EEG-NEUROFEEDBACK HAS POTENTIAL TO RISE FROM THE DUST WITH HELP OF INSIGHTS FROM COGNITIVE NEUROSCIENCE

ABSTRACT

EEG-NF is widely applied in the treatment of psychopathologies, even though its efficacy has not been proven (yet). In this paper possible explanations for this lack of proof have been considered. It could either be caused by current implementation of EEG-NF protocols, or methodological limitations in EEG-NF study designs, or EEG-NF truly has no effect. Current EEG-NF protocols are generally based on empirical findings, however they could rather be based on knowledge of the functional role of neuronal oscillations. Conforming hypothesis-driven EEG-NF paradigms were suggested for the treatment of ADHD, ASD and schizophrenia. Furthermore, possible improvements of EEG-NF study designs were discussed. We have argued that cross-fertilization between EEG-NF and cognitive research domains could be fruitful.

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Introduction

Electroencephalography neurofeedback (EEG-NF) is widely used in the treatment of several psychopathologies such as attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and schizophrenia (SZ). It has been estimated that in 2007 there were between eight to fourteen thousand EEG-NF practitioners worldwide (Evans, J., 2007). Besides being used as a therapy, it is also applied to enhance performance with respect to cognitive, creative and sportive skills. Despite its broad application, research on the efficacy of EEG-NF as a treatment show inconsistent results, mainly due to a lack of proper control conditions, a scientifically grounded hypothesis, or reproducibility (Vollebregt et al., 2014b). Therefore, EEG-NF has been ignored by the scientific community and at best been criticized for a long time (Heinrich et al., 2007).

Operant conditioning is thought to be the underlying mechanism of biofeedback systems like EEG-NF. Ultimately, participants learn to gain self-control over physiological functions, that usually are not consciously perceived or controlled, and thereby alleviate undesired symptoms. Recordings of these functions are translated to tactile, visual, and/or auditory signals, which are fed back to the participant in real time (Schwarz & Andrasik, 2003). Modulations that are made in the desired direction are rewarded while modulations in the undesired directions are punished. Neurofeedback (NF) is a type of biofeedback in which brain activity can be modulated. There are different types of NF. The most commonly applied form is EEG-NF and its feedback is based on the amount of occurring brain waves in certain frequency bands. Other types of NF are functional magnetic resonance imaging NF (fMRI-NF) and magnetoencephalographic NF (MEG-NF), which are both spatially more precise than EEG-NF but require devices that are expensive to purchase and use. Here we primarily focused on EEG-NF to manipulate brain activity, since this cheaper way of NF is suitable to apply in larger populations. EEG-NF modulates neuronal oscillations, which is explained in more detail further in this paper.

The first known application of EEG-NF was around 1960 when Joe Kamiya, a psychologist at the University of Chicago, taught an adult to alter his brain wave frequencies. It was previously thought that they arose solely unconsciously, beyond voluntary control (Lofthouse, 2011). A decade later, the first theta/beta EEG-NF was performed on hyperactive children and resulted in behavioral changes reported by their schoolteachers (Lubar and Shouse, 1976). Since then, there has been a significant increase in the clinical application of EEG-NF as well as a dramatic rise, particularly in the 21st century, in the number of published studies investigating the efficacy of EEG-NF (Fig. 1). Although the increasing amount of published work may indicate that voluntary modulation of brain activity patterns might be possible, methodological limitations of these studies make it impossible to offer unambiguous proof.

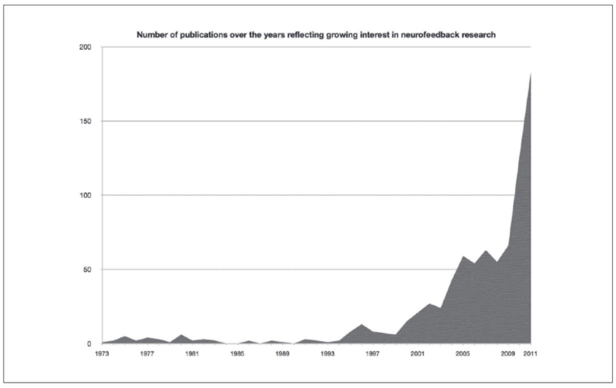

Fig.1The growing interest expressed by the number of publications covering the term "Neurofeedback" or "EEG Biofeedback" from 1973 untill 2011. (Source: Data obtained by The Collaborative Neurofeedback Group from Scopus, Kerson et al., 2013)

It was recently found that EEG-NF increased grey and white matter volume in healthy adults, and although they used a small sample this may be an indication that EEG-NF is valuable in the treatment of neuronal connectivity problems (Ghaziri et al., 2013). This paper provides a discussion of the implementation of EEG-NF in neuropsychiatric disorders, with a focus on ADHD, ASD and SZ. These specific disorders were chosen because the symptoms of these disorders seem to be the result of connectivity problems between multiple brain regions (Castellanos, 2012; Mazaheri et al., 2010; Liu et al, 2007; Muller et al., 2008;), making the application of EEG-NF for their treatment of interest. This paper gives an overview of the current application of EEG-NF in these disorders and suggests ways to improve it. The differences in technical protocols of EEG-NF are compared. Then the methodology of EEG-NF study designs and suggestions for improvements of these designs are provided, and the ways in which sham EEG-NF conditions are designed thus far are described. A recommendation for the best sham protocol is given. The problems with conducting double blind research when studying EEG-NF are discussed. Finally, we argue that EEG-NF studies should be more focused on recent insights gained from fundamental cognitive research.

Achievements and limitations of EEG-NF in ADHD, ASD, and SZ

ADHD is characterized with problems of attention, hyperactivity, and impulsivity. Patients display behavioral problems like failure to pay close attention to details, difficulty organizing tasks and activities, excessive talking, fidgeting, and/or an inability to remain seated in appropriate situations (American Psychiatric Association, 2013). It is the most common childhood disorder with a prevalence of 5% of all children worldwide (Polanczyk et al., 2007). Several medications have been developed to treat the symptoms of ADHD (Chang et al., 2012), from which only a proportion of the ADHD population benefits and many experience side effects (Kidd, 2000). Moreover, long-term effects of medication are still unknown (Berger et al., 2008; van de Loo-Neus et al., 2011) For this reason and also because patients suffering from ADHD show aberrant brain activity compared to healthy controls, EEG-NF became widely applied and researched as a potential treatment for ADHD.

Until now, especially the methodologically flawed studies that lack placebo conditions found positive results of EEF-NF in ADHD. The better-designed studies failed to find a solid effect of EEG-NF compared to placebo-NF (Perreau-Linck et al., 2010; Arnold et al., 2012; van Dongen-Boomsma et al., 2013; Vollebregt et al., 2014). However, these studies have their own limitations, like using small samples or lack of double blinding. Following from these studies it can be concluded that either EEG-NF truly has no effect or a true effect of EEG-NF is hidden by methodological flaws which means that the optimal way to apply or study this therapy is not yet known (Vollebregt et al, 2014b). EEG-NF in ADHD is pioneering the field of EEG-NF in psychopathologies and counts the most publications in EEG-NF research.

The protocols that were used in the ADHD EEG-NF studies were based on the protocols that are currently being used by EEG-NF practitioners. A lot of the studies even outsource the application of EEG-NF to these experienced centers. This approach is useful to investigate whether the EEG-NF as it currently is being offered is effective. However, these EEG-NF centers might not necessarily offer the best available protocols, considered how many variations in protocols are possible. Therefore, it may not be fair to reject EEG-NF in general as a potential treatment based on these studies in which no effect was found.

ASD patients tend to have communication deficits, such as responding inappropriately in conversations, misreading nonverbal interactions, or have difficulty building friendships appropriate to their age (American Psychiatric

Association, 2013). In addition, people with ASD may be overly dependent on routines, highly sensitive to changes in their environment, or intensely focused on inappropriate items. The brains of individuals with ASD show both areas of excessively high connectivity and areas with deficient connectivity (Belmonte et al., 2004). Prevalence of ASD is estimated to be around 1% in the general population (Fombonne et al., 2003).

The first study of EEG-NF in ASD that used a control-group was published in 2002 and was a pilot study with quite some methodological flaws (Jarusiewicz, 2002). For example, the control group did not receive sham NF, hence it was not known whether the findings were caused by specific or non-specific treatment factors. Nevertheless, the article has still been cited as evidence for the efficacy of NF in ASD in numerous popular scientific publications (Holtmann, 2011). After that, five controlled studies have been published that all reported improvements of autism specific symptoms, such as deficiencies in communication and social interaction (Cohen et al., 2007; Kouijzer et al., 2012; Kouijzer, 2009., Thompson et al., 2010; Pineda et al., 2008; Pineda et al., 2014) In one study the effects of EEG-NF remained stable at 1-year follow-up (Kouijzer, 2009). This research group was the only one that included long term follow-ups and neuropsychological tests to measure the effects of EEG-NF.

SZ is a chronically disabling mental disorder characterized by delusions, hallucinations, disorganized speech and behavior, and other symptoms that cause social or occupational dysfunction (American Psychiatric Association, 2013).The prevalence of SZ is around 1% of the population (Hafter et al., 1997). People with SZ are thought to have reductions in gray matter in specific areas of the cortex, which is thought to be the result of down regulation of dopamine in the cortex while excessive dopamine is apparent in the limbic structures (Pantelis et al., 2003). The most common treatment of SZ is administrating antipsychotic medications that alleviate the symptoms. However, with the current knowledge it is still impossible to cure the disease. Antipsychotics have a lot of aversive side effects such as headaches, dizziness, and tiredness (Leucht et al., 1999), which demonstrates need for (non-) pharmacological alternatives to treat schizophrenia and better ways to manage the disease.

One study on EEG-NF for SZ used the slow cortical potential NF protocol (explained further below). No effect was found of alleviating schizophrenia-specific symptoms (Schneider, 1992). The authors did find an increase in cognitive functions and a decrease of sleeping problems. Methodological limitations of the studies were the use of a healthy control group as control condition rather than a methodologically sound control condition, and lack of double blindness. Another study did find clinical improvement of the schizophrenia-specific symptoms (Surmeli, 2012). They used topographical specificity for the EEG-NF protocol. In general, the brain areas that showed increased coherence (hyper-coherence) according to a z-score analysis were inhibited. Hyper-coherence can be considered as a lack of differentiation of brain functions or as a decrease in “flexibility” of functioning (Coben, 2008). However, this approach goes against the theories that anatomical precision of non-invasive EEG recordings is not high enough to verify the spatial specificity of the measured neuronal oscillations (Horschig, 2014) and that there is little support for topographical specificity from the experimental studies (Gruzelier, 2014). It was found that even posterior training predominantly leaded to stronger frontal than posterior effects. Therefore, spatial-specific training using EEG seems to be redundant. These oversights of current EEG-NF studies indicate that improvements are needed in experimental designs.

Neuronal oscillations are the basis of EEG-NF

As discussed before, EEG-NF aims to influence neuronal oscillations (further referred to as oscillations), ultimately leading to behavioral changes. Electrical brain activity was first measured in 1924 by psychiatrist Hans Berger, and was thought to change according to the functional state of the brain while awake or asleep, or in brain diseases such as epilepsy (Berger, 1924). Since the advent of EEG recordings, several other hypotheses have been proposed about the interaction between oscillations and behavior. EEG is a measure of a spatially organized population of neurons that is active in a coordinated way in time, called a local field potential (LFP)(Lopes da Silva, 2013). Oscillations represent rhythmic or repetitive neural activity in the central nervous system. Oscillations have been grouped into different frequency bands and these bands have been associated with different brain functions. Classically, these EEG frequencies were clustered into infraslow (<0.2 Hz), delta (0.2-3.5 Hz), theta (4-7.5 Hz), alpha and SMR (8-13 Hz), beta (14-30 Hz), gamma (30-90 Hz) and high frequency oscillations (>90 Hz) (Lopes da Silva, 2011b).

While lower frequencies are often associated with long-range connectivity between cortical regions, higher frequencies seem to reflect the local firing pattern of neurons

(Horschig, 2014). The exact biological basics of most frequency bands are still speculative. The neuronal basis of oscillations in the gamma range is thought to reflect the interaction between synaptic excitation produced by glutamatergic neurons and inhibition produced by GABAergic neurons (Bosman et al., 2014). The lack of biological knowledge about other frequency bands makes a reductionist approach to investigate the function of oscillations impossible for now. Therefore, the correlation between behavior and oscillations can only be studied by observing behavior while recording oscillations. Some researchers do not regard the lack of knowledge a problem, but reject the whole idea of oscillations having a function (Sejnowski and Paulsen, 2006). They rather view that oscillations are merely a byproduct or "epiphenomena" of ongoing processes in the brain. However, in the last decades experimental evidence supports the contention that EEG signals are neurophysiologic mechanisms that are relevant to understand how cognitive processes emerge (Lopes da Silva, 2013). In general, different types of oscillations denote different brain activity states and oscillatory fluctuations across time represent the dynamic interplay between different cell types in various cortical and subcortical circuits (Buzsaki, 2006, In: Bosman et al., 2014). These findings were especially collected subsequent to electrical field recordings of the brain were analyzed as oscillations instead of as timelocked-evoked or event-related-potentials (ERPs)(Wang, 2010). The downfall of ERPs, compared to the oscillations approach, is that in ERPs the non-phase-locked oscillations may be missed, because they are being 'smeared' in time (Tallon-Baudry & Bertrand, 1999). This 'rediscovering' of EEG as a way to measure brain activity and brain functioning could yield an increase in EEG research. With the hereby-gained insights about cognitive processes that correlate with oscillations, new EEG-NF protocols could be developed.

Hypotheses-driven EEG-NF

Underlying mechanisms of oscillations are still not well understood. Therefore, the physiological or anatomical basis of oscillations cannot readily be assumed. Consequently, a reductionist approach for studying EEG-NF is currently impossible, resulting in a mainly empirically driven approach in EEG-NF research. For example, based on their 2009 study on EEG-NF for autistic children Kouijzer et al. changed the protocol of their 2010 study. In 2009 the protocol was inhibition of theta activity (4-7 Hz) and rewarding low beta activity (12-15 Hz) over the right hemisphere. It was found that the best result was achieved by training theta activity, so they discontinued the training of low beta activity. These kinds of alterations of EEG-NF protocols based on new insights are common in EEG-NF research. Empirical strategies to improve EEG-NF can yield important findings not only to improve EEG-NF protocols but also to provide a better understanding of how the human brain works. The augmentation of human cognition by manipulating neuronal oscillations provides valuable knowledge for neuroscience, because it allows for application of new neuroscience insights to improve oscillations in vivo. Yet the field of neuroscience is progressing and new evidence of a direct relationship between neuronal oscillations and cognitive processes can in turn contribute to improve EEG-NF.

To prove that neuronal oscillations stand for certain behaviors, it would be best to test a hypothesis about a causal relation between an oscillatory change and a behavioral result. Recently it has been proposed that the knowledge that is collected by neuroscientists about neuronal oscillations can help to develop hypotheses-driven methods to augment cognition by optimizing cortical oscillations (Horschig et al, 2014). This is a new approach since most of the EEG-NF is based on empirical findings. Hypothesis-driven NF (HD-NF) is building on the principals of using hypothesis-driven brain-computer interfacing to improve behavior (Jensen, 2011). The robustness and reliability of correlation between cognitive tasks and neuronal correlations makes it possible to establish a priori hypotheses when applying EEG-NF.

The authors suggested that using a control signal that shows strong correlations with behavior, such as frontal theta activity during working memory performance or alpha lateralization during visual spatial attention task performance, and could be used to train the participants to gain awareness and control of that signal (Horschig, 2014). Accordingly, the specific task that is used and the oscillations that are trained need to reflect the underlying cognitive mechanism to be trained. A number of behavioral tasks that measure similar cognitive skills as the trained task before and after the training serve as verification of changes in behavior. If an improvement in cognitive skills in the trained domain is evident, it can be concluded that oscillations are probably causally related to cognition. In the following section HD-NF protocols for ADHD, ASD and SZ were suggested based on their aberrant cognitive mechanisms and brain activity.

Hypothesis-driven EEG-NF protocols for ADHD, ASD and SZ

As discussed earlier, there is no final consensus about which EEG-NF protocol to use for specific psychopathologies. A commonly used protocol in all pathologies is reduction of the theta/beta ratio, mainly based on findings in ADHD (Arns et al., 2012). The protocols of EEG-NF studies in ADHD, ASD and SZ can be based on their specific impaired cognitive functioning, according to the idea of hypothesis-driven NF.

ADHD

The founders of the idea of HD-NF have already discussed the way in which the EEG-NF protocols could better fit to ADHD specific impairments. Well-known characteristics of ADHD are problems with attention and hyperactivity. Horschig et al argued that modulation of alpha power could increase the performance on a mental rotation task and therefore alpha power in thought to play a role in inhibition of distracters. Namely, for a mental rotation task it is necessary to be able to inhibit distracting stimuli. HD-NF for ADHD could entail strengthening alpha power during a spatial attention task (Horschig, 2014). This impairment was found during a cognitive task and using these findings for EEG-NF differs from other EEG-NF protocols because they are solely based on resting state EEG. Trouble with maintaining alpha lateralization has been found in inattentive ADHD patients (ter Huurne et al., 2013). Therefore HD-NF training on maintaining a high degree of alpha lateralization could possibly help restore this ability in this ADHD subtype. Only one study in this direction has been conducted so far, and shows potential at least for healthy control participants (Horschig, 2014). The recent finding that the EEG of ADHD subtypes deviate may also be useful to insert into the HD-NF for ADHD. The inattentive subgroup showed less post-cue alpha suppression, suggesting diminished processing of the cue in the visual cortex, whereas the combined group showed significantly less beta suppression at the electrode contralateral to the cued response hand, suggesting poor motor planning (Mazaheri, 2014). If the subtype of the ADHD patient is known, custom EEG-NF protocols can be applied by subtype. The inattentive subgroup could benefit more from alpha suppression feedback and the combined group could benefit more from beta suppression feedback. Another possible ADHD HD-NF protocol could be based on the finding that frontal theta is relatively high in ADHD during working memory encoding compared to a control group which can be caused by reduced posterior alpha prior to the cue according to the authors (Lenartowicz et al., 2014). For HD-NF it is crucial that the impairments in brain frequency were found during a task and that this same task is part of the EEG-NF protocol during which the concerning frequency band is normalized. This is important, because the oscillations while processing stimuli are likely to differ from resting state oscillations when no stimulus is being processed (Horschig, 2014). It seems plausible that an increase in posterior alpha in anticipation of the stimulus would improve working memory performance in ADHD. Horschig et al only discussed HD-NF for ADHD and performance enhancement in the elderly. On the basis of these suggestions by Horschig et al, as well as the EEG literature on the psychopathologies, new HD-NF protocols for ASD and SZ were elaborated in the following sections.

ASD

Wang (2010) found no correlation between behavioral differences and the reported abnormality in EEGs between ASD patients and a healthy control group. Probably the reason for this finding is that in all published work until 2010 the participants were either in resting state or viewing visual stimuli, without being engaged in processes (such as mentalizing, or communicative intent) that are dysfunctional in ASD. Hence, studies about behavioral functioning and EEG abnormalities were conducted quite distinct from each other. In 2012 a study that measured EEG during ASD- specific tasks was published. MEG measurements were conducted to explore emotional face processing in children with ASD. The results showed that while lower band responses to faces were similar between the ASD and typically developing children, the gamma response in occipital areas was largely absent when viewing emotions on faces in the ASD group (Wright, 2012). These findings might open doors to apply neuroscientific knowledge for the development for new EEG-NF for ASD protocols. In 2013 another study with a task targeting specific ASD symptoms, namely eye-gaze processing, was carried out. Impaired gamma oscillatory activity was found in the prefrontal cortex of ASD patients during eye-gazing and led to the conclusion that impaired prefrontal gamma oscillations are associated with impairments in social cognitive functions such as eye-gaze processing in ASD (Richard et al, 2013). This impairment may be normalized with EEG-NF by modulating gamma oscillations during a gaze cuing task. Yet another functional oscillatory difference between ASD patients and healthy controls that shows potential to be applied in EEG-NF was seen in the research field of mirror neurons. In typically developing individuals, the mirror neuron network becomes active during observation or imagination of action, and when motor tasks are executed they disappear. Mirror neurons play an important role in human social behavior. Dysfunctions in the mirror neuron system (MNS) contribute to social deficits. The frequency bands measured in the motor cortex of healthy controls while observing motor tasks were alpha (8-12 Hz), and beta (15-25 Hz) ranges. These frequencies together were called the mu rhythm (Pfurtscheller et al., 2006). Reduced activity of mu rhythm was observed in ASD during tasks in which mirror neurons play a role, such as observing a person doing motor tasks (Pineda et al, 2013). This may indicate that their mirror neuron system possibly does not engage normally when observing someone else's movement. None of the EEG-NF studies have tried to reward mu rhythm in ASD during observations of someone doing a motor task, and this is something that a new HD-NF study could try to do.

The findings of these three studies can be combined to develop a new EEG-NF protocol to be able to manipulate brain activation in a hypothesis-driven way. Occipital gamma band oscillations could be rewarded during emotional face recognition, prefrontal gamma band oscillations could be rewarded during eye-gazing processing, and mu band oscillations could be increased during observation of motor tasks.

Schizophrenia

The HD-NF for SZ protocols could be based on three studies in which SZ patients showed impairments in discrimination tasks and in their EEG recordings. Impaired discrimination of stimuli is often found in schizophrenia and seems to be responsible for the symptoms of delusions and hallucinations (Wang, 2010). In addition, detection of human faces and working memory has been found to be impaired in SZ (Basar-Eroglu et al., 2007; Cho et al., 2006). A new HD-NF paradigm for SZ could be based on tasks in which skills that specifically SZ patients have difficulty with are being trained. During these 'SZ-specific tasks', the exact frequency bands that are abnormal in schizophrenics must be normalized. For example, SZ patients performed poorly in the Gestalt-stimulus task and showed reduced phase coherence between cortical areas compared to controls (Wang, 2010). Therefore, the Gestalt-stimulus task could be an appropriate SZ-specific task. By rewarding phase coherence in the gamma and beta frequency range with use of EEG-NF, a reduction of SZ-specific symptoms could possibly follow. Another task that SZ patients have shown to have difficulty with is a human faces detection task (Chen et al., 2008). Facial stimulus induced changes in theta amplitude and phase locking were found to be significantly weaker in patients compared with healthy controls. (Csukly et al, 2014). Because the SZ patients had trouble with detecting human faces and also impaired theta frequency in their EEG while detecting faces, this may be an indication for an HD-NF paradigm for SZ. A human faces detection task while theta synchronization is rewarded in parietal cortical sites could be a fitting application of the SZ HD-NF protocol. Thirdly, performing a working memory task, such as an N-back paradigm, while feeding back gamma band oscillations could be considered a potential HD-NF protocol for SZ. Namely, in conditions requiring high cognitive control (respond with incongruent hand) was found that evoked frontal theta and evoked gamma activity increased with working memory load in healthy participants. In SZ patients attenuated evoked theta activity and high gamma band activity was shown, but did not increase with WM load (Basar-Eroglu et al., 2007). Therefore, frontal theta and gamma activity could be rewarded during high working memory load in the EEG-NF protocol for SZ.

The suggestions for hypothesis-driven EEG-NF protocols are based on findings in studies using EEG and MEG measurements. The ideas may not yet be ready for application in EEG-NF practice and must be considered as first attempts to make EEG-NF protocols more psychopathology-specific.

Unconscious-EEG-NF

A totally different approach from the hypothesis-driven EEG-NF is the consideration that protocols would not necessarily require conscious awareness (Gruzelier, 2014). To some extent, all EEG-NF is thought to work unconsciously. The participants are probably not aware of how they modulate their brain activity, although they do observe the visual cue change in the desired direction. Unconscious EEG-NF also has potential to be effective according to the mismatch negativity theory. Mismatch negativity (MMN) is a deviation from the normal EEG pattern evoked by an aberrant stimulus. MMN serves as an evolutionary purpose since it makes human able to discriminate between sensory stimuli. Without MMN our ability to understand spoken language would be impaired. Unconscious EEG-NF could be applied by adding unexpected disturbances to our sensory systems in cues that are expected to be continuous, like brief noise in music or disturbances in moving images. A disadvantage of unconscious EEG-NF is that the training cannot easily be transferred to daily life. The participant does not have to consciously modulate the brain activity and thus would have a hard time applying the new-learned techniques outside the experimental setting. Some of the advantages of unconscious NF are that it can facilitate learning and it makes animal studies possible (Birbaumer, 2013). Animal studies could be valuable to understand the working mechanisms of EEG-NF because in animals the effects on brain anatomy, neurophysiology, and connectivity can be researched post mortem. There is still much to find out about the properties of unconscious EEG-NF before assuming the possible effect for unconscious EEG-NF (Brandmeyer et al., 2013). For example, the effect of the evoked MMN on the subsequent frequency bands and the endurance of the evoked frequency band must be clear before implementing unconscious EEG-NF in practice. Especially the difficulty to translate the learned effect to daily life seems to be problematic.

Optimization of EEG-NF research design

Not only the EEG-NF protocols are subject to room for improvement, the experimental study design of the EEG-NF studies could be optimized as well. A methodological topic that was recently debated in EEG-NF is the necessity for doubleblind, placebo-controlled randomized trials (Hurt et al, 2014; Gruzelier, 2014; Vollebregt, 2014b) Open-label studies, with no double-blind or sham-placebo controls, often show stronger effects than rigorously designed studies, but are unable to separate the specific from the nonspecific effects of treatment (Hurt, 2014). In addition, to verify the intended oscillation modulation, it is important always to report learning functions within sessions, between sessions and with successive baselines, especially since training of one frequency band could lead to changes in another frequency band. Because the effects of EEG-NF can be deviant from what would be expected, research needs to include a full EEG spectrum recording following training (Gruzelier, 2014).

Non-specific treatment factors can be determined by: standardization of solid EEG-NF protocols, triple blinding (participants, EEG-NF trainers, raters), testing validity of blinding, testing inertness of sham, reporting of adverse effects, controlling for concurrent treatments (medications, psychotherapy, special education), increased sample size, and monitoring of long term follow-up. Especially the sham conditions appear to be problematic in EEG-NF studies, due to technical difficulties. The sham protocols are necessary to make double or triple blind conditions possible. In the following section was focused on sham conditions in EEG-NF research and blinding. Placebo controlled trials are sparse in EEG-NF research and even new studies still fail to include sham conditions. In ADHD research, only a part of the randomized, controlled trial (RCT) studies used a sham-NF design. When an EEG-NF study is not placebo controlled, treatment expectancy, implicit training of attention, and intensive one to one contact with the therapist can be confounding factors (Heinrich, 2007).

Commonly used sham protocols are basing the feedback on an earlier recorded EEG record (Sonuga-Barke, 2013), or a random signal similar to real EEG (Vollebregt, 2014). These sham protocols make it suitable to double blind the research, since participants and investigators do not know whether real or sham EEG-NF is given. Only the trainer is not blinded when 'manual thresholding' (an often regarded preferred way of applying EEG-NF) is used. This could bias the results because the trainer can unconsciously influence the participants in the experiment. If the participants are familiar with EEG-NF they can also be aware of the sham. However, recent studies showed that participants were unable to notice the condition they were in. Another way to work around the expectancy bias could be achieved by adjusting an automatic threshold for the desired settings (Vollebregt et al., 2014; Bink, et al., 2014). Then both the trainer and the participant are blinded from the condition. None of the RCTs for ADHD examined the validity of the sham's inertness, which is the chance that the sham feedback accidentally synchronized with the participant's brain activity and thus acted as real feedback (Hurt, 2014). So it is not known whether they compared the EEG-specific feedback to the EEG-nonspecific feedback because they could have given unintentional active feedback in the sham conditions. There could be an unknown number of occasions in the long course of sham NF when the child's brainwaves will fall in the desired EEG sham treatment target range when random reinforcement is given. This could also result in contrariwise feedback if rewards occur at undesired moments and thus worsen the symptoms. No such side effects were found in recent studies (Vollebregt, 2014).

In the autism research field, six small evidence based studies were conducted. As was discussed earlier, all studies found an improvement in autism specific features. Unfortunately, the control condition of most of the studies consisted of a waiting list group. This makes the possibility of existing confounding factors more likely than in placebo-controlled protocols that simulate the normal protocol without the active component. In one study the control condition consisted of feedback of an artificially produced EMG signal (Pineda, 2008). Participants from the control group received feedback based on EMG activity and an artificially generated mu-like signal filtered at 8-13 Hz. However, the electrode was placed on a shoulder muscle and thus both the participant and the trainer were not blinded. In a more recent study the control condition consisted of skin conductance biofeedback (Kouijzer, 2012).

Skin conductance is believed to measure arousal and thus inhibition of skin conductance is achieved by relaxation. The participants were instructed to decrease the skin conductance response and thereby trained their selves to relax. A benefit of both EMG and skin conductance control conditions is that the effect of one-to-one contact with the therapist is diminished. Moreover, attention training is not responsible for the effect since attention training is present in both the active and sham conditions. Furthermore, both EMG and skin conductance feedback are biofeedback systems, thus operant conditioning mechanisms are thought to be active, as with EEG-NF. A non-specific treatment effect caused by this skin conduction protocol could be that relaxation also resulted in improvements of the problems associated with autism. Another non-specific difference between EEG-NF and skin conductance conditions could arise from the 'superstitious' effect of electrodes attached to the brain. The functioning of the human brain can have a mysterious association for the participants. Therefore, attaching electrodes to their brains can enlarge placebo effects compared to attaching electrodes to fingers or shoulders. These considerations need to be further elucidated in future research.

Sham treatments in EEG-NF research have been questioned on both ethical and practical levels. (The Collaborative Neurofeedback Group, 2011). The declaration of Helsinki states that designs that would withhold or deny 'the best proven diagnostic and therapeutic' treatment to any participant should be prohibited. This has been an argument against using a sham NF treatment (La Vague & Rossiter, 2001). Especially because EEG-NF training requires quite an amount of sessions, it seems unethical to assign participants in need of help to a sham condition that takes them a lot of effort. Others have argued against this argument because it is difficult to define the best-proven treatment, it is difficult to interpret results with no significant difference between two active treatments and it is necessary to include a placebo condition (Lofthouse et al, 2010). Due to lack of evidence for its efficacy, EEG-NF is not thought to be the best-proven treatment for any psychopathology. The current best proven treatment is for ADHD is the medicine methylphenidate. To our knowledge, the use of methylphenidate has never been an exclusion criterion for EEG-NF studies and thus the declaration of Helsinki is not applicable in EEG-NF studies for ADHD. The most common treatments for ASD and SZ are medication and behavioral therapy, and to our knowledge neither of them have been an exclusion criterion for EEG-NF studies. A new approach for sham protocols was proposed recently and could offer a solution to earlier concerns that sham conditions unblind the EEG-NF trainer and thereby not fully control for non-specific treatment effects (Kerson, 2013). In this new sham EEG-NF treatment, sham consists of prerecorded files and arrives in the trainer's software as if they are real time EEG recordings. Crucially the stored sham signal is responsive to any artifact activity that arises in the simultaneously recorded real-time EEG, so that the trainer cannot differentiate between live and simulated data. Since NF training is known to require quite an amount of training sessions, the sham EEG should also show the trainer a progress in EEGs across sessions. This can be reached by using the EEGs of the same age-matched clinical cases as the sham group that show progress just like real NF would do. Furthermore, despite this build-in progress, the occurrence of learning via unintentional feedback can be controlled. This can be done by searching in the sham EEG signal, the recorded EEG signal from the sham participant, and looking for moments in time where they overlap. If they overlap it must be sorted out whether feedback was given at that certain time. Then it must be decided if the given feedback is a reason to exclude the sham participant from the study (Kerson, 2013).

Another consideration in EEG-NF research is the way to measure the effects. For example, ADHD-specific symptoms were rated by parents and teachers in many of the ADHD EEG-NF studies (Sonuga-Barke, 2013). It would be better if these subjective ratings are done alongside with neuropsychological and EEG measures. The baseline EEG before and after the training must elucidate the effect of EEG-NF. In the proposed HD-NF, paradigm specific tasks must be added to the design to measure whether an improvement can be noticed in pathology-specific skills.

Conclusions and future research

In this thesis suggestions were made about the protocols and study design of current EEG-NF research, focusing on ADHD, ASD, and SZ. EEG-NF protocols in their current form deviate too much from the findings in EEG research so far. It would be fruitful for EEG-NF researchers and neuroscience researchers to start working together. On the one hand EEG-NF could benefit from knowledge collected by cognitive neuroscience to improve their protocols and study designs and in the best case to be able to prove its efficacy. On the other hand, the cognitive neuroscience could profit from the large number of EEG measurements done by EEG-NF centers and studies to investigate the functioning of the brain. Due to the often-problematic methodological study design or wrong implementation, EEG-NF has ended up in the black books of science, while the often very fundamental application of EEG science lacks a bridge to clinical application of EEG-NF. Current findings of EEG-NF studies in ADHD indicate that skepticism towards EEG-NF is not misplaced (Perreau-Linck et al., 2010; Arnold et al., 2012; van Dongen-Boomsma et al., 2013; Vollebregt et al., 2014). However, recently HD-NF has been proposed as a potential improvement in implementation of EEG-NF and the first attempt to apply HD-NF showed potential in a healthy control group (Horschig, 2014) and they were the first to develop EEG-NF protocols on the basis of cognitive research.

In the current paper, the technical features of EEG-NF were discussed. EEG-NF intents to down-regulate unwanted oscillations and up-regulate desired oscillations. The cognitive neuroscience field is just carefully considering that oscillations could be correlated with behavior (Lopes da Silva, 2013). Therefore, EEG-NF practitioners should prevent themselves for oversimplifying the complex mechanisms that underlie EEG. Suggestions were made for different types of HD-NF protocols for ADHD, ASD, and SZ. A standardized protocol for specific psychopathologies should be developed with use of insights from the EEG research field. Moreover, the possibility to train frequency bands unconsciously was briefly discussed. Furthermore, the best methods for EEG-NF study designs were discussed. The use of a newly invented sham protocol in which not only the participants and raters but also the trainers should be blinded while preventing use of placebo data that was not inert (Kerson, 2013) was recommended. The inertness of the sham conditions could be measured with this protocol, so that no accidental feedback is given in the control condition. With this protocol the possibility that the effectiveness of EEG-NF is 'hidden' by methodological flaws could finally be banished.

All in all, it seems that there are still a lot of directions to be explored in EEG-NF research. EEG-NF can benefit from the leap EEG research has made in the previous decades, and must more actively adjust their protocols to the findings in this field. Only in this way EEG-NF has potential to escape their fate to end up in history as quackery.

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