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Review

Neurofeedback in ADHD and insomnia: Vigilance stabilization through sleep spindles and circadian networks

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ABSTRACT

In this review article an overview of the history and current status of neurofeedback for the treatment of ADHD and insomnia is provided. Recent insights suggest a central role of circadian phase delay, resulting in sleep onset insomnia (SOI) in a sub-group of ADHD patients. Chronobiological treatments, such as melatonin and early morning bright light, affect the suprachiasmatic nucleus. This nucleus has been shown to project to the noradrenergic locus coeruleus (LC) thereby explaining the vigilance stabilizing effects of such treatments in ADHD. It is hypothesized that both Sensori-Motor Rhythm (SMR) and Slow-Cortical Potential (SCP) neurofeedback impact on the sleep spindle circuitry resulting in increased sleep spindle density, normalization of SOI and thereby affect the noradrenergic LC, resulting in vigilance stabilization. After SOI is normalized, improvements on ADHD symptoms will occur with a delayed onset of effect. Therefore, clinical trials investigating new treatments in ADHD should include assessments at follow-up as their primary endpoint rather than assessments at outtake. Furthermore, an implication requiring further study is that neurofeedback could be stopped when SOI is normalized, which might result in fewer sessions.

Contents

1. Introduction

Recent years have seen a re-emergence of research covering the application of neurofeedback. Neurofeedback is a method based on operant learning mechanisms (Sherlin et al., 2011) which is hypothesized to 'normalize' deviant brain activity. Neurofeedback has been classified as an efficacious treatment for ADHD based on guidelines of the American Psychological Association (APA)

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(Arns et al., 2009). Neurofeedback has also been investigated in the treatment of epilepsy (Tan et al., 2009), insomnia (Cortoos et al., 2010; Hauri et al., 1982; Hauri, 1981; Hoedlmoser et al., 2008; Sterman et al., 1970) and cognition (See Gruzelier in this issue). However, APA standards do not require single or double-blinded experimental designs. This certainly contributes to the limited understanding of how exactly neurofeedback exerts its clinical effects in these disorders. Fathoming the exact mechanisms underlying neurofeedback's effect is crucial for improving clinical trial designs investigating the efficacy of neurofeedback as well as for optimizing the efficacy of neurofeedback.

Recently there have been new insights into the clinical pathophysiology of ADHD. These include insights from the EEG-Vigilance model (Hegerl et al., this issue), the role of sleep onset-insomnia and the possible efficacy of chronobiological treatments for ADHD such as melatonin and morning bright light (Rybak et al., 2006; Van der Heijden et al., 2005, 2007; Van Veen et al., 2010). These insights provoke new considerations regarding the specific effects of neurofeedback in ADHD and insomnia.

This review paper will provide a review of neurofeedback research focused on the application in ADHD and sleep The new insights above will be further reviewed and integrated into a model that can explain the clinical effects of neurofeedback and circadian advancing treatments in ADHD and insomnia, and also provides insight into the development of new treatments for ADHD.

1.1. From EEG conditioning to Neurofeedback

Classical conditioning of the EEG has been demonstrated as early as in 1935 in France (Durup and Fessard, 1935), and 1936 in the United States (Loomis et al., 1936), just a few years after the first description of the EEG by Berger in 1929. In the 1940s classical conditioning of the alpha blocking response in the EEG was more systematically investigated It was found that the EEG alpha blocking response fulfilled all of the Pavlovian types of conditioned responses (Jasper and Shagass, 1941; Knott and Henry, 1941). These early studies clearly demonstrate that principles of classical conditioning can be applied to EEG parameters such as the alpha blocking response. Further support for this comes from several recent studies demonstrating that not only cortical EEG can be conditioned (reviewed in Sherlin et al., 2011), but that it is also possible to condition more focal neuronal activity such as the activity in monkey frontal eye fields (Schafer and Moore, 2011), marmoset intra-cortical Sensori-Motor Rhythm or SMR (Philippens and Vanwersch, 2010), and human medial temporal cortex (Cerf et al., 2010) and early visual processing areas such as V1 and V2 (Shibata et al., 2011).

A first attempt of classical conditioning of spike-wave discharges in patients with epilepsy was unsuccessful (Stevens and Stevens, 1960) or at least difficult (Stevens et al., 1967). Operant conditioning of epileptic multi-unit activity has been demonstrated, albeit without sustained effects of decreased seizure rates (Fetz and Wyler, 1973; Wyler et al., 1974). This was recently confirmed by Osterhagen et al. (2010) who were unable to demonstrate an *increase* in seizure rates in rats when the occurrence of spike-wave discharges was reinforced, suggesting that spike-wave discharges cannot be 'conditioned' or trained directly. The difficulty of this direct conditioning of epileptic states may be the result of the decreased level of consciousness during such states precluding efficient learning from taking place *during* the occurrence of a seizure. The first successful applications of EEG conditioning on seizures were not reported until the early 1960s by Barry Sterman. His work involved the training of Sensori-Motor Rhythm, also called SMR, in the cat. In a serendipitous finding the anticonvulsant effects of operant conditioning of this rhythm in cats exposed to the pro-convulsant Monomethylhydrazine was demonstrated (Sterman et al., 1969, 2010).

During those early days this technique was referred to as 'EEG Biofeedback'. The first demonstrations of SMR neurofeedback with potential clinical implications were reported in cats related to epilepsy (Sterman et al., 1969, 2010) and sleep (Sterman et al., 1970), shortly followed by the clinical applications in humans with epilepsy (Sterman and Friar, 1972) and ADHD (Lubar and Shouse, 1976). Contemporaneously Kamiya demonstrated voluntary control over alpha activity and alpha peak frequency (APF) (Kamiya, 1968). This work has resulted in, among others, the application of alpha/theta neurofeedback in the treatment of addictions and optimal performance (reviewed in Gruzelier, 2009) and inspired several well controlled studies investigating training of upper-alpha power resulting in improved cognitive performance (Hanslmayr et al., 2005; Zoefel et al., 2011; for more details also see Gruzelier, this issue).

In parallel with the development of SMR and alpha related 'frequency' neurofeedback or Alternating Current (AC) Neurofeedback, the first demonstration of voluntary control over the 'Contingent Negative Variation' or CNV was demonstrated in 1966 by McAdam et al. (1966). Elbert and Birbaumer further pioneered the first studies on voluntary control of slow cortical potentials (SCPs) employing a biofeedback procedure, with the goal of investigating the functional relationship between SCP and the performance during a signal detection task (Lutzenberger et al., 1979; Elbert et al., 1980). Neurofeedback of these slow cortical potentials, or SCP's is also referred to as Direct Current (DC) neurofeedback. The difference is that feedback is not provided based on the amplitude of a given frequency band, but rather on the polarity of the slow EEG content, e.g. surface-positivity or surface-negativity. Based on the observation that pro-convulsive procedures such as hyperventilation resulted in increased surface-negativity and anticonvulsants result in decreased surface-negativity, this SCP procedure was investigated in drug refractory epilepsy patients in a double-blind placebo controlled design. In this study SCP neurofeedback was compared to alpha-power neurofeedback, and only the group who received SCP neurofeedback demonstrated a significant reduction in seizure frequency (Rockstroh et al., 1993).

In 2004, the first application of SCP neurofeedback in the treatment of ADHD was published (Heinrich et al., 2004). Generally the effects of SCP Neurofeedback appear similar to the effects of SMR and Theta/Beta neurofeedback for epilepsy (Tan et al., 2009) and for ADHD (Leins et al., 2007; Arns et al., 2009; Gevensleben et al., 2009a,b). Q3

Fig. 1 visualizes this history further, by graphing the number of publications per year for 3 different keywords, which have historically been used to refer to neurofeedback related techniques since 1941.

The early research focused on investigating classical conditioning of the EEG, in Fig. 1 this is visualized by the green bars and green trend line (floating average, 2 points). During the 1940s and 1950s some research on this topic was published, but this research actually surged in the beginning of the 1960s with a peak in 1975. Following the first publications on operant conditioning of EEG by Wyrwicka and Sterman (1968), as well as the work on conscious control of EEG alpha activity by Kamiya in 1968 (Kamiya, 1968, 2011) and studies showing voluntary control over the CNV (McAdam et al., 1966), we see an increase in publications referring to 'EEG Biofeedback', which remained the pre-dominant term for neurofeedback until the end of the 1990s. The term 'neurofeedback' was first used by Nahmias, Tansey and Karetzky in 1994 (Nahmias et al., 1994). Since that time neurofeedback has become the predominant term as is clearly visible in Fig. 1, with the number of publications covering this term dramatically increasing in 2010 and 2011.

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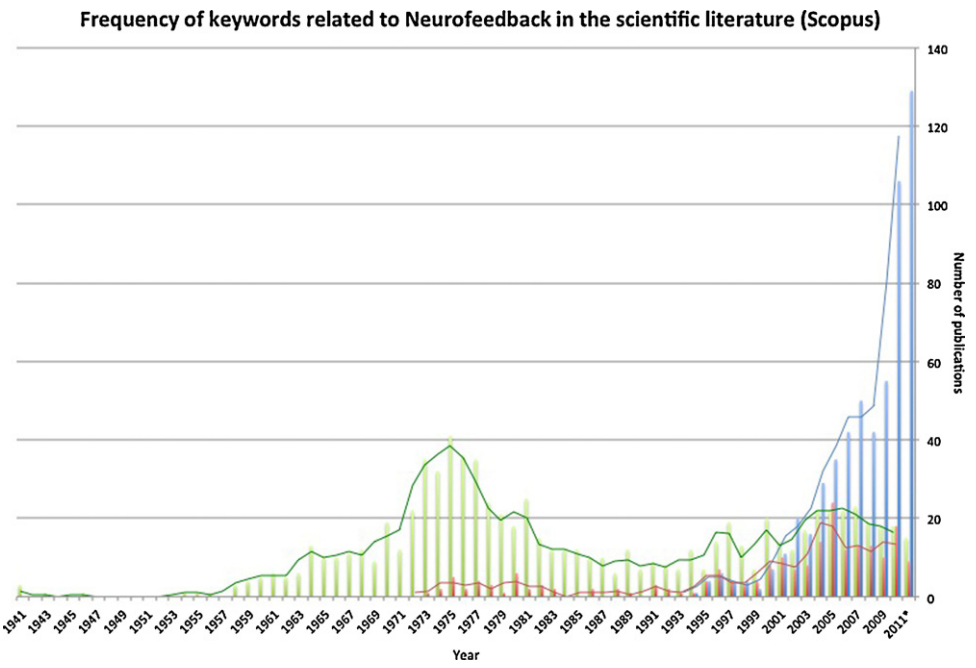

Fig. 1. Frequency of different keywords related to neurofeedback and their frequency of occurrence in the scientific literature per year. Green reflects 'EEG AND conditioning'; Red reflects 'EEG Biofeedback' and Blue reflects 'Neurofeedback'. Note that 2011* indicates the extrapolated number for 2011; based on the absolute numbers from August 15th 2011 (obtained using SCOPUS).

1.2. Current status of neurofeedback for ADHD and insomnia

Since the initial report of Lubar and Shouse (1976) on SMR neurofeedback in ADHD and the initial report of Heinrich et al. (2004) of SCP Neurofeedback in ADHD, much research has been conducted on these 2 neurofeedback protocols in ADHD. SMR Neurofeedback is also referred to as Theta/Beta neurofeedback, where it is interesting to note that although the beta frequency band often used is broader (e.g. 12–20 Hz) than either Sterman's original 11–19 Hz range for SMR or the more traditional 12–15 Hz used for SMR; all studies still include the SMR band along with a theta inhibit used for both protocols. Furthermore, all these studies have trained at fronto-central locations (also see Arns et al., 2009; Table 1) typical for SMR. Therefore, in this review where we refer to SMR Neurofeedback this also includes Theta/Beta neurofeedback.

Currently, there are 8 published randomized controlled trials (RCT's), which investigated SCP neurofeedback and/or SMR neurofeedback (Linden et al., 1996; Levesque, Beauregard, Mensour, 2006; Leins et al., 2007; Gevensleben et al., 2009a,b; Holtmann et al., 2009; Perreau-Linck et al., 2010; Steiner et al., 2011; Bakshayesh et al., 2011). All these studies except Perreau-Linck et al. (2010) demonstrated significant improvements on measures of inattention, hyperactivity or impulsivity compared to the control groups. This was confirmed by a meta-analysis conducted in 2009 by Arns and colleagues incorporating 15 studies (total $N = 1194$) where it was concluded that neurofeedback resulted in large and clinically relevant effect sizes (ES) for inattention and impulsivity and a low to medium ES for hyperactivity. Furthermore, the specificity of neurofeedback treatment in ADHD has been demonstrated by normalizations of Event Related Potentials (ERP's) after treatment, reflecting an improved information-processing (Arns et al., 2012; Heinrich et al., 2004; Kropotov et al., 2005, 2007; Wangler et al., 2011), normalizations of EEG power post-treatment (Doehnert et al., 2008; Gevensleben et al., 2009a,b) and effects on neural substrates of selective attention imaged with fMRI (Lévesque et al., 2006).

Several studies have also directly compared the efficacy of neurofeedback with stimulant medication. Most have found the effects to be similar for measures of inattention, impulsivity and hyperactivity (Rossiter and La Vaque, 1995; Monastra et al., 2002; Fuchs et al., 2003; Rossiter, 2004), which was also confirmed in the meta-analysis (Arns et al., 2009). However, none of these studies used a randomized group assignment design, and patients self-selected their preferred treatment. This may bias the results. Based on these studies it cannot be concluded that neurofeedback is as effective as stimulant medication. Interestingly, the ES reported for methylphenidate in a recent meta-analysis is comparable to the ES for neurofeedback (NF) for improvements in measurements of inattention (ES NF = 0.81; ES Methylphenidate = 0.84), whereas for impulsivity/hyperactivity the ES for methylphenidate is higher (ES NF = 0.4/0.69; ES Methylphenidate = 1.01) (Faraone and Buitelaar, 2009; Sherlin et al., 2010a,b; Arns et al., 2009). This suggests that the effects of neurofeedback and methylphenidate appear similar, at least for inattention. Further randomized controlled studies are required to substantiate this observation.

The most adequately designed randomized controlled trials (RCTs) investigating neurofeedback in ADHD have used semi-active control groups such as attentional training (Gevensleben et al., 2009a,b) or EMG Biofeedback (Bakhshayesh et al., 2011), but none have used a double-blind placebo controlled design. The current controversy regarding the efficacy of neurofeedback in ADHD is centered around the appropriate design standards for these studies. Some suggest that neurofeedback should be evaluated as a psychological treatment using the APA guidelines (Arns et al., 2009; Sherlin et al., 2010a,b), though others prefer designs used for rating new drugs requiring a double-blind placebo controlled study (e.g.: Lofthouse et al., 2010, 2011). Given the fact that neurofeedback is based on operant conditioning principles, it is crucial that the active treatment and planned control condition be in line with principles of learning theory and conditioning principles. Adhering to these basic principles is required for any learning to take place, including paying heed to such aspects as latency of reinforcement,

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specificity of reinforcement, shaping and generalization. A double-blind design often demands a deviation from such principles. For example such studies often use auto-tresholding to remain double-blinded. With auto-tresholding the child will always be rewarded, whether active learning is taking place or whether the child is doing nothing, whereas motivating or coaching the child to perform better (shaping or scaffolding) will promote the occurrence of the reinforced behavior and thus facilitate learning. Another example is the use of non-contingent feedback or random reinforcement as a control condition. Though this is often interpreted as an inert condition, such a random reinforcement schedule is known to result in 'superstitious behavior' in pigeons (Skinner, 1948) and man (Koichi, 1987), bringing into question whether these control conditions truly represent an inert condition.

Four recent studies have employed a placebo-controlled design and failed to find a difference between neurofeedback and sham-neurofeedback (Lansbergen et al., 2010; Perreau-Linck et al., 2010; deBeus and Kaiser, 2010; Arnold et al., 2012). Note that only Perreau-Linck et al. (2010) employed SMR Neurofeedback, whereas the other studies employed an unconventional neurofeedback protocol such as 'QEEG-based' protocols with 2-channel training (Lansbergen et al., 2010) or training of the 'engagement index' involving beta, theta and alpha (deBeus and Kaiser, 2010; Arnold et al., 2012). Furthermore, these studies employed: (1) a control condition consisting of non-contingent feedback or random-reinforcement (DeBeus and Kaiser, 2011; Lansbergen et al., 2011; Perreau-Linck et al., 2010); and (2) auto-tresholding. As indicated above, these approaches deviate from principles of learning theory. DeBeus and Kaiser (2011) supported this notion further in their randomized double-blind placebo controlled study. They did not find a difference between neurofeedback and placebo groups on ADHD symptoms (DeBeus, personal communication). However, when comparing 'learners', who demonstrated an increase of at least 0.5 SD in the 'engagement index' between baseline to end of treatment (74% of the sample) vs. 'non-learners', there were significant effects of neurofeedback on teacher ratings and a CPT test. Thus further confirming the importance of implementing principles of learning theory in neurofeedback. None of the other placebo-controlled studies reported evidence of learning actually having taken place, such as learning curves. Non-specific or placebo effects as an explanation for the effects of neurofeedback in these studies cannot be ruled out at this moment and still requires further study. Future double-blind placebo controlled studies should employ well-investigated neurofeedback protocols such as SMR or SCP protocols and ensure that learning actually takes place. For a review proposing a double-blind design fulfilling these principles, also see The Collaborative Neurofeedback Group (submitted for publication).

Several randomized studies have demonstrated that the effects of neurofeedback in ADHD are maintained following training at the 6 month follow-up (Gevensleben et al., 2010; Leins et al., 2007; Strehl et al., 2006) and 2-year follow-up (Gani et al., 2008). These results show a tendency to improve further with time, as seen in Fig. 2. This figure depicts the within-subject ES between pre- and post-treatment; between pre-treatment and 6 month follow-up and between pre-treatment and 2 years follow-up for 3 RCTs. The ES has been plotted for the control group from both the 6 month (Gevensleben et al., 2010) and 2 year follow up, and they show the improvement on the FBB-HKS (a German ADHD rating scale) between 7–10 years and 14–17 years of age in a normative group (Erhart et al., 2008). These ES associated with long-term follow-up indicate improvements associated with non-specific effects and aging effects. It is interesting and promising to note that the effects of neurofeedback in ADHD tend to improve further with time. This also hints to perhaps the most attractive aspect of neurofeedback, namely the perspective that a finite treatment may yield permanent beneficial effects. A limitation of such studies is always the low follow-up rates, such as 63% of Neurofeedback treated, 66% of the control group in the Gevensleben study (2010a) and the 44–55% rate after 2 years follow up in the Gani et al. (2008) study. Furthermore, the number of studies where follow-up was conducted is very limited, making generalization of these findings difficult and requiring further study.

After the first report on operant conditioning of SMR in cat (Wyrwicka and Sterman, 1967), Sterman, Howe and Macdonald in 1970 convincingly demonstrated that SMR enhancement training during wakefulness resulted in increased sleep spindle density, accompanied by a reduction of phasic movements during sleep. Conversely, rewarding beta (excluding SMR), did not demonstrate this effect during sleep. Furthermore, after SMR training the sleep spindle density during sleep, remained increased at post-assessment, suggesting these effects were long-lasting. Hoedlmoser et al. (2008) replicated this finding in humans in a placebo controlled RCT where SMR enhancement training resulted in shorter sleep latencies, accompanied by an increased sleep spindle density during sleep and improvements in declarative memory. More recently, Cortoos et al. (2010) conducted a RCT where patients were randomized to EMG Biofeedback or SMR Neurofeedback. Improvements were initially expected for both groups, based on Sterman's work and relaxation related improvements of EMG Biofeedback. They demonstrated that SMR neurofeedback in patients with primary insomnia resulted in increased total sleep time as compared to EMG biofeedback.

These studies provide clear evidence of SMR neurofeedback's effect of improving sleep. Placebo-effects in these studies are ruled out due to the placebo-control design used in these studies including randomized frequency conditioning (Hoedlmoser et al., 2008) and EMG biofeedback (Cortoos et al., 2010) as well as by the observation that SMR training during wakefulness resulted in increased sleep spindle density during sleep, only for the SMR Neurofeedback group (Sterman et al., 1970; Hoedlmoser et al., 2008). The clinical relevance of these effects in insomnia should be investigated further by replicating these effects in a group of clinical insomnia patients, investigating the usefulness of this approach in actual clinical practice.

2. Impaired vigilance regulation in ADHD

The most consistent EEG findings reported in the literature on ADHD are those of increased absolute power in Theta (Bresnahan et al., 1999; Chabot and Serfontein, 1996; Clarke et al., 1998, 2001a,b; DeFrance et al., 1996; Janzen et al., 1995; Lazzaro et al., 1998, 1999; Mann et al., 1992; Matsuura et al., 1993) and sometimes increased absolute Delta EEG power (Bresnahan et al., 1999; Clarke et al., 2001a,b; Kuperman et al., 1996; Matsuura et al., 1993). Conceptually, these EEG findings in ADHD are consistent with the EEG Vigilance model originally developed by Bente (1964) and presented in more detail in this issue by Hegerl et al. More specifically these findings of slower EEG content reflect impaired vigilance regulation (Sander et al., 2010 and reviewed below), 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). Other neurophysiological sub-groups in ADHD have also been reported such as an excess beta group and a 'maturational lag' subgroup (Arns, 2012; Clarke et al., 2011), however coverage of these neurophysiological sub-groups is beyond the scope of this review, though the interested reader is referred to Barry et al. (2003) or Arns (2012).

The EEG is considered the gold standard for classifying the sleep stages based on the Rechtshaffen and Kales criteria (1968). Qualitatively different stages are defined such as stages 1–4, which are

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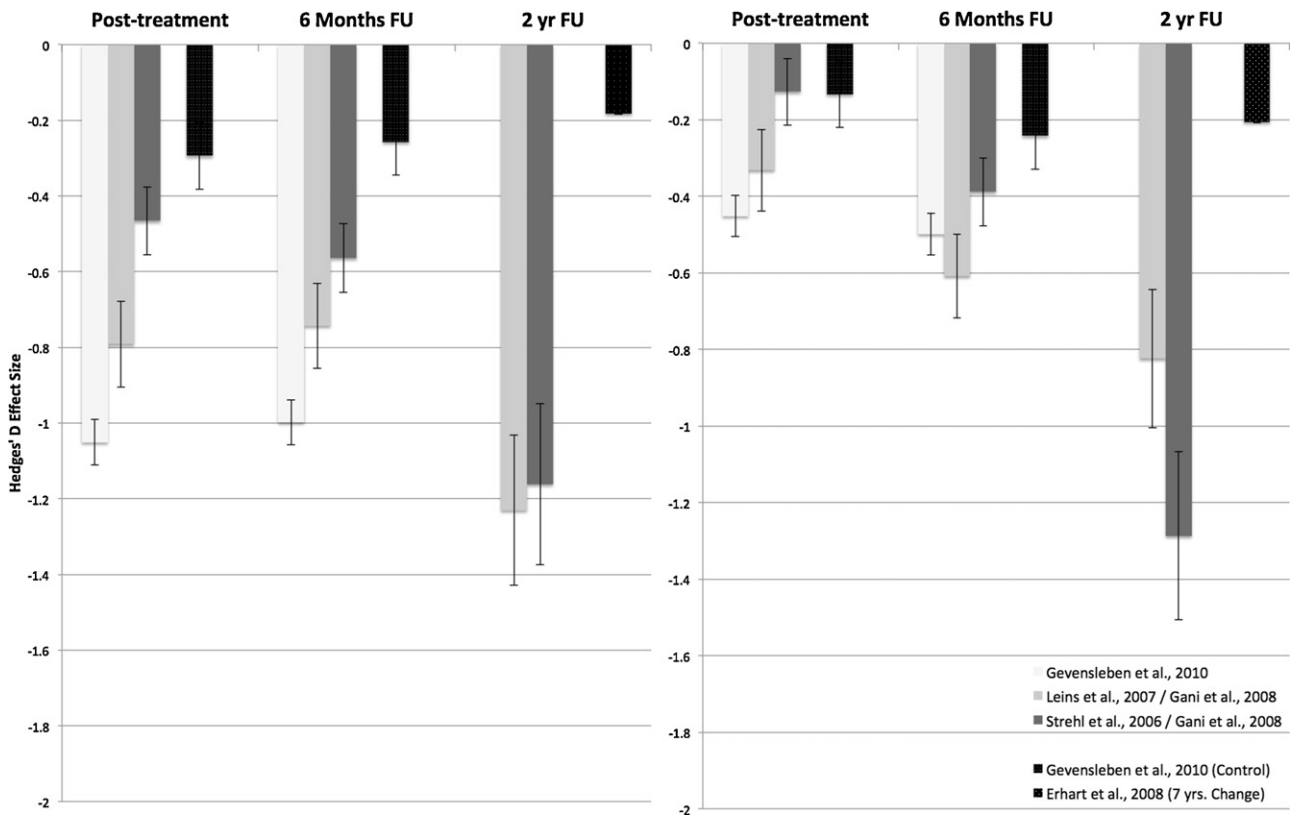

Fig. 2. Within subject Hedges' D ES for 3 randomized studies who have performed 6 month and 2 year follow-up data for inattention (left) and hyperactivity (right). For Post-Treatment and 6 month follow-up the ES for the control group from the Gevensleben et al. (2010) study has been plotted as a comparison for non-specific effects across time. For the comparison at 2 years follow-up the ES of 7–10 yr. vs. 14–17 yr. children has been plotted as an indication of improvements of ADHD symptoms related to aging from Erhart et al. (2008). Note that for all studies the effects of neurofeedback tend to increase with time, most specifically for hyperactivity. (Error bars are Variability of the ES.)

non-rapid eye movement sleep (NREM) with increasing sleep depth from stage I through stage 4. Stage 3 and 4 are referred to as Slow Wave Sleep (SWS), and rapid eye movement sleep (REM) represents "dreaming". The EEG Vigilance model can be regarded as an extension of this sleep stage model with a focus on the transition from relaxed wakefulness through drowsiness to sleep onset, which is seen in stage 2. These vigilance model stages find their origins in the early work of Loomis et al. (1937), later modified by Roth (1961) and Bente (1964). In this model the EEG stages described reflect decreasing levels of vigilance from A1, to A2, A3, B1, B2 to B3. The three A stages reflect stages where alpha activity is dominant posterior (A1), followed by alpha anteriorization (A3), whereas B stages are reflective of the lowest vigilance stages, which are characterized by an alpha drop-out or low-voltage EEG (B1) followed by increased frontal theta and delta activity (B2/3). These vigilance stages are followed by the occurrence of K-complexes and sleep spindles, which mark the transition to stage C in the vigilance model, or classically to stage II sleep (NREM).

This EEG Vigilance regulation is a reflection of the process of 'falling asleep' and is measured during an eyes closed condition. EEG Vigilance regulation can be 'rigid', meaning 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 alpha (stage A1), which is often seen in Depression (Ulrich and Fürstenberg, 1999; Hegerl et al., 2011). On the other hand, EEG Vigilance regulation can be 'labile' or 'unstable', meaning 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.

These different EEG stages and their relationship to vigilance have been well described in the literature (e.g. theta as a sign of drowsiness). Several recent validation studies have demonstrated the validity of these EEG Vigilance stages (e.g. Olbrich et al., 2009, 2011, 2012) and are reviewed in a recent publication (Arns et al., 2010).

The EEG Vigilance model explains the relationship between EEG states and behavior by means of vigilance regulation, which is a phenomenon we are all familiar with. The following example illustrates this further: After a tiring day, EEG vigilance regulation in a healthy individual will become unstable and demonstrate more of the lower vigilance stages. This has a classical EEG signature often referred to as 'fatigue' or 'drowsiness', which is expressed as alpha anteriorization (Broughton and Hasan, 1995; Connemann et al., 2005; De Gennaro et al., 2001, 2004, 2005; Pivik and Harman, 1995) and increased frontal slow waves (Strijkstra et al., 2003; Tanaka et al., 1996, 1997). In the EEG vigilance model these changes seen in drowsiness are referred to as stage A2–A3 for the anterior alpha and B2–B3 for the anterior theta, respectively (see Hegerl et al., this issue). In young children we all know the example of the hyperactive, 'high-spirited' behavior in over-tired children. This is a clear example of vigilance autostabilization behavior (i.e. keeping himself awake by moving). A healthy adult displaying this type of EEG at home and near bedtime will feel sleepy and decide to 'withdraw', seeking an environment with low external stimulation, thus increasing the probability of falling asleep. However, when this same healthy adult is driving a car with the same reduced

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EEG Vigilance, he will: turn up the volume of the music, open the window, turn-down the air-conditioning, and so on, all to avoid further drowsiness. Hence the healthy adult will exhibit autostabilization or externalizing behavior in order to keep himself awake. Furthermore, when the car in front of him unexpectedly brakes, he is more likely to respond slowly (impaired sustained attention) and the likelihood of a car accident is increased due to this reduced vigilance or drowsiness (Miller, 1995).

A summary of this model is depicted in Fig. 3. An unstable vigilance regulation explains the cognitive deficits that characterize ADHD and ADD, such as impaired sustained attention. This vigilance stabilization behavior explains the hyperactivity aspect of ADHD as an attempt to up regulate vigilance.

To summarize, 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 demonstrate at the end of the day). In turn, some unknown factor induces autostabilization or externalizing behavior, which can be either adaptive (i.e. keeping oneself awake while driving a car) or mal-adaptive (i.e. the hyperactivity in ADHD), depending on the circumstance.

Conceptually, unstable vigilance has repercussions for the cortical vigilance network as proposed by Posner and Petersen (1990) and Corbetta and Shulman (2002). Part of this network is the right inferior frontal gyrus, which is hypothesized to control a flexible inhibitory link between cortical sensory and motor systems; this link is in turn instrumental in processing of eternal signals that prompt a change in behavioral priorities or strategies (Bekker et al., 2005a). Off medications, adult ADHD patients are characterized by impairments in both the behavioral and electrocortical aspects of this flexibly controlled inhibitory link (Aron et al., 2003; Bekker et al., 2005b; Overtoom et al., 2009).

2.1. Sleep and ADHD

Reduced EEG Vigilance is observed in our earlier example of driving a car very late at night while being tired, but reduced vigilance can also be caused by enduring sleep restriction.

A recent meta-analysis incorporating data from 35,936 healthy children reported that sleep-duration is positively correlated with school performance, executive function, and negatively correlated with internalizing and externalizing behavior problems (Astill et al., 2012). ADHD has also been associated with daytime sleepiness (Golan et al., 2004) and primary sleep disorders, sleep related movement disorders and parasomnias (Chervin et al., 2002; Konofal et al., 2010; Walters et al., 2008). Symptoms associated with ADHD can be induced in healthy children by sleep restriction (Fallone et al., 2001, 2005; Sadeh et al., 2003; Beebe et al., 2008), suggesting an overlap between ADHD symptoms and sleep-disruptions.

Several open-label studies have demonstrated dramatic improvements in ADHD symptoms after normalizing sleep. For example, Walters and colleagues reported that ADHD children who were unresponsive to stimulant medication, and were treated with levodopa or a dopamine-agonist for restless legs syndrome (resulting in normalized sleep) demonstrated dramatic improvements in ADHD symptoms measured with the Conners Rating Scale (CRS) and Child Behavior Checklist (CBCL) (Walters et al., 2000). Huang et al. (2007) reported that in ADHD children with sleep apnea, adenotonsillectomy resulted in substantial clinical improvements in attention and ADHD complaints (measured with the CBCL and TOVA). These improvements were larger when compared to stimulant medication. These studies suggest that a sub-group of children with 'ADHD complaints' actually suffers from a sleep disorder, and if the sleep disorder is treated effectively the 'ADHD complaints' improve. However, these specific sleep disorders, e.g. restless legs and breathing disorders, present in a limited percentage of the ADHD patients, estimated between 20% for sleep related breathing disorders (Silvestri et al., 2009) and 26% for restless legs syndrome (Konofal et al., 2010; Silvestri et al., 2009).

2.2. Sleep onset insomnia and circadian phase delay in ADHD

Several studies have investigated the occurrence of 'idiopathic sleep-onset insomnia' (SOI) also called 'delayed sleep phase syndrome' in ADHD (Van der Heijden et al., 2005). SOI is defined as a difficulty falling asleep at a desired bedtime and/or a sleep onset latency of more than 30 min for at least 4 nights a week, existing for at least 6–12 months and leading to impairment in several areas (Smits et al., 2001; Van Veen et al., 2010). SOI should not be regarded as a full-blown sleep disorder, but rather as an inability or difficulty falling asleep. In general SOI is not related to 'sleep hygiene' (van der Heijden et al., 2006), is already present before the age of 3 years in 70% of children (Van der Heijden et al., 2005), and is also associated with a delayed Dim Light Melatonin Onset (DLMO) suggesting a circadian phase delay (Van der Heijden et al., 2005; Van Veen et al., 2010). Van Veen et al. (2010) reported SOI in 78% of a sample of adult ADHD patients, and a similar rate of 72–75% SOI has been reported in large samples of unmedicated pediatric ADHD (Van der Heijden et al., 2005). In further agreement with these findings, Rybak et al. (2007) reported that adult ADHD is characterized by a higher prevalence of 'evening types', characteristic for a delayed circadian phase, strongly correlated with self-reported and neuropsychological measures of ADHD symptoms (CPT impulsivity errors).

These studies suggest that at least a subgroup of patients with ADHD is characterized by a circadian phase delay, associated with delayed sleep onset, already present before the age of 3. These ADHD patients during the day are characterized by lower vigilance stages (e.g. more frontal theta and frontal alpha) and these EEG subtypes also respond well to stimulant medication (Arns et al., 2008), by virtue of its vigilance stabilizing properties. However, stimulant medications do not affect the core-symptomatology in the circadian phase delay subgroup, which is the cause of the lower vigilance levels.

2.3. Chronic sleep-restriction and the effects on attention and externalizing behavior

Van Dongen et al. (2003) systematically investigated the cumulative effects of sleep restriction in healthy volunteers over the course of 14 days, and found clear dose–response effects on cognition of restricting sleep to 4, 6 or 8 h per night. Furthermore, they also reported that these effects progressively eroded performance on a psychomotor vigilance task and working memory over time, where performance was still worsening at day 14. This suggests that a chronic but slight reduction in total sleep time can result in cumulative effects across time on vigilance, attention and cognition. Similar findings have also been reported after 5–7 days of restricted sleep (Axelsson et al., 2008; Belenky et al., 2003). Performance improved after 3 recovery nights albeit not to pre-sleep restriction levels as opposed to 1 night of total sleep deprivation, which does normalize after a recovery night (Belenky et al., 2003).

Normalization was also reported for reaction times and sleepiness within 7 recovery days, but 'lapses' (reflective of inattention) did not normalize after 7 recovery nights (Axelsson et al., 2008), demonstrating that the effects of chronic sleep restriction do not normalize after few recovery nights of sleep. Sleep restriction studies have also been conducted in children, albeit not as extensively as in adults. In general sleep restriction studies in healthy children have all demonstrated impairments of attention (Fallone et al., 2001, 2005; Sadeh et al., 2003; Beebe et al., 2008), whereas only Beebe et al. (2008) found increased externalizing behavior (e.g.

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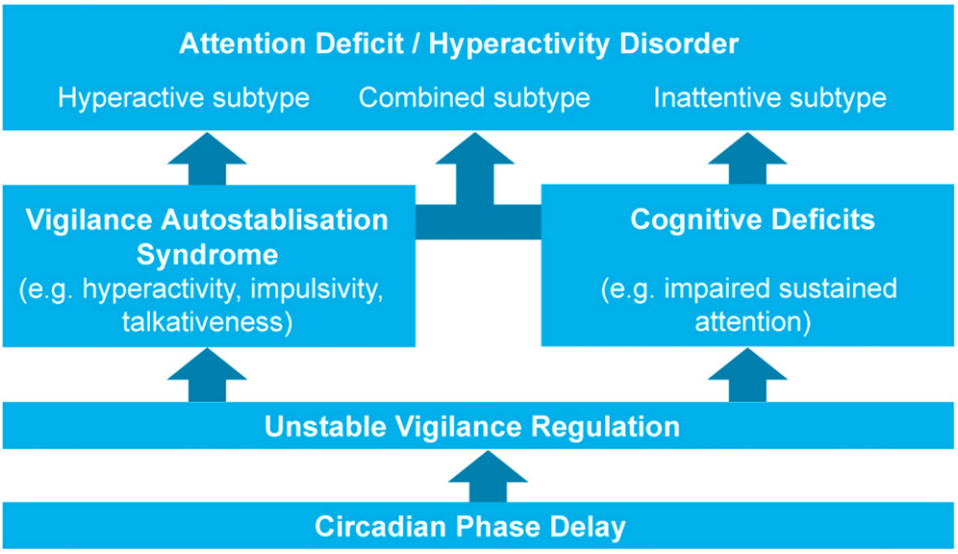

Fig. 3. Overview of the relation between an unstable vigilance regulation and the behavioral symptoms of ADHD.

hyperactivity and oppositional/irritable behaviors rated with the BRIEF) after 1 week of sleep restriction. Interestingly, in a replication study with a more naturalistic design (simulated classroom set-up and blinded video-ratings), they replicated the findings for inattention but also found that Theta EEG power tended to be increased after a week of sleep restriction (effect size = 0.53) (Beebe et al., 2010) demonstrating that sleep restriction resulted in impaired vigilance regulation (excess theta) as well as impaired attention. The relationship with externalizing behaviors such as hyperactivity and impulsivity was only found in Beebe et al. (2008) but not in other studies. On the other hand, the earlier mentioned meta-analysis by Astill et al. (2012) did clearly demonstrate a relationship between total sleep time and externalizing behavior. This meta-analysis failed to find a relationship with sustained attention in children, whereas large effects sizes for this measure are found in adults (Lim and Dinges, 2010). The interventional sleep restriction studies above clearly indicated that attentional problems are caused by chronic sleep restriction, whereas the meta-analytic results suggest an effect from decreased sleep duration on externalizing behavior. Obviously these studies have been performed in healthy children and this may not generalize to ADHD children.

This suggests that interventions aimed at restoring the SOI and/or circadian phase delay might not have immediate effects, as opposed to psychostimulants which acutely increase vigilance during the day, but might take more time to exert their effects on behavior. In this view, SOI caused by a circadian phase delay is the underlying pathophysiology in a significant number of patients with ADHD, for which normalizing the circadian phase delay may result in clinical improvements, albeit with a delayed onset.

A large placebo controlled RCT investigation of ADHD showed the effects of 4-weeks melatonin on sleep-onset latency and circadian phase, as assessed with the DLMO (Van der Heijden et al., 2007). Post-treatment sleep-onset and DLMO latencies were shorter relative to placebo, which may be due to melatonin-enhanced signals from the nucleus suprachiasmaticus (SCN) to the pineal gland. However, no improvements of ADHD symptoms and cognition were reported after this period of 4 weeks (Van der Heijden et al., 2007). A follow-up study revealed that after long-term treatment (2–3 years) improvements of behavior and mood were present only for children still using melatonin. It also showed that discontinuation of melatonin resulted in a relapse of sleep onset insomnia, probably also in a delayed circadian phase (Hoebert et al., 2009). In a study of Rybak et al. (2006), adult ADHD patients were treated with early morning bright light, which also has circadian phase advancing effects. They reported improvements on the Brown adult ADD scale and neuropsychological measures (e.g. CPT, Wisconsin Card Sorting Test) after 3 weeks of morning bright light therapy, with medium effect sizes (Rybak et al., 2006). These effects appeared faster compared to the effects of melatonin, suggesting bright light might have faster effects. On the other hand, these were only medium effect sizes, and might have increased when a follow-up was performed after 6 months. These results suggest that in this sub-group of ADHD patients, normalizing SOI can be achieved by advancing the circadian phase delay by using melatonin or morning bright light, albeit with a delayed-onset of effect on ADHD symptoms for melatonin compared to bright light. The fact that these complaints are already present in the majority of ADHD patients with SOI before the age of 3 (Van der Heijden et al., 2005), and that ADHD is most often diagnosed after the age of 5 or 6, further suggests that SOI results in an accumulation of impaired sleep (extended sleep restriction) across time which eventually results in unstable EEG vigilance regulation, as demonstrated by Beebe et al. (2010).

2.4. *Sleep spindles and Sensori-motor rhythm*

Sensori-motor rhythm or SMR is characterized by a frequency of 12–15 Hz being most pronounced across the sensorimotor strip (EEG locations C3, Cz and C4). This rhythm is too date still used in most neurofeedback studies in ADHD along with changing other frequencies such as Theta. Interestingly, this rhythm shares overlap with sleep-spindles during stage-2 NREM sleep which have an identical topographical distribution but also an identical frequency. The first report of sleep spindles, also referred to as sigma waves, stems from the work by Loomis in 1935 where he described: '*. . .but frequently very regular bursts lasting 1 to 1.5 seconds of 15 per second frequency appear. The amplitude builds regularly to a maximum and then falls regularly so that we have designated these "spindles", because of their appearance. . .*'. Sleep spindles are considered the hallmark of stage 2 NREM sleep (De Gennaro et al., 2001; De Gennaro and Ferrara, 2003) and are reduced in the night after sleep deprivation (Borbély et al., 1981; De Gennaro and Ferrara, 2003; Dijk et al., 1993; Huber et al., 2008), perhaps due to increased SWS pressure after deprivation. Furthermore, the density of sleep spindle occurrence exhibits a strong circadian modulation comparable to the melatonin rhythm (De Gennaro and Ferrara, 2003; Dijk et al.,

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1997). Full-developed sleep spindles are already present at 8–9 weeks after birth and stabilize at 23 weeks (De Gennaro and Ferrara, 2003) and hence do not display the typical maturational effects on frequency, characteristic for posterior alpha activity (Niedermeyer and Da Silva, 2004).

As pointed out in section 1.2 several studies have demonstrated that SMR neurofeedback, results in increased sleep spindle density during sleep (Hoedlmoser et al., 2008; Sterman et al., 1970), decreased sleep latency (Hoedlmoser et al., 2008) increased total sleep time (Cortoos et al., 2010; Hoedlmoser et al., 2008) and sleep improvements in ADHD (Arns, 2011). Research has also demonstrated that melatonin results in an increased sleep spindle density (Dijk et al., 1995) and decreased sleep latency (Van der Heijden et al., 2007), suggesting overlap in the working mechanisms of SMR neurofeedback and melatonin. Could there also be an overlap with SCP's and sleep spindles?

2.5. Sleep spindles and slow cortical potentials

Given that the results of SCP neurofeedback and SMR neurofeedback in ADHD are rather similar, and no differential effects have been reported on measures such as inattention, impulsivity and hyperactivity (Arns et al., 2009; Gevensleben et al., 2009a,b), it has been speculated that these two forms of neurofeedback might share a similar working mechanism.

In SCP neurofeedback surface positivity and surface negativity are both trained. That is, patients are required to demonstrate surface positivity or negativity within a 6–8 s time frame, depending on the instruction provided by the software ('activation' or 'deactivation'). However, both have different neurophysiological implications. Surface negativity indicates depolarization of apical dendrites reflective of increased excitation, whereas surface positivity probably reflects inhibition or a reduction of cortical excitation (Birbaumer et al., 1990). SCP neurofeedback hence seems to differ from SMR neurofeedback in that patients are taught 'self regulation'.

Currently there is no published evidence that SMR neurofeedback results in increased EEG power in this frequency range post-treatment. Several studies have demonstrated learning curves of SMR power increases *within* training sessions e.g. Sterman & Friar (1972) and Lubar and Shouse (1976) reflective of a learning process. One recent study actually reported a

decreased SMR power post-treatment with SMR enhancement neurofeedback in ADHD patients who all were responders to treatment (Arns et al., 2012). Furthermore, Pineda et al. (2008) in a double-blind, placebo controlled design demonstrated that mu-enhancement training (8–13 Hz) in autism resulted in improved mu-suppression post-treatment as well as improvement in autism symptoms. Therefore, these results rather suggest that SMR neurofeedback is not about increasing the EEG power in a specific frequency range, but rather about regulating activity within a functional network (reticulo-thalamocortical network, also see Section 2.6), thereby increasing the synaptic strength within this network, resulting in long-term potentiation (LTP) which increases synaptic sensitivity and the probability of future activation in this network (Sterman and Egner, 2006). This is further supported by studies that actually trained SMR neurofeedback in the exact same way as SCP's are trained, e.g. patients had to increase or decrease their Theta/Beta ratio during a pre-set interval depending on the instructions from the software (arrow up, 'activation' or arrow down, 'deactivation'), and these studies also demonstrated clinical effects in ADHD (Leins et al., 2007; Holtmann et al., 2009).

The sleep EEG during NREM sleep is not only characterized by sleep spindles and delta oscillations, but also by cortically generated slow oscillations at frequencies lower then 1 Hz (Azica and Steriade, 1997; Evans, 2003; Sinha, 2011). Although the sleep spindle oscillations are generated in a reticulo-thalamocortical network (Sinha et al., 2011), neocortical control over this sleep spindle circuit is established via generation of slow oscillations, where the depolarizing phase is associated with increased neuronal firing, which drives the thalamic spindle generator via cortico-thalamic efferents (Marshall et al., 2003; Steriade and Amzica, 1998; Steriade, 1999; Timofeev et al., 2000).

The transition from wakefulness to sleep in humans is characterized by a negative DC shift (Marshall et al., 1996, 2003). Furthermore, clear temporal interrelations between the occurrence of sleep-spindles and brief shifts to surface negativity have been described (Caspers and Schulze, 1959; Marshall et al., 2003) and a clear cross-correlation between the negative DC potential and sleep spindle activity across time with correlation coefficients around .80 with zero time lag have been reported (Marshall et al., 2003). Furthermore, Mölle et al. (2002) concluded that slow oscillations serve a function in 'grouping' sleep related EEG activities such as sleep spindles (Mölle et al., 2002) in agreement with the conclusion that these cortical slow waves are known to trigger sleep spindles and control the faster delta waves originating from the thalamus (Azica and Steriade, 1997; Evans, 2003; Sinha, 2011). Interestingly, transcranial slow oscillation stimulation (0.75 Hz) during NREM sleep, but not stimulation at 5 Hz, improved declarative memory (Marshall et al., 2005, 2006) and resulted in increased sleep spindle density (both increased power in the sleep spindle range and increased spindle counts) (Marshall et al., 2006), further demonstrating the causal nature between these slow oscillations and sleep spindle generation, or as Marshall et al. (2006) concluded: '. . . *agrees well with the notion that neocortical slow oscillations drive the thalamic generation of spindles*. . .' (Marshall et al., 2006; p. 611).

Therefore, it is proposed that SCP neurofeedback and SMR neurofeedback share their mechanism by both tapping into a network related to induction and triggering of sleep spindles.

2.6. Sleep spindles and circadian regulation

Sleep spindles are generated by the GABA-ergic thalamic reticular neurons and are synchronized through glutamatergic cortico-thalamic projections (De Gennaro and Ferrara, 2003). The spindle oscillation generated in the reticular neurons is transferred to thalamocortical relay cells in the dorsal thalamic nuclei through GABAergic synapses, producing inhibitory postsynaptic potentials (IPSPs) and travel through glutamatergic thalamocortical axons to generate rhythmic excitatory postsynaptic potentials (EPSPs) in the cortex (Sinha, 2011). As pointed out above, cortical slow oscillations trigger sleep spindles from the thalamus (Azica and Steriade, 1997; Evans, 2003; Sinha, 2011; Marshall et al., 2006), thereby explaining how SCP neurofeedback training might influence sleep spindle generation. Furthermore, SMR neurofeedback is hypothesized to directly train the sleep spindle circuit given the overlap in frequency and location and as evidenced by studies demonstrating an increase in sleep spindle density after SMR neurofeedback (Hoedlmoser et al., 2008; Sterman et al., 1970).

As stated earlier, there is a strong circadian modulation of sleep spindles (De Gennaro and Ferrara, 2003; Dijk et al., 1997) and melatonin has been demonstrated to result in increased sleep spindle density (Dijk et al., 1995) suggesting an interplay between the SCN and the sleep spindle circuitry. Interestingly, Aston-Jones et al. (2001) have described an indirect connection from the SCN to the noradrenergic locus coeruleus (LC) via projections to the dorsomedial nucleus of the hypothalamus (DMH). In turn the noradrenergic LC is part of a set of subcortical nuclei that regulate activation of the sleep spindle generating circuitry (Sinha, 2011). Furthermore, as explained in more detail by Hegerl in this same issue, the noradrenergic LC plays a crucial role in vigilance stabilization.

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3. Conclusion

In this review article the history and current status of neurofeedback for the treatment of ADHD and insomnia have been summarized.

We have demonstrated that SMR and SCP neurofeedback have the ability to directly impact the sleep spindle circuit resulting in increased sleep spindle density during sleep. Increased sleep spindle density has been demonstrated to be associated with improved sleep quality, including decreased sleep latency and increased sleep duration, resulting in normalization of SOI. This normalization of SOI (and thus the relief of sustained sleep restriction) will eventually result in vigilance stabilization mediated by the noradrenergic locus couruleus in turn resulting in improvements of inattention, hyperactivity and impulsivity in ADHD. The effects of activation (e.g. LC) on the sleep spindle circuitry have been documented (Sinha, 2011), however to the authors knowledge no direct link from the sleep spindle circuitry on the LC has been documented, therefore we speculate this is a reciprocal link and LC activation will occur along with the normalization of sleep and the model predicts that this will occur with a time lag, and will not occur during neurofeedback but will be seen better at follow-up.

In this view then, a circadian phase delay characterized by SOI is considered the core pathophysiology in this sub-group of ADHD, with an estimated prevalence of 72–78% (Van der Heijden et al., 2005; Van Veen et al., 2010). Although neurofeedback does not target this circadian phase delay in the SCN or pineal gland directly, it does so at the level of subcortical and cortical structures, which mediate sleep spindle production and sleep onset. These improvements on ADHD symptoms will most likely occur with a delayed effect of onset, as was found for melatonin treatment in ADHD (Hoebert et al., 2009). This is also supported by the tendency for further improvements at follow-up for neurofeedback, which was seen in Fig. 2 and by the effects of long-term sleep restriction in healthy volunteers where the impairments on attention take more recovery nights to normalize than the actual number of nights of sleep restriction (Axelsson et al., 2008; Belenky et al., 2003). The model also predicts that QEEG normalizations such as reduced frontal theta and frontal alpha seen after neurofeedback will be most prominent at follow-up, rather than directly at outtake.

In line with this delayed onset of effect of ADHD symptoms, an interesting hypothesis deserving further study is that neurofeedback might require fewer sessions. Sessions might be terminated when SOI is normalized, with other findings normalizing over time with no additional neurofeedback. Improvements in sleep are the most often reported 'side-effects' of children and adults with ADHD treated with neurofeedback, and the biggest improvements in sleep take place in approximately 20 sessions as measured with the Pittsburgh Sleep Quality Inventory (PSQI) (Arns, 2011). Note that, in the present view, once sleep-onset latencies and sleep quality have been normalized, it takes an additional amount of time for ADHD symptoms to improve (see Fig. 2). In contrast to the persistent and improving findings in Neurofeedback studies, the effects of melatonin disappear when the treatment is discontinued. Hence future studies should incorporate polysomnography, and actigraphy (Hoebert et al., 2009; Van der Heijden et al., 2007; Van Veen et al., 2010), and investigate whether the normalization of SOI is consistently related to improvements in ADHD symptoms and to quantify the delay in onset more completely. Furthermore, clinical trials of new treatments for ADHD should consider evaluating primary treatment endpoints at follow-up, after 6–12 months, rather than directly at the end of treatment, in order to identify treatments that have lasting effects. Differentiating long term versus temporary treatment effects is especially important since it was recently concluded based on the large NIMH-MTA trial that conventional treatments in ADHD such as stimulant medication, multicomponent behavior therapy and combined treatment had no effects beyond 2 years following treatment (Molina et al., 2009). This identification of the longer term failure of conventional ADHD treatment approaches further stresses the need for the identification and development of new treatments with long-term effects.

4. Limitations and directions for future research

This review provides a model which can explain the behavioral complaints in a sub-group of ADHD, and how chronobiological treatments and neurofeedback exert their clinical effects in ADHD and insomnia. Obviously such a model results in more testable questions than answers. Obviously there are also inherent limitations and weaknesses to this model.

The effects of sleep restriction in children have been most clearly replicated for inattention, but only 1 study found effects on externalizing behaviors such as hyperactivity. On the other hand, the extensive meta-analysis by Astill et al. (2012) in 35.936 children found clear relationships between sleep duration and school performance, executive function and externalizing behavior, but not for sustained attention. Therefore, this aspect of the model requires further study such as longer sleep restriction studies, sleep restriction studies in 'ADHD risk' populations. The implications of this model thus are clearest for the circadian delay sub-group of ADHD patients, and might not generalize to explain all of the forms of ADHD.

Currently the debate about whether neurofeedback has specific effects beyond a 'sham' condition continues. This debate is mainly centered around whether to evaluate neurofeedback based on APA norms, or based on pharmaceutical norms which require a double-blind placebo controlled study. Although this pharmaceutical standard based approach is not impossible, there are considerable methodological issues to address. One such design-proposal was recently submitted for publication by the Collaborative Neurofeedback Group, which is constituted by Neurofeedback experts, mainstream ADHD investigators and clinical trial experts (The Collaborative Neurofeedback Group, submitted for publication). Such a study might provide more definitive answers though this requires further implementation of their proposed study.

We have construed our review and model narrowly around ADHD and insomnia. There is a rich literature on many other applications for which this framework might not provide a valid explanation. Some of these include SMR Neurofeedback resulting in reduction of seizures (Tan et al., 2009), in improving micro-surgical skills (Ros et al., 2009) and creative acting performance (Gruzelier et al., 2010). Therefore, other effects and explanations of SMR and SCP neurofeedback should not be ruled out. Furthermore, this review focused on the effects of SCP's and SMR, and the effects of the often included inhibition of Theta, as well as rewarding of the higher beta-band and inhibition of EMG activity, none of which have been covered in this review. Further research should focus on investigating the independent contribution of these additional inhibits and rewards.

This review focused on the relationship between circadian phase delay resulting in sleep restriction and changes in vigilance. As pointed out earlier, other sleep disorders are also prevalent in ADHD, such as restless legs, sleep apneas and parasomnias. Such sleep disorders obviously require a different treatment approach. Chronobiological treatments, such as light therapy and melatonin, as well as treatment with neurofeedback are not indicated for these sleep disorders. For a review of these as well as other sleep disorders, see Miano et al. (2012) who have described in more detail

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the different 'sleep phenotypes' in ADHD as well as their related treatments.

Q16 Uncited references

Cormier (2008), De Jong et al. (1990), DSM-IV (1994), Marshall et al. (2005), Schabus et al. (2008), Sterman (1977, 1981), and Werth et al. (1997).

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