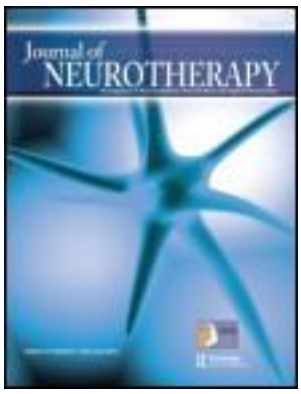

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EEG-Based Personalized Medicine in ADHD: Individual Alpha Peak Frequency as an Endophenotype Associated with Nonresponse

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REVIEW ARTICLE

EEG-BASED PERSONALIZED MEDICINE IN ADHD: INDIVIDUAL ALPHA PEAK FREQUENCY AS AN ENDOPHENOTYPE ASSOCIATED WITH NONRESPONSE

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This review article summarizes some recent developments in psychiatry such as personalized medicine, employing biomarkers and endophenotypes, and developments collectively referred to as neuromodulation with a focus on ADHD. Several neurophysiological subtypes in ADHD and their relation to treatment outcome are reviewed. In older research the existence of an ''abnormal EEG'' or ''paroxysmal EEG'' was often reported, most likely explained by the high occurrence of this EEG subtype in autism, as the diagnosis of autism was not coined until 1980. This subgroup might respond best to anticonvulsant treatments, which requires more specific research. A second subgroup is a beta-excess or beta-spindling subgroup. This group responds well to stimulant medication, albeit several studies suggesting that neurophysiologically this might represent a different subgroup. The third subgroup consists of the ''impaired vigilance'' subgroup with the often-reported excess frontal theta or excess frontal alpha. This subgroup responds well to stimulant medication. Finally, it is proposed that a slow individual alpha peak frequency is an endophenotype related to treatment resistance in ADHD. Future studies should incorporate this endophenotype in clinical trials to further investigate new treatments for this substantial subgroup of patients, such as NIRS-biofeedback, transcranial Doppler sonography biofeedback, hyperbaric oxygen therapy, or medications such as nicotine and piracetam.

INTRODUCTION

Recently the landscape in psychiatry has undergone a dramatic change. Some recent large-scale studies investigating the effects of conventional treatments for ADHD and depression in clinical practice have demonstrated on the group level limited efficacy of antidepressant medication and cognitive behavioral therapy in depression (STAR*D: Rush et al., 2006), an overestimation of the effects of cognitive-behavioral therapy for depression as a result of publication bias (Cuijpers, Smit, Bohlmeijer, Hollon, & Andersson, 2010) and limited long-term effects of stimulant medication, multicomponent behavior therapy, and multimodal treatment in ADHD (NIMH-MTA trial: Molina et al., 2009). Furthermore, several large pharmaceutical companies have announced that they will ''pull the plug on drug discovery in some areas of neuroscience'' (Miller, 2010, p. 502), including GlaxoSmithKline and

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AstraZeneca. This can be considered a worrying development, as there is still much to improve in treatments for depression and ADHD. Therefore, a move beyond data regarding the average effectiveness of treatment, to identify the best treatment for any individual (Simon & Perlis, 2010) or personalized medicine, is crucial. In personalized 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 or endophenotypes.

In addition to this development we also witness a shift from a ''systemic treatment approach'' (i.e., systemically applying medication to the whole body) to a more ''focal treatment approach,'' also subsumed under the term ''Neuromodulation.'' In this development there are currently many new treatments developed and applied, such as deep-brain stimulation in depression (Hamani et al., 2011), Parkinson's (Zahodne et al., 2009), intracranial stimulation of primary and secondary auditory cortex in tinnitus (De Ridder et al., 2006), rTMS in depression (Schutter, 2009, 2010), fMRI neurofeedback in pain (deCharms et al., 2005), neurofeedback in ADHD (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009), Vagus Nerve Stimulation in depression (Daban, Martinez-Aran, Cruz, & Vieta, 2008), and so on. Along with the development of these new techniques it is interesting to note that the application of some of these neuromodulation approaches do not solely rely on a *Diagnostic and Statistical Manual of Mental Disorders* (4th ed. [*DSM–IV*]; American Psychiatric Association, 1994) diagnosis but lean more toward identifying dysfunctional brain networks and application of treatment to specifically modulate those networks. For example, deep brain stimulation studies specifically aim to modulate the subcallosal cingulate gyrus (Hamani et al., 2011), fMRI neurofeedback patients learn to specifically regulate activity in the rostral anterior cingulate (deCharms et al., 2005), and for neurofeedback treatment in ADHD, the protocol can be personalized to specific deviating EEG patterns (Arns, Drinkenburg, & Kenemans, 2012).

PERSONALIZED MEDICINE: BIOMARKERS AND ENDOPHENOTYPES

In personalized 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. Genotypic and phenotypic information or ''Biomarkers'' lie at the basis of personalized medicine. Usually in this context genetic markers are considered, which can predict effects of medication such as the classical example of herceptin. Herceptin is a drug used to treat breast cancer, but only for patients showing an overexpression for a specific protein better known as human epidermal growth factor receptor 2 (HER2). This drug only works well with this specific subgroup of patients, who are easily distinguished by a genetic test where HER2 is considered the biomarker. At this moment there is no psychiatric disorder, which is completely genetically determined. Furthermore, 2011 marked the 10-year anniversary of the completion of the Human Genome project, which has sparked numerous large-scale Genome Wide Association studies 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 personalized medicine for psychiatry will be not so fruitful. The notion of personalized medicine suggests *heterogeneity* within a given *DSM–IV* disorder, rather than *homogeneity*, at least from a brain-based perspective. Therefore a variety of ''endophenotypes'' or ''biomarkers'' are expected within a single *DSM–IV* disorder such as ADHD or depression, expected to require a different treatment.

The concept of endophenotypes has been described as early as in 1966 and originated from a review on geographical distribution in insects where a clear case was made for not only investigating the exophenotype (''the obvious and the external'') but also the endophenotype (''the microscopic and internal''; John & Lewis, 1966). This term was further adopted by Gottesman and Shields (1967, 1972) in their studies on schizophrenia as ''biochemical test

or microscopic examination'' (Gottesman & Gould, 2003, p. 637). The idea behind an endophenotype is that it is the intermediary step between genotype and behavior and thus is more closely related to genotype than behavior is. 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, and so on. 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.

EEG AS AN ENDOPHENOTYPE?

Many studies have investigated the heritability of the EEG in twin studies and family studies (see Martinović, Jovanović, & Ristanović, 1997; Vogel, 1970) and found that many aspects of the EEG are heritable. In a meta-analysis, van Beijsterveld and van Baal (2002) demonstrated high heritability for measures such as the alpha peak frequency (APF; 81%), alpha EEG power (79%), P300 amplitude (60%), and P300 latency (51%), all suggesting that EEG and event-related potential (ERP) parameters fulfill the definition of an endophenotype, by some also referred to as EEG Phenotypes (Johnstone, Gunkelman, & Lunt, 2005). Next, some of the best investigated EEG Endophenotypes are summarized:

1. Low-voltage (alpha) EEG: This 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'' (Adrian & Matthews, 1934, p. 382). The low-voltage alpha EEG has been known to be heritable (autosomal dominant) and the heritability of alpha power is estimated at 79 to 93% (Anokhin et al., 1992; Beijsterveld & van Baal, 2002; Smit et al., 2010; Smit, Posthuma, Boomsma, & Geus, 2005; Vogel, 1970). Low-voltage EEG is a well-described endophenotype in anxiety and alcoholism (Bierut et al., 2002; Ehlers, Garcia-Andrade, Wall, Cloutier, & Phillips, 1999; Enoch, Schuckit, Johnson, & Goldman, 2003; Enoch et al., 1999; Pine & Pine, 1953). Alpha power and LVA have been successfully associated with a few chromosome loci (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, White, Waheed, & Goldman, 2008), a gamma-amino butyric acid (GABA)-B receptor gene (Winterer et al., 2003), and with the BDNF Val66Met polymorphism in depression (Veth et al., 2012).
2. Frontal alpha: In addition to the high heritability of parieto-occipital alpha power referred to above, heritability of alpha at frontal sites is also high (85–87%; Anokhin, Heath, & Myers, 2006) but generally lower as compared to parieto-occipital sites (van Beijsterveldt & van Baal, 2002).
3. Hyperrigid or continuous alpha: Vogel (1970) described a ''Monotonous High Alpha Waves'' pattern, a characteristic that is heritable in a simple autosomal dominance manner. The description of this EEG pattern (''Kontinuität'') is very similar to the ''hyperrigid'' EEG described in the EEG Vigilance model (also see Arns, Gunkelman, Olbrich, Sander, & Hegerl, 2010).
4. The APF has been shown to be the most reproducible and heritable EEG aspect (Posthuma, Neale, Boomsma, & de Geus, 2001; Smit et al., 2005; van Beijsterveldt & van Baal, 2002) and has been associated with the COMT gene, with the Val/Val genotype being marked by a 1.4 Hz slower APF as compared to the Met/Met group (Bodenmann et al., 2009); this difference could explain a considerable amount of variability in this measure.

5. Spindling excessive beta: Family studies have shown that frontal and fronto-central beta spindles and excess beta exhibit an autosomal dominant mode of inheritance in healthy persons, but these patterns can also occur as a result of brain damage. Furthermore, the pattern of fronto-precentral beta has a lower frequency in Japanese (Vogel, 1970). A strong linkage between beta frequencies and GABA-A receptor genes has been reported, in line with the often-reported medication effects of benzodiazepines resulting in a ''beta buzz'' (Porjesz et al., 2002).
6. Epileptiform EEG: Several types of paroxysmal EEG or epileptic EEG have also been demonstrated to be heritable and genetically linked (Haug et al., 2003; Kaneko, Iwasa, Okada & Hirose, 2002; Vaughn, Greenwood, Aylsworth & Tennison, 1996).

EEG-BASED PERSONALIZED MEDICINE

In the context of Personalized Medicine in Psychiatry, Gordon (2007) proposed the term ''neuro-marker,'' and Johnstone et al. (2005) proposed the term ''EEG Phenotype'' as examples of biomarkers or intermediate phenotypes, of which several have been in the previous section. In another context EEG-vigilance regulation has also been proposed as a state-dependent trait (Hegerl, Himmerich, Engmann, & Hensch, 2010; Hegerl, Sander, Olbrich, & Schoenknecht, 2009). The underlying idea behind these concepts is that neuroimaging data such as from EEG, fMRI, PET scans, and so forth, can be considered stable endophenotypes or biomarkers incorporating both the effects of nature and nurture. This potentially makes such markers ideal candidate biomarkers, which have the potential to predict treatment outcome for treatments such as antidepressants or stimulants but also to neuromodulation treatments such as rTMS and neurofeedback. These developments, currently subsumed under the umbrella term ''personalized medicine,'' are not completely new.

The quest for biomarkers to predict treatment outcome has a long history. For example Satterfield and colleagues (Satterfield, Cantwell, Saul, Lesser, & Podosin, 1973; Satterfield, Lesser, & Podosin, 1971) were the first to investigate the potential use of EEG in predicting treatment outcome to stimulant medication (results outlined next). In 1957 Roth and colleagues (Roth, Kay, Shaw, & Green, 1957) investigated barbiturate induced EEG changes (delta increase) and found that this predicted to some degree the long-term outcome (3–6 months) to ECT in depression. This latter finding was replicated measuring delta activity during the interseizure period, and as Fink (2010) summarized this finding eloquently, ''Slowing of EEG rhythms was necessary for clinical improvement in ECT'' (p. 163). In this development of personalized medicine, the focus is hence more on ''prognostics'' rather than ''diagnostics.''

The topic of this review is personalized medicine in ADHD with a main focus on neurophysiological techniques such as the EEG and ERPs.

ADHD

In the following section, the literature on several neurophysiological subgroups in ADHD is summarized and implications for treatment discussed.

Paroxysmal EEG Abnormalities and Epileptiform Discharges

Older studies preceding the era of quantitative EEG (QEEG) have mainly employed visual inspection of the EEG such as identification of epileptiform or paroxysmal EEG. These older studies estimated the incidences of paroxysmal EEG in ADHD (or former diagnostic classes of ADHD) between 12 and 15% (Capute, Niedermeyer. & Richardson, 1968; Hemmer, Pasternak, Zecker, & Trommer, 2001; Satterfield et al., 1973) to approximately 30% (Hughes, DeLeo, & Melyn, 2000), which is high compared to 1 to 2% in normal populations (Goodwin, 1947; Richter, Zimmerman, Raichle, & Liske, 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 in the absence of convulsions. In autism a

prevalence of 46 to 86% for paroxysmal EEG or epileptic 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, because 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 EEG activity in subjects without overt signs of epilepsy are not very well understood, and many neurologists will see no need to treat these subjects as epileptics. In a very large study among healthy jet fighter pilots, Lennox-Buchtal, Buchtal, and Rosenfalck (1960) classified 6.4% as ''marked and paroxysmally abnormal'' (p. 368). Moreover, they found that pilots with such EEGs were three times more likely to have their 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 (Davids, Kis, Specka, & Gastpar, 2006; Itil & Rizzo, 1967; Silva, Munoz, & Alpert, 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, Crager, Delap, & Heiskell, 2007). Furthermore, some studies have demonstrated that interictal and/or subclinical spike activity has detrimental effects on neuropsychological, neurobehavioral, 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). 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.

Excess Beta Subgroup

There is clear evidence for a subgroup of ADHD patients that are characterized by excess beta or beta spindles, and make up 13 to 20% of the ADHD population (Arns, Gunkelman, Breteler, & Spronk, 2008; Chabot & Serfontein, 1996; Clarke et al., 1998, 2001b). Several studies demonstrated that these patients do respond to stimulant medication (Chabot et al., 1999; Clarke et al., 2003; Hermens, Cooper, Kohn, Clarke, & Gordon, 2005). Relatively little is known about this excess beta group and about beta spindles. The latter are generally observed as a medication effect due to benzodiazepines (Blume, 2006) or barbiturates (Schwartz, Feldstein, Fink, Shapiro, & Itil, 1971). Furthermore, Clarke, Barry, McCarthy, and Selikowitz (2001c) reported this ADHD subgroup was more prone to moody behavior and temper tantrums, and Barry, Clarke, McCarthy, Selikowitz, and Brown (2009) reported that the ERPs of this subgroup differed substantially from ADHD children without excess beta, suggesting a different dysfunctional network explaining their complaints. Of interest, the ERPs of the excess beta subgroup appear more normal than those of the ADHD subgroup without excess beta.

Originally, Gibbs and Gibbs (1950) 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 and Gibbs only considered the F2 type as ''abnormal.'' However, currently electroencephalographers have shown a more lenient philosophy toward fast tracings (Niedermeyer & Lopez Da Silva, 2004, p. 161). At this moment the only abnormal EEG pattern in the beta range is the ''paroxysmal fast activity'' or ''beta band seizure pattern,'' which most often occurs during non-REM sleep, but also during waking (Stern & Engel, 2004). This pattern is quite rare (4 in 3,000) and most often seen in Lennox-Gastaut syndrome (Halasz, Janszky, Barcs, & Szcs, 2004). Vogel (1970) also described an EEG

pattern of ''occipital slow beta waves'' or also termed ''quick alpha variants 16–19/sec,'' 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; 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, neurophysiologically this can be considered a separate subgroup of ADHD, which does respond to stimulant medication (Chabot et al., 1999; Clarke et al., 2003; Hermens et al., 2005). 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.

''Excess Theta'' and ''Theta/Beta Ratio'': Impaired Vigilance Regulation

The most consistent findings reported in the literature on ADHD since the introduction of QEEG are those of increased absolute power in Theta (Bresnahan, Anderson, & Barry, 1999; Chabot & Serfontein, 1996; Clarke et al., 1998, 2001b; DeFrance, Smith, Schweitzer, Ginsberg, & Sands, 1996; Janzen, Graap, Stephanson, Marshall, & Fitzsimmons, 1995; Lazzaro et al., 1999; Lazzaro et al., 1998; Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992; Matsuura et al., 1993) and sometimes increased absolute Delta EEG power (Bresnahan et al., 1999; Clarke, Barry, McCarthy, & Selikowitz, 2001; Kuperman, Johnson, Arndt, Lindgren, & Wolraich, 1996; Matsuura et al., 1993). In 1991 Lubar laid the foundation for the concept of the Theta/Beta power ratio as a measure, which could discriminate ''normal'' children from children with ADD, learning disorders, and ADHD (Lubar, 1991). Many others investigated this measure further, with the clearest replication from Monastra et al. (1999), who demonstrated in a multicenter study in 482 subjects that using a single electrode location (Cz) they could classify with an accuracy of 88% children with ADHD based on the Theta/Beta power ratio. Boutros et al. (2005), using a meta-analysis incorporating more than 1,100 subjects with ADHD/ADD, concluded that increased theta activity in ADHD is a sufficiently robust finding to warrant further developing as a diagnostic test for ADHD, with data suggesting that relative theta power is even a stronger predictor. Although this marker is indeed very consistently found to deviate in ADHD, careful inspection of the EEG is required to reliably dissociate a slowed individual alpha peak frequency (iAPF) from real excess theta as has been shown recently by Lansbergen, Arns, Dongen-Boomsma, Spronk, and Buitelaar (2011) and is pointed out next and in Figure 1.

Conceptually, this excess theta subgroup can be interpreted as a subgroup with impaired vigilance regulation. For an in-depth review on this subtype in ADHD and the relationship to circadian-phase delay, sleep-onset insomnia and locus coeruleus activity, also see Arns and Kenemans (2012).

The ''Slow individual Alpha Peak Frequency'' Subgroup

As previously indicated, it is very important to dissociate the excess theta group from patients with a slow iAPF since the neurophysiology for theta and alpha rhythms is different (Niedermeyer & da Silva, 2004). Of interest, since the introduction of QEEG in the 1960s almost no studies have reported on the iAPF in ADHD, whereas older studies have consistently reported on this measure with the first reports dating back as far as 1938 by Jasper, Solomon and Bradley (1938; for a review, also see Arns, Gunkelman, et al., 2010a). Because it has been shown that ADHD children with a slow iAPF do not respond well to stimulant medication (Arns et al., 2008), whereas ADHD children with excess theta do (Arns et al., 2008; Clarke, Barry, McCarthy, Selikowitz, & Croft, 2002; Suffin & Emory, 1995), this is even more crucial from a personalized medicine perspective. In Figure 1 (adapted from Arns

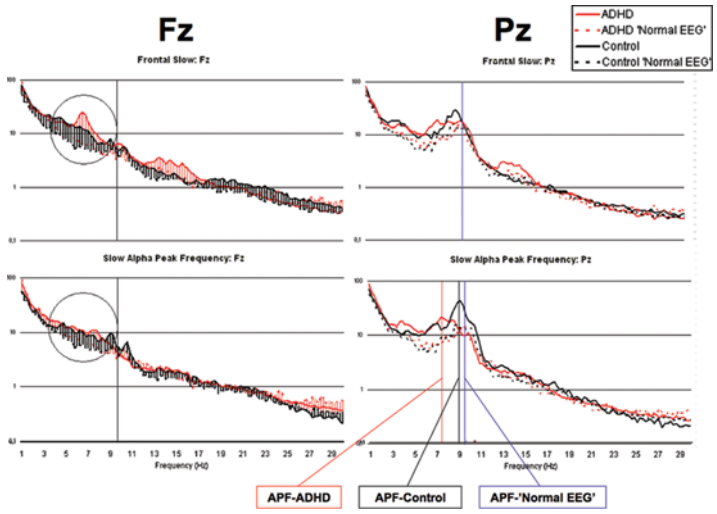

FIGURE 1. This figure clearly demonstrates that the subgroup with a slowed alpha peak frequency (bottom), present parietally, also exhibit elevated ''theta EEG Power'' at frontal sites. However, this is not true ''frontal slow,'' but simply the effect of the slowed alpha peak frequency. This demonstrates that a raised theta/beta ratio at least also includes the slow APF sub-group, which neurophysiologically is a different group, as demonstrated with respect to treatment outcome to stimulant medication. Copyright 2008 World Scientific Publishing Company; http://www.worldscinet.com/jin/. (Color figure available online.)

et al., 2008) this is illustrated in more detail. This figure shows the spectral content of ADHD children (red) and data from a control group (black) for both frontal (Fz) and parietal (Pz) locations. The dotted lines reflect the groups with a ''normal EEG'' and the solid lines show the spectral power of the subgroups with a ''Frontal Slow'' (top) or ''Slowed Alpha peak frequency'' (bottom). As can be seen, the spectral content for the Frontal Slow group is increased in the theta frequency range mainly at Fz, as would be expected. However, the ADHD group with the Slowed iAPF at Pz showed an average APF of 7.5 Hz. In the frontal locations this also shows up as ''increased theta EEG power,'' whereas this obviously is due to the excessive slowing of the iAPF and should be considered slow alpha, not theta.

In Lansbergen et al. (2011), it was further demonstrated using a quantitative approach that the often-reported increased theta/beta ratio in ADHD actually combines both the excess frontal theta group (interpreted as the ''impaired vigilance regulation subgroup''; see previously) as well as the slow iAPF subgroup. Therefore, although the theta/beta ratio and the ''excess theta'' can discriminate well between a group of children with a *DSM–IV* diagnosis of ADHD from healthy controls (Boutros, Fraenkel, & Feingold, 2005; Monastra et al., 1999), this measure is probably not a *specific* measure because it incorporates different subtypes of ADHD. From a personalized medicine perspective this is not optimal, because these subtypes respond differentially to medication and are hypothesized to have a different underlying pathophysiology.

This also helps explain the contradictory findings between Chabot and colleagues (Chabot, di Michele, Prichep, & John, 2001; Chabot et al.,1999), who found that their excess theta group (described as ''generalized excess of theta absolute and relative power, decreased alpha mean frequency, and frontal theta hypercoherence'' [Chabot et al., 2001, p. 180, underline added]) exhibited a lower response to stimulant medication, suggesting they included patients with a low iAPF, versus Clarke et al. (2002), Arns et al. (2008), and Suffin and Emory (1995), who found that responders to stimulant medication demonstrated increased theta and increased theta/beta ratios.

In Arns, Drinkenburg, and Kenemans (2012) it was found that there was no relation between a slow iAPF and the outcome to neurofeedback in ADHD in inattention and

impulsivity/hyperactivity. In this sample the prevalence of a slow iAPF was probably too low (iAPF <8 Hz: $n = 1$ for parietoccipital iAPF and $n = 6$ for frontal iAPF from $N = 19$) to find a clear relationship between a slow iAPF and treatment outcome on ADHD rating scales. Therefore the conclusion that neurofeedback can be considered an effective treatment for those patients with a slow iAPF who do not respond to stimulant medication is unjustified at this moment. More research with larger samples is required to further investigate that conclusion.

Several studies have now demonstrated that a slow iAPF is associated with nonresponse to several treatments such as stimulant medication (Arns et al., 2008), rTMS (Arns, Drinkenburg, Fitzgerald, & Kenemans, 2012; Arns, Spronk, & Fitzgerald, 2010), antidepressant medication (Ulrich, Renfordt, Zeller, & Frick, 1984) and antipsychotic medication (Itil, Marasa, Saletu, Davis, & Mucciardi, 1975). This suggests that a slow iAPF might be considered a nonspecific predictor for nonresponse to treatments across disorders. This subgroup comprises a substantial proportion of patients—28% in ADHD (Arns et al., 2008), 17% in depression (Arns, Drinkenburg, Fitzgerald, et al., 2012)—and hence the question arises, ''To what treatment might these patients respond?''

Neurophysiology of the iAPF. Much research has been conducted on the relationship between iAPF and cognition; for an extensive review, see Klimesch (1999). Most of these studies have been performed in healthy subjects, and these mainly provide information about the neuropsychological significance of this measure in ''normal'' brain function such as its relation to memory. In this section we are specifically interested in methods that influence the iAPF in order to evaluate what specific methods might be worthwhile exploring as a treatment for the previously described subgroup of patients with a slow iAPF. Hence, here a focus is laid on studies that have demonstrated to increase or decrease the iAPF, to elucidate possible treatments for this subgroup.

The iAPF is highly stable across time within subjects (Kondacs & Szabó, 1999) and is considered a highly heritable trait, with between 71 and 83% of the variance explained by heritability (van Beijsterveld & van Baal, 2002; Posthuma et al., 2001), hence the iAPF can be considered a true endophenotype in line with the definition by Gotessman and Gould (2003) as explained in the introduction. Alpha activity has been shown to be generated in thalamocortical feedback loops of excitatory and inhibitory nerve cells (Lopes da Silva, 1991; Steriade et al., 1990). The thalamo-cortical basis of alpha suggests that the iAPF might be reflective of the cortex polling information from the thalamus, and the cortex relaying back information to the thalamus. A higher iAPF may therefore reflect faster information processing, in line with the many studies suggesting that a high iAPF is associated with improved cognitive performance such as working memory (Clark et al., 2004), semantic memory (Klimesch, 1996), and with faster reaction times in complex tasks (Jin, O'Halloran, Plon, Sandman, & Potkin, 2006). Conversely, the most typical neurological syndrome exhibiting a slow iAPF is Alzheimer's disease (AD), whereby the degree of slowing is also associated with the severity of AD (Rodriguez, Copello, Vitali, Perego, & Nobili, 1999) and AD is also characterized by impaired semantic memory and working memory.

In pain research it has been found that in healthy patients, noxious stimuli will acutely result in an increased iAPF (Nir, Sinai, Raz, Sprecher, & Yarnitsky, 2010), possibly reflective of a ''fight–flight'' response. Furthermore, in this study there also was a significant correlation between baseline iAPF and the subjective pain rating to the same noxious stimulus, where patients with a higher iAPF rated the same pain stimulus as more painful (Nir et al., 2010). In contrast, in chronic pain patients a slow iAPF has been reported (Boord et al., 2008; Sarnthein, Stern, Aufenberg, Rousson, & Jeanmonod, 2006); however, when such patients are treated with central lateral thalectomy (which resulted in 95% pain relief at 12 months) the iAPF normalized again to normal

levels (Sarnthein et al., 2006). These studies suggest that even though the iAPF is a stable heritable and reproducible trait (Kondacs & Szabó, 1999; Posthuma et al., 2001), the iAPF is responsive when ''threat'' is perceived such as pain stimuli. It can be speculated that this ''threat''-related increase in iAPF serves the function of increased alertness in order to respond faster in threat situations. However, when a threat becomes chronic in nature, a slower iAPF is observed as in the previously cited pain studies, which has also been demonstrated in burnout syndrome (van Luijtelaar, Verbraak, van den Bunt, Keijsers, & Arns, 2010), maybe serving a ''gating function'' to reduce the amount of information projected to the cortex in order to better cope with the pain or with the information processing demands in burnout syndrome. Of interest, when the pain is resolved a complete normalization of the iAPF occurs (Sarnthein et al., 2006).

Medication and the iAPF. Ulrich et al. (1984) reported that nonresponders to antidepressant medication were characterized by a posterior slower iAPF (8 Hz vs. 9.5 Hz) at baseline, and furthermore that responders to medication exhibited an increase in iAPF, suggesting that antidepressants do increase the iAPF but only in patients with a ''normal'' iAPF to start with. Furthermore, nicotine has been shown to acutely result in an increased iAPF (Foulds et al., 1994; Knott, 1988; Lindgren, Molander, Verbaan, Lunell, & Rosén, 1999) and so does acute piracetam (Saletu, Grünberger, Linzmayer, & Stöhr, 1984).

Neuromodulation and the iAPF. Modulation of the iAPF by neurofeedback was first shown by Kamiya (1968, 2011), and subsequent studies in healthy volunteers have clearly demonstrated that people are able to uptrain their upper alpha, suggestive of increasing the iAPF, with subsequent behavioral improvements in a mental rotation task (Hanslmayr, Sauseng, Doppelmayr, Schabus, & Klimesch, 2005; Zoefel, Huster, & Herrmann, 2010). However, all these studies have been performed in healthy volunteers with generally ''normal'' iAPFs, so it is unclear if this technique could be helpful for patients with a slow iAPF. Also in Arns, Drinkenburg, and Kenemans (2012) it was not possible to draw any definitive conclusions about the possible role of neurofeedback for this subgroup on ADHD complaints, and future studies are required to investigate this.

Only one study employing 10 Hz rTMS over the left frontal cortex has reported an acute increase of iAPF, which lasted for 2 min (Okamura, Jing, & Takigawa, 2001). However, earlier studies have demonstrated that nonresponders to rTMS were characterized by a slow iAPF (Arns, Drinkenburg, Fitzgerald, et al., 2012; Arns, Spronk, et al., 2010), suggesting that regular rTMS is unlikely to be a likely candidate for this subgroup. One study demonstrated in schizophrenia that rTMS at the iAPF demonstrated better effects on negative symptoms than LF or HF rTMS (Jin et al., 2006); however, we have been unable to replicate this in depression (Arns, Spronk, et al., 2010).

Cerebral blood flow. In 1934 Hans Berger already described a slowing of the EEG as a result of reduced oxygen (see Kraaier, Van Huffelen, & Wieneke, 1988). Since that time a decrease in iAPF is considered the most sensitive measure to demonstrate the effects of low oxygen supply to the brain, such as in cerebral ischemia (Kraaier et al., 1988; van der Worp, Kraaier, Wieneke, & Van Huffelen, 1991) and carotid artery occlusion (Mosmans, Jonkman, & Veering, 1983). In patients with minor cerebral ischemia with visually assessed normal EEGs, slowing of the iAPF is found on the affected side (van der Worp et al., 1991). Carotid endarterectomy is a procedure used to prevent stroke by correcting stenosis in the carotid artery, hence enhancing the blood supply to the brain. This procedure has been shown to improve cerebral circulation and subsequently resulted in an increased iAPF after treatment (Uclés, Almarcegui, Lorente, Romero, & Marco, 1997; Vriens, Wieneke, Van Huffelen, Visser, & Eikelboom, 2000), specifically in those patients with an iAPF below 9 Hz (Vriens et al., 2000). Another study also demonstrated clear increases of more than 1 Hz in the iAPF in patients with carbon monoxide poisoning after hyperbaric oxygen treatment (Murata, Suzuki, Hasegawa, Nohara, & Kurachi, 2005).

Recently, a direct relationship between regional CBF and iAPF has been established, where increased iAPF was associated with increased rCBF, most specifically in the bilateral inferior frontal gyrus (BA 45) and right insular cortex (BA 13; Jann, Koenig, Dierks, Boesch, & Federspiel, 2010). These structures are suggested to play a role in the modulation of attention and preparedness for external input or arousal, relevant for task execution (Jann et al., 2010). These results further demonstrate a direct relationship between iAPF and cerebral perfusion, on one hand, and their relationship to the modulation of attention and arousal, on the other hand, which are also impaired in both ADHD and depression.

In this light it is also interesting to note that midazolam (a benzodiazepine) has been shown to decrease cerebral blood flow (CBF) by 30%, whereas a benzodiazepine antagonist reversed this effect but had no effects on CBF when administered alone (Forster, Juge, Louis, & Nahory, 1987). Furthermore, in another study, hyperbaric oxygen (which increases oxygen availability in the brain) and flumazenil (a benzodiazepine antagonist) both counteracted the EEG activation induced by midazolam (Russell, Vance, & Graybeal, 1995). Given that benzodiazepines have been shown to decrease the iAPF (specifically carbamazepine, and oxcarbazepine: Clemens et al., 2006), these studies suggest interplay between the GABA-ergic system and CBF.

Development of new treatments for this subgroup? Summarizing, patients exhibiting a slow iAPF have been found nonresponders to various treatments. After reviewing the literature on the iAPF presented previously, it is concluded that a slow iAPF is clearly associated with reduced CBF and it is proposed that this measure is an endophenotype reflective of treatment resistance. Several medications have demonstrated small increases in iAPF such as nicotine and piracetam. However, more studies are required to investigate if these medication effects are specific and substantial effects on the iAPF.

Future studies should further investigate in this subgroup of patients if any organic explanations for this subtype exist, such as cerebral ischemia, stenosis, and oxygen deficiencies during birth. If such organic explanations are confirmed, such causes should be investigated further and if possible treated directly to investigate if that results in a normalization of the iAPF and also resolves the depressive or ADHD complaints presented with. If such factors are ruled out, speculatively, the most likely candidate for achieving treatment response in this subgroup is by methods that increase the CBF, given the improvements in iAPF as demonstrated with carotid endarterectomy (Uclés et al., 1997; Vriens et al., 2000) or hyperbaric oxygen therapy (Murata et al., 2005).

Other potential techniques that deserve further study in this regard are as follows:

1. Near-infrared spectroscopy biofeedback: This technique measures blood oxygenation and deoxygenation in the underlying cortex (Plichta et al., 2006), and real-time applications of this technique for brain–computer interfaces have already been developed (Kanoh, Murayama, Miyamoto, Yoshinobu, & Kawashima, 2009). This technique should not be confused with HEG. For HEG no data have been published demonstrating that HEG has the capability to penetrate the skull and thus reflect cortical oxygenation ad deoxygenation.
2. Transcranial Doppler Sonography Biofeedback: This technique measures the blood flow velocity in the basal cerebral arteries and can feed these back in real time. The feasibility of this approach was demonstrated in a recent study (Duschek, Schuepbach, Doll, Werner, & Reyes Del Paso, 2010).
3. Hyperbaric oxygen therapy: This technique consists of exposing people to higher oxygen concentrations in an atmospheric pressure chamber in order to improve the oxygen availability in the body and is proposed to decrease inflammatory responses (Granpeesheh et al., 2010). This technique is an evidence-based treatment for decompression sickness, under investigation for wound healing, and often applied in the treatment of autism (Granpeesheh et al., 2010). However, whereas an initial study

found beneficial effects of this treatment for autism (Rossignol et al., 2009), several recent controlled studies were unable to find an effect (Granpeesheh et al., 2010; Jepson et al., 2010). Rather then investigating this treatment in a *DSM–IV*-based group of patients, future studies should investigate this treatment specifically in the slow iAPF subgroup to investigate if this treatment might provide benefit.

The question arises whether for these patients it is sufficient to ''normalize'' their iAPF for their ADHD symptoms to improve, or whether the normalization of the iAPF will make them more susceptible to regular treatments, which should also be further investigated.

CONCLUSIONS

In line with the recent developments outlined in the beginning of this article, this review has summarized a clear biomarker for nonresponse to treatments in ADHD. The iAPF has been found to be a solid marker for nonresponse to various treatments such as stimulant medication in ADHD, and antidepressant medication and rTMS in depression. Given that iAPF is the most reproducible and heritable aspect of the EEG (Posthuma et al., 2001; Smit et al., 2005; van Beijsterveldt et al., 2002), has been associated with the COMT gene (Bodenmann et al., 2009) and is clearly associated with CBF, it is proposed here that this measure is an endophenotype related to treatment resistance in ADHD. Future studies should incorporate this endophenotype in clinical trials to further investigate new treatments for this substantial subgroup of patients.

Finally, it can be concluded that especially in the field of electroencephalography, it is important to be aware of the long and rich history of research rather than focusing only on recent research, as the example of the iAPF clearly demonstrates that with the introduction of new techniques such as QEEG, old well-established facts might be overlooked and result in blind spots, such as illustrated with the example of the excess ''theta'' in ADHD research actually combining a slow iAPF *and* real theta and the robust status of the iAPF as an endophenotype for nonresponse.

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