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ERP-BASED BCI TRAINING FOR CHILDREN WITH ADHD: MOTIVATIONS AND TRIAL DESIGN

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ABSTRACT: Neurofeedback is a promising treatment for children with ADHD. However, although several studies have investigated its efficacy, the effectiveness of current approaches is still debated. This might be partly due to the biomarkers that are used and might not be enough specific of ADHD core symptoms. We here motivate the evaluation of P300-based BCI training as an alternative. We review the arguments in favor of this approach and reveal the design of an ongoing randomized and controlled clinical trial. Essentially, the P300 EEG evoked response is affected in ADHD. It does reflect selective attention and action selection. It is modulated by successful pharmacological intervention in ADHD. And it can be used in BCI for training purposes, through varied and engaging games. Interestingly, these games enable the use of precise instructions as well as multi-level feedbacks to favor learning. Finally, this new type of Neurofeedback allows for instantiating a highly specific control condition that is compatible with a double-blind design.

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder, affecting 3-5% of children. ADHD refers to a variable cluster of inattention, hyperactivity and impulsivity symptoms. It is also associated with impaired social skills, poor school performance and even accidents or substance use [1]. The predominant treatment for these children is pharmacological, with dopaminergic stimulant medication. The long-term effects of these treatments remain unclear, and close to 30% of children with ADHD do not fully respond to them. Moreover, some adverse effects of psychostimulants have been reported such as a decreased appetite and insomnia [2]. Hence a substantial number of parents are quite reluctant to give these drugs to their children. Additional, complimentary or alternative non-pharmacological interventions are therefore needed. In this paper, we briefly review the converging arguments supporting the hypothesis that P300-BCI based training of attention could potentially be effective in children with ADHD. We also describe the main aspects of a double blind design that we just initiated to evaluate its efficacy. Results of such a heavy longitudinal study will only be available after months, but discussing its theoretical grounds and practical aspects should already be useful to many readers in the field.

CLASSICAL NEUROFEEDBACK IN ADHD

One attractive and non-pharmacological alternative is EEG-based Neurofeedback. The aim of this technique is to enable the patient to learn how to modulate his own brain activity through operant or classical conditioning. By providing positive reinforcement when changes in brain activity are made in the desired direction, the subject can learn how to self-regulate her neuronal activity and normalize it [3]. It is expected that repeated practice will relief the patient of the main symptoms. ADHD is by far the disorder that is most targeted by Neurofeedback treatments today.

Three main types of Neurofeedback protocols are typically used. They all rest on the modulation of an endogenous, spontaneous and continuous measure of some brain signals.

The first application of Neurofeedback in hyperkinetic children aimed at training the sensory-motor rhythm (SMR) between 12 and 14Hz. This was motivated by the relationship between this rhythm and the process of motor inhibition. An increase in SMR amplitude would be associated with a decrease of ADHD symptoms [4].

Besides, several quantitative EEG (QEEG) studies found excess power in the theta band (4–8 Hz) and diminished power in the beta band (13-30) in ADHD children compared to healthy children of the same age [5]. This led to proposing the online training of the theta/beta ratio (TBR) to reduce the activity in the theta band while increasing the one in the beta band [6].

Finally, a very slow component of the EEG known as the contingent negative variation (CNV) has been found to be reduced in ADHD children. This component is characterized by a negative shift of the signal, in anticipation of an expected event. Its reduction in ADHD children would reflect an impairment of self-regulation abilities [7]. To improve control on this component,

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Neurofeedback training protocol targeting Slow Cortical Potentials (SCP) are carried out. SCPs are broadly assume to reflect the regulation of cortical excitability. With SCP training, children seem to become able to regulate their brain potentials and to produce more negative SCPs (i.e. CNV) [8].

Five meta-analysis have assessed the effectiveness of Neurofeedback. The first one showed that this technique has a large effect on inattention and impulsivity and a medium size effect on hyperactivity [9]. All of the fifteen studies reported in this analysis did include a control condition but only a few of them were randomized trials. When including only the randomized studies, the effect on hyperactivity appeared to be reduced. Sonuga-Barke et al., 2013 [10], analyzed 8 randomized controlled trials (RCTs) and reported a significant effect of Neurofeedback when evaluation was based on “probably not blind assessments”, i.e., scores from raters closest to the therapeutic setting (e.g. parents), while they simply concluded to a trend when evaluation was based on “probably blinded assessments”, i.e. scores from placebo controlled trials or made by adults likely to be blind to treatment allocation.

More recently, another meta-analysis based on 5 RCTs reported a significant effect of Neurofeedback on attention, when comparing it to semi-active or placebo conditions and when evaluated based on both “probably blinded” and “probably not blinded” assessments. An effect on hyperactivity/impulsivity was also found but only for “probably not blinded” assessments [11].

Finally, a last meta-analysis based on 13 RCTs [12] yielded a similar conclusion, namely that Neurofeedback training had a significant effect on inattention, hyperactivity and impulsivity as well as on the total score of the ADHD rating scale (ADHD-RS) but only with most proximal raters, not with probably blinded raters.

Despite the growing number of studies and meta-analysis assessing the effect of Neurofeedback in ADHD children, the effectiveness of current treatments remains debated, calling for more studies and as well as new methods [13]–[16]. Studies that are included in these meta-analyses are in fact hard to compare with each other. First because different biomarkers are targeted by the Neurofeedback training (TBR, SMR or SCP). Also, because sample sizes are quite different between studies. Finally, different controlled groups are used. Semi-active conditions refer to treatments with no expected clinical benefit (e.g. EMG-based Biofeedback). They aim at controlling for the non-specific effect of Neurofeedback such as the interaction between the therapist and the children. Then active conditions aim at comparing the effect of Neurofeedback with another therapy (e.g. pharmacological intervention or behavioral therapy). Finally, rare placebo controlled studies have also been performed in order to control for all the nonspecific effects of Neurofeedback treatments. They can allow for a double-blind design but have proven difficult to instantiate. All these different control conditions between studies may have contributed to the heterogeneity of the results.

Importantly, it has recently been questioned whether the above exploited biomarkers are specific enough of the targeted deficits. In particular, recent studies have reported an excessive TBR for a subgroup of ADHD children only [17]. Ogrim, Kropotov, & Hestad, 2012 [18] found a significant increase of the TBR in 25.8% of ADHD patients, but also in 2.6% of healthy controls. Moreover, it has been shown that lots of cognitive processes elicit an increase in frontal-midline theta power [19], such as working memory or episodic memory. It has also been shown that sustained internalized attention or meditation can yield an increase of frontal-midline theta power. More recently, it has been reported that the up-regulation of frontal-midline theta power facilitates memory updating and mental set shifting in healthy subjects [20]. Hence and contrary to the rational of TBR training, a correlation was observed between an improvement in the control of attentional resources and an increase in theta power. Finally and in line with those findings, the increase of TBR found in ADHD children seems to be more important when the children are engaged in a task, suggesting that this increase may simply reflect a compensatory mechanism [21]. The same authors suggested that TBR Neurofeedback “*may not produce the best possible therapeutic effect as far as executive control functions are concerned*”. These findings raise the question of whether current training protocols rely on the appropriate neurophysiological targets.

ERP-BASED NEUROFEEDBACK

Over the past two decades, electrophysiology has been used increasingly to investigate differences in cortical activity between children with and without ADHD. An often occulted research stream investigating deficits in children with ADHD has used Evoked-Related Potentials (ERPs) and several ERP components have proven altered [22]. The most consistent report is the reduction in amplitude of the P300 component, both in auditory [23] and visual tasks [24]. The P300 is a large positive complex that reaches its peak at approximately 300 milliseconds after stimulus onset. It is in fact made of two subcomponents, a frontal P3a reflecting attentional capture by some external stimulation, followed by a parietal P3b elicited by the voluntary orientation of attention [25]. The amplitude of the P300 grows with the amount of attentional resources engaged in processing the external event [26]. This biomarker has never been used in Neurofeedback protocols for ADHD children so far. In contrast, it is very much used online for the control of Brain-Computer Interface (BCI) applications such as the well-known P300-speller [27]. The P300-speller aims at enabling Locked-in people to communicate by spelling a text on a computer screen. It is based on the principle of the visual oddball paradigm. The user must pay attention to a specific item on the screen while groups of items are lit up in a pseudo-random fashion. Every time the target letter is lit up, the brain produces a P300.

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Conversly, no P300 will be produced for non-target letters. This way, but only if the user performs the task as requested, the computer can detect the target letter to be spelled. This selection process based on the orientation of spatial attention can be used in different settings, beyond spelling applications, such as in games for instance [28]. Interestingly, a few studies have investigated the effect of training on performances in P300-based BCIs. This was done on healthy adults [29]–[31], or adults with motor impairments [32]. Although the training were quite short, and included only a few participants with no control group, results suggested that performances can indeed be improved with practice. This corroborates our own informal observations on a several volunteers who did practice with the P300-speller a lot in our lab. Since a good performance in P300-based BCI involves being able to selectively pay attention to the target, it appears very well suited for training children with ADHD who show difficulties in both sustaining focused attention (towards a target) and avoiding being distracted (by a non-relevant stimulation).

P300 AND ADHD

Overall, the P300 amplitude has been suggested to quantify the degree of engaged attentional resources in processing a particular stimulus [26]. Importantly, it has been shown that children with ADHD have a reduced P300 amplitude which can be up-regulated by Methylphenidate (MPH) intake . Sawada et al., 2010 [33] have shown an increase of P300 amplitude after intake of osmotic-release MPH in ADHD children. Seifert et al., 2003 [34] have found that after the intake of MPH, ADHD children had no more P300 amplitude difference compared to control children. Moreover, two studies have shown an increase of the P300 amplitude following the intake of MPH but also a concomitant improvement of behavioral measures of attention in a Stroop [34] or a CPT task [35]. Yan-ling & Xu, 2013 [35] have found that good performers (i.e. children who improved their behavior after taking MPH), showed no difference of P300 amplitude compared to control children. On the contrary, poor performers (i.e. children who did not significantly improve their behavior), still showed a significantly reduced P300 compared to control children. To conclude, P300 is a specific neurophysiological marker of selective attention which, in one hand, is affected in ADHD children and, in the other hand, can evolve positively along with behavioral symptoms.

P300-BASED NEUROFEEDBACK FOR ADHD CHILDREN

All the above arguments speak quite strongly in favor of attempting to design a Neurofeedback like training that would yield an improvement of the P300 in ADHD children. If successful, we would then expect that this non-pharmacological treatment would yield a concomitant improvement of behavioral symptoms.
However, since the P300 is a transient neurophysiological marker that is evoked by an external stimulation, this calls for drastically different Neurofeedback interfaces compared to classical trainings based on endogenous and continuous signals.
Interestingly, P300-based BCI games have already been designed [28], [36]. They have shown that various and particularly engaging and entertaining games can be easily designed thanks to the transient and reactive nature of the targeted signal. These games typically involve an opponent and require from the user to develop a strategy (see for instance the well-known Connect 4, Space invader or Battleship). The mental effort needed to derive a strategy is independent from the one that has to be made to focus attention and send the proper neurophysiological command, but it certainly contributes to the engagement of the user and should thus favor the learning. This aspect is usually absent from classical Neurofeedback interfaces. Moreover, those games naturally instantiate an interaction where a clear instruction can be given to the user (e.g. to focus its gaze on the targeted screen location and to count the number of times it is lit up). Hence the user can easily infer the causal relationship between a successful attentional effort and a successful outcome in the game (having selected the desired location on screen).

A DOUBLE BLIND RCT

To demonstrate the effectiveness and specificity of Neurofeedback, it is important to conduct double blind, controlled and randomized studies. Interestingly, ERP-based training as we propose makes this requirement from evidence-based medicine attainable.

In our study, 60 children diagnosed with ADHD (aged between 8-17 years) will be recruited. 30 will be assigned following a randomized minimization procedure, to a P300-based Neurofeedback (group A, n = 15) or to an active control group (group B, n=15). 30 other children will be assigned to a third and passive control group (Group C). Children in groups A and B will undergo 30 individual training sessions at a rate of 2 sessions per week. Each session will last an hour, including at least 30 minutes of Neurofeedback training. During these training sessions, children will be offered to play various P300-based video games to keep up their motivation. All these games are based on the same principle as the well-known visual P300-speller. Importantly though, an eye tracking system will be used to know which target the child is aiming at. This eye-tracking system will be useful for two reasons. First, by indicating to us what the target is, we will be able to assess the child's accuracy in controlling the BCI over trials and sessions. Second, in active control group B, it will replace the BCI control so that the interaction with the game will only be based on gaze direction and will not depend upon the attentional effort. Importantly, this active control is thus identical to the P300-based condition in every aspect, except for the signal that will be accounted for to control the interface. Precisely, gaze location on the screen will be monitored

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online for both groups. In group A, selection will be based on the most attended location, while in group B, selection will be based on the most looked-at location. In group A, although the most attend location also corresponds to the one that was mostly looked-at, the control will only be efficient with attentional effort. In contrast, children in group B will be able to control the BCI game by simply looking at the targeted location, no matter how they master their attentional control.
This specific control condition further enables a double-blind comparison of treatments A and B. Indeed, neither the children and the parents, nor the therapists will know if the children are controlling the interface with their EEG signals or with their gaze.
For our recruitment, we will privilege children who are not under medication. However, a few children under medication will also be included inevitably, so that can meet our objectives in terms of inclusion. Children under medication will be asked not to take their drugs on days of training and evaluation. Indeed, the P300 can be up-regulated by MPH intake, suggesting that being trained while under medication would not be useful. To control for a putative interaction of medication and training, children under medication will be randomized between the two groups.
The feasibility of this blind approach was assessed during a preliminary testing with about 30 healthy children who underwent a single session where they blindly switched from one type of control to the other in blocks. This way, we can control for all the non-specific effects of the Neurofeedback training. Children in both groups will receive exactly the same number of training sessions, they will enjoy the same games and receive the same instructions and support.

Unlike classical BCI protocols, children will not have to perform any calibration prior to using the interface. Instead, template signals derived from the above mentioned 30 healthy children will be used. Classificaiton based on these template signals operate in the space of covariance matrices, using Riemannian geometry [37]. Making use of a template from healthy subjects has a twofold advantage. First, it eschews the need for a cumbersome calibration stage at the beginning of each Neurofeedback session. Second, since ADHD children typically exhibit a reduced P300 amplitude, it is more sensible to use template signals derived from a healthy population as model signals to be achieved by the patients with training.

For the quantitative and qualitative evaluation of the treatment, four evaluation sessions will be performed by each child: one prior to any training, one after half the number of training sessions (i.e. 15), one at the end of the training (after the 30 sessions), and a final one two months after the end of the training, as a follow-up measure. During those sessions, children will undergo several paper-pencil and computerized tests in order to evaluate the evolution of their ADHD symptoms. Parents will also complete some questionnaires to evaluate the evolution of the symptoms and the quality of life of their child.

Children included in the passive control group (group C) are only going to carry out these four evaluation sessions.

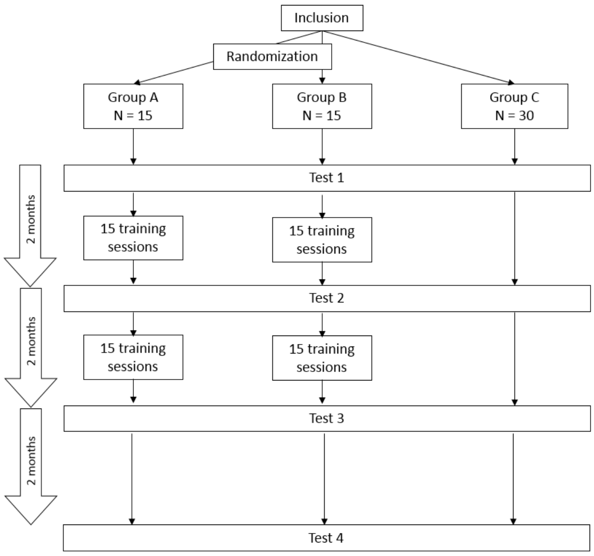

Figure 1: flow chart of the RCT design for the evaluation of a P300-bsed BCI training for ADHD children.

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