only EEG pattern in the beta range considered abnormal is the 'paroxysmal fast activity' or 'beta band seizure pattern', which most often occurs during non-REM sleep, but also during waking (Stern and Engel 2004). This pattern is quite rare (4 in 3,000) and is most often seen in Lennox–Gastaut syndrome (Halasz et al. 2004). Vogel (1970) also described an EEG pattern of 'occipital slow beta waves' or also termed 'quick alpha variants 16–19/s' which responds in the same way as alpha to eyes opening and also has a similar

topographic distribution. This pattern was only found in 0.6 % of a large population of healthy air force applicants and given its very low prevalence and occipital dominance, this subtype is unlikely the explanation of the ‘excess beta’ or ‘beta spindling’ subtype observed in ADHD. Therefore, the ADHD subgroup with excess beta or beta spindling (assuming the paroxysmal fast activity has been excluded) can neurologically be considered a ‘normal variant’. However, neuro-physiologically this can be considered a separate subgroup of ADHD, which does respond to stimulant medication (Chabot et al. 1999; Hermens et al. 2005). Probably, the ‘beta-spindle’ group also represents a subgroup with impaired vigilance (see above), as beta-spindles are common signs for sleep onset. More research is required to investigate the exact underlying neurophysiology of this subtype and if other treatments could more specifically target this excess beta or beta spindling.

5 Depression

Lemere published the first description of EEG findings related to depression in 1936 (Lemere 1936). After inspecting the EEG of healthy people and several psychiatric patients he concluded: ‘...*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...*’. This increased alpha power is to date still considered a hallmark of depression (e.g. see Itil (1983)) and recent studies suggest this endophenotype to be the mediator between the BDNF Val66Met polymorphism and trait depression (Gatt et al. 2008; Zoon et al. 2013).

One of the first attempts at using the EEG as a prognostic tool in depression stems from 1957. Roth et al. (1957) investigated barbiturate-induced EEG changes (delta increase) and found this predicted to some degree the long-term outcome (3–6 months) of ECT in depression. Many subsequent studies have demonstrated that greater ‘induced’ delta EEG power predicts favourable outcome to ECT (Ictal EEG power (Nobler et al. 2000); ECT-induced delta (Fink and Kahn 1957; Fink 2010; Volavka et al. 1972) and barbiturate-induced delta (Roth et al. 1957)). Or, as Max Fink concluded in a recent review, ‘*slowing of EEG rhythms was necessary for clinical improvement in ECT*’ (Fink 2010).

5.1 Metabolic Activity in the Anterior Cingulate (ACC) and Other Structures

In 1997 Mayberg et al. [see: Mayberg et al. (1997)] reported that pre-treatment increased resting glucose metabolism of the rostral anterior cingulate (BA 24a/b) and predicted favourable treatment response to antidepressants. Two earlier studies

already demonstrated a similar finding for the relation between increased ACC metabolism and response to sleep deprivation (Ebert et al. 1994; Wu et al. 1992), which was also confirmed in later studies (Smith et al. 1999; Wu et al. 1999). 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 well-investigated finding in treatment prediction in depression. In order to integrate all these findings recently a meta-analysis was performed that included 23 studies (Pizzagalli 2011). Nineteen studies reported that responders to antidepressant treatments demonstrated increased ACC activity pre-treatment whereas the remaining four studies found the opposite. The overall effect size (ES) was a large effect size (ES=0.918). The relationship between increased ACC activity and favourable antidepressant response was found consistently across treatments (SSRI, TCA, ketamine, rTMS and sleep deprivation) and imaging modalities, and did not depend upon medication status at baseline (Pizzagalli 2011). 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.

Most studies have used PET, SPECT and fMRI for assessing activity in the ACC. However with LORETA (low resolution brain electromagnetic tomography) as an algorithm for computation of intracortical EEG source estimates it is also possible to assess activity in the ACC using scalp-EEG time series (Pascual-Marqui et al. 1994). Increased theta in the ACC assessed with LORETA has been shown to reflect increased metabolism in the ACC (Pizzagalli et al. 2003). Furthermore, several studies have used this technique to probe ACC activity successfully [reviewed in Pizzagalli (2011)].

5.2 EEG Markers in Depression

In QEEG research, various pre-treatment differences in EEG measures have been reported to be associated with improved antidepressant treatment outcomes. The following summarises findings that have been replicated in at least one study and relate to baseline measures predicting treatment outcome. It should be the goal to identify biomarkers that not only yield valid and effective prediction of treatment response but also can be linked to the underlying pathomechanisms of depression. Only a marker that can be integrated into the prevailing view of pathogenesis or even widens the scope of our understanding will be trusted in the field of clinical routine diagnostic. Therefore EEG research on prediction biomarkers has to bridge the gap between the mere analyses of electrophysiological time series on the one side and psychopathology, behaviour and clinical picture on the other side.

Decreased theta has consistently been reported to be related to a favourable treatment outcome to different antidepressant treatments (Arns et al. 2012b;

Iosifescu et al. 2009; Olbrich and Arns 2013) (with the exception of (Cook et al. 1999)) as well as lower delta power (Knott et al. 2000). Given that most LORETA studies found an association between increased theta in the ACC and treatment response, these findings appear contradictory. However, Knott et al. (2000) and Arns et al. (2012b) analysed the EEG activity across all sites and Iosifescu et al. (2009) only looked at Fp1, Fpz and Fp2. Given that frontal-midline theta has been localised to the medial pre-frontal cortex and anterior cingulate (Ishii et al. 1999; Asada et al. 1999), one would thus expect that only frontal-midline sites would reflect the increased theta, which was indeed reported by Spronk and colleagues who found increased theta at Fz to be associated with favourable treatment outcome (Spronk et al. 2011). Hence these findings have to be interpreted in that increased generalised slow EEG power is a predictor for non-response, whereas increased ACC theta or frontal-midline theta is a positive predictor for response. These reflect different types of theta activity: ACC theta, also referred to as phasic theta, reflective of frontal-midline theta related to information processing versus tonic theta, reflective of widespread frontal theta and related to drowsiness or unstable vigilance regulation (for a review of the different roles of tonic and phasic theta refer to [Klimesch 1999]).

Hegerl et al. (2012) and Olbrich et al. (2012) demonstrated a clear difference in EEG vigilance regulation in patients with depression compared to matched controls. Depressed patients exhibited a hyperstable vigilance regulation expressed by increased A1 stages (parietal alpha) and decreased B2/3 and C stages (frontal theta) which is consistent with a study by Ulrich and Fürstenberg (1999) and other studies demonstrating increased parietal alpha (Itil 1983; Pollock and Schneider 1990), as first observed by Lemere (1936). Vogel (1970) described a pattern of 'Monotonous High Alpha Waves', with a simple autosomal dominance of inheritance. The description of this EEG pattern found by Vogel ('Kontinuität') is very similar to the 'hyperrigid' or 'hyperstable' EEG vigilance found by Hegerl and Hensch (2012) and hence suggests this indeed reflects a 'trait' like EEG vigilance regulation.

Furthermore, increased pre-treatment alpha has been associated with improved treatment outcome to antidepressant medication (Ulrich et al. 1984; Bruder et al. 2001; Tenke et al. 2011) and most antidepressants also result in a decrease of alpha activity [see: Itil (1983) for an overview]. Therefore, the subgroup of non-responders characterised by frontal theta might be interpreted as a subgroup characterised by a *decreased* EEG vigilance regulation (Hegerl and Hensch 2012; Olbrich and Arns 2013), as opposed to the typically reported *increased* or *hyperstable* vigilance regulation ('hyperstable' parietal alpha). Given that patients with a decreased EEG vigilance regulation respond better to stimulant medication (manic depression: Hegerl et al. 2010; Bschor et al. 2001; Schoenkecht et al. 2010; ADHD: Arns et al. 2008; Sander et al. 2010), it is tempting to speculate whether this subgroup of non-responders might respond better to stimulant medication or other vigilance stabilising treatments. Although a recent Cochrane review did report significant improvements of depressive and fatigue symptoms for short-term stimulant medication as add on therapy in depressed patients (Candy et al. 2008),

the clinical significance remained unclear and there were very few controlled studies which could be included, thus limiting the generality of this finding (Candy et al. 2008). However, stimulant medication has been applied successfully in a subgroup of depression with excess theta by Suffin and Emory (1995), which was replicated in a prospective randomised controlled trial (Debattista et al. 2010). Therefore, along the same lines as discussed above in relation to sleep problems as the core pathophysiology of ADHD, future research should focus on investigating EEG vigilance regulation and the existence of sleep problems in this subgroup of non-responders in order to develop an appropriate treatment for these patients, who are found to be non-responders to gold-standard antidepressant treatments.

In summary, responders to antidepressant treatments such as antidepressants and rTMS are generally characterised by increased parieto-occipital alpha (or a 'hyperstable' vigilance regulation) and increased theta in the rostral anterior cingulate (Pizzagalli 2011) reflected as frontal-midline theta. A subgroup of non-responders to antidepressant treatments are characterised by generalised increased frontal theta reflective of decreased EEG vigilance regulation. It is hypothesised that this latter group might be better responders to vigilance stabilising treatments such as psychostimulants or chronobiological treatments such as melatonin or early morning bright light.

5.3 Alpha Peak Frequency in Depression

In one of the earliest studies investigating EEG predictors of treatment response in depression, Ulrich et al. (1984) found that non-responders to a tricyclic antidepressant (TCA), specifically amitriptyline, and pirlindole (a tetracyclic compound) demonstrated slower APF (8 Hz) as compared to responders (9.5 Hz). Furthermore, they also found that after 4 weeks of treatment only responders demonstrated an increase of 0.5 Hz in their APF, whereas the non-responders did not. More recently, it has also been shown that depressed patients with a pre-treatment slow APF also respond less well to rTMS (Arns et al. 2010, 2012b). Furthermore, as discussed above, a slow APF could represent a generic biomarker for non-response.

5.4 Treatment Emergent or Pharmacodynamic Biomarkers in Depression

The measures discussed above all involved baseline measures, which were investigated for their capability of predicting treatment outcome. However, another well-investigated line of research relates to 'treatment emergent biomarkers' or

‘pharmacodynamic’ biomarkers (Savitz et al. 2013) which measure the EEG at baseline and subsequently after treatment for several days, with the changes used to predict treatment outcome. This approach has been mainly applied to antidepressants as, given that this class of drugs generally takes 4–6 weeks to demonstrate its clinical effects, knowing whether a drug is likely to prove efficacious within several days has clinical relevance. Two of these methods will be discussed in more detail in the following, namely EEG cordance and the Antidepressant Treatment Response.

5.5 EEG Cordance

The EEG cordance method was initially developed by Leuchter and colleagues to provide a measure, which had face-validity for the detection of cortical deafferentation (Leuchter et al. 1994a, b). They observed that the EEG over a white-matter lesion often exhibited decreased absolute theta power, but increased relative theta power, which they termed ‘discordant’. Therefore, the EEG cordance method combines both absolute and relative EEG power. Negative values of this measure (discordance)—specifically in theta or beta—reflect low perfusion or metabolism, whereas positive values (concordance)—specifically in alpha—reflect high perfusion or metabolism (Leuchter et al. 1994a, b). This has been confirmed by comparing cordance EEG with simultaneous measuring perfusion employing PET scans (Leuchter et al. 1999).

In a first study, it was found that depressive patients characterised by a ‘discordant’ brain state at baseline could be characterised as non-responders (Cook et al. 1999). Subjects were classified into ‘discordant’ if >30 % of all electrodes exhibited discordance or if fewer electrodes that are highly deviant. Furthermore, central (Cz, FC1, FC2) theta cordance was related to treatment outcome after ECT (Stubbeman et al. 2004). More recent studies have focused on EEG cordance in the theta frequency band at pre-frontal electrodes (Fp1, Fp2, Fpz) and have found that theta cordance *change (decrease)* across 48 h to 2 weeks of treatment predicted longer-term treatment outcome (Cook et al. 2002, 2005). In an independent replication study, Bares et al. (2007, 2008, 2010) also found that responders were characterised by a decrease in pre-frontal (Fp1, Fp2, Fz) theta cordance after 1 week. Furthermore, Cook et al. (2005) demonstrated that a medication wash-out period for assessing the quantitative EEG is not critical in reliably using EEG cordance. This further suggests that change in frontal theta cordance is a reflection of the early beneficial effects of the treatment and is hence not dependent upon treatment type since the same cordance effects have been observed with SSRI, SNRI, TCA, rTMS and ECT. Across studies of depressive patients treated with various antidepressant medications, decreases in pre-frontal theta cordance 1 week after start of medication have consistently predicted response, with overall accuracy ranging from 72 to 88 % (Iosifescu et al. 2009).

A pre-frontal theta cordance *increase* was found in placebo-responders (Leuchter et al. 2002). A more recent study from this group refined this further by examining right-medial frontal sites and found that theta cordance after 1 week was only decreased in the medication responders but not in the placebo-responders (Cook et al. 2009), hence demonstrating specificity of this measure to treatment outcome and not to placebo response.

As a limitation of this measure it should be noted that the mentioned mixture of absolute and relative EEG power values for calculation of the cordance measure lowers the possibility for interpretation of the underlying neuronal activities (Kuo and Tsai 2010).

5.6 Antidepressant Treatment Response

The ATR measure was also developed by Leuchter and colleagues (2009a, b) and is commercialised by Aspect Medical Systems. The first results of this measure were published in 2009 by Iosifescu et al. (2009), demonstrating that the ATR measure was able to predict treatment outcome to an SSRI or Velafaxine with an accuracy of 70 % (82 % sensitivity; 54 % specificity). Recently, the results of a large clinical trial (BRITE-MD) investigating the ATR were published (Leuchter et al. 2009a, b). This measure is based on EEG recorded from Fpz (FT7 and FT8) and is the non-linear weighted combination of (1) combined relative alpha and theta (3–12 Hz/2–20 Hz) at baseline and (2) the difference between absolute alpha1 power (8.5–12 Hz) at baseline and absolute alpha2 power (9–11.5 Hz) after 1 week of treatment (Leuchter et al. 2009a, b). It was demonstrated that a high ATR value predicted response to an SSRI with 74 % overall accuracy (58 % sensitivity, 91 % specificity). Interestingly, in another study, they reported that patients with a low ATR responded better to the atypical antidepressant bupropion (Leuchter et al. 2009a, b) thereby demonstrating that this measure identified two subgroups of depressive patients with subsequent implications for two types of antidepressants.

The disadvantage of this method is that patients already need to be prescribed the medication before any prediction can be made and this method could not be used on 15 % of the patients due to ECG artefacts (Leuchter et al. 2009a, b), hence also reflecting a ‘treatment emergent biomarker’.

6 Conclusion

Much research has been conducted in ADHD and depression to investigate the potential of predicting treatment outcome using EEG as a marker, and the results are promising. The next step would be to integrate these different metrics further, make advantage of the different information they provide about the underlying

neuronal activity and investigate the similarities and differences in order to further our knowledge, so that EEG- and ERP-based data can be used in practice to predict treatment outcome. Finally, some examples have been presented where the identification of EEG-based subgroups sheds more light on the underlying pathology of the disease state, and can thus be used to develop more effective treatments for the different subgroups.

Acknowledgment This work has been adapted and updated from the PhD thesis: ‘Personalized medicine in ADHD and Depression: A quest for EEG treatment predictors’ by Martijn Arns.

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