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## Remote neurocognitive interventions for attention-deficit/hyperactivity disorder – Opportunities and challenges

Da-Wei Zhang<sup>a,b,\*</sup>, Stuart J. Johnstone<sup>c,d</sup>, Bruno Sauce<sup>e</sup>, Martijn Arns<sup>f,g,h</sup>, Li Sun<sup>i,j</sup>, Han Jiang<sup>k</sup>

<sup>a</sup> Department of Psychology/Center for Place-Based Education, Yangzhou University, Yangzhou, China

<sup>b</sup> Department of Psychology, Monash University Malaysia, Bandar Sunway, Malaysia

<sup>c</sup> School of Psychology, University of Wollongong, Wollongong, Australia

<sup>d</sup> Brain & Behaviour Research Institute, University of Wollongong, Australia

<sup>e</sup> Department of Biological Psychology, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

<sup>f</sup> Research Institute Brainclinics, Brainclinics Foundation, Nijmegen, Netherlands

<sup>g</sup> Department of Experimental Psychology, Utrecht University, Utrecht, Netherlands

<sup>h</sup> NeuroCare Group, Nijmegen, Netherlands

<sup>i</sup> Peking University Sixth Hospital/Institute of Mental Health, Beijing, China

<sup>j</sup> National Clinical Research Center for Mental Disorders, Key Laboratory of Mental Health, Ministry of Health, Peking University, Beijing, China

<sup>k</sup> College of Special Education, Zhejiang Normal University, Hangzhou, China

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### ABSTRACT

Improving neurocognitive functions through remote interventions has been a promising approach to developing new treatments for attention-deficit/hyperactivity disorder (AD/HD). Remote neurocognitive interventions may address the shortcomings of the current prevailing pharmacological therapies for AD/HD, e.g., side effects and access barriers. Here we review the current options for remote neurocognitive interventions to reduce AD/HD symptoms, including cognitive training, EEG neurofeedback training, transcranial electrical stimulation, and external cranial nerve stimulation. We begin with an overview of the neurocognitive deficits in AD/HD to identify the targets for developing interventions. The role of neuroplasticity in each intervention is then highlighted due to its essential role in facilitating neuropsychological adaptations. Following this, each intervention type is discussed in terms of the critical details of the intervention protocols, the role of neuroplasticity, and the available evidence. Finally, we offer suggestions for future directions in terms of optimizing the existing intervention protocols and developing novel protocols.

### 1. Introduction

Attention-deficit/hyperactivity disorder (AD/HD) is a common neurodevelopmental disorder (Polanczyk et al., 2014) that is characterized by heterogeneous etiology (Loo et al., 2018; Luo et al., 2019; Nigg et al., 2005) and pervasive influence (Karam et al., 2015). Current front-line treatments include pharmacological and behavior therapies (e.g., stimulant drugs and parent training), with stimulants being the most prescribed intervention (AAP, 2011; Caye et al., 2019). However, as is the case with other psychological and psychiatric disorders, a one-size-fits-all approach to treatment is unlikely to result in the best outcomes when considering the complexities of the brain (Arns et al., 2022; Merzenich et al., 2014) and the heterogeneity of AD/HD. Indeed, it has

been reported that patients with AD/HD respond differently to medication therapies (e.g. Gilbert et al., 2006). Furthermore, the current prevailing medication therapies have been criticized for their side effects (Graham et al., 2011), lack of long-term effects (Wang et al., 2013), and economic impact (Chorozoglou et al., 2015). These shortcomings pose significant challenges for primary care professionals and patients to initiate or continue treatment (French et al., 2019; Wright et al., 2015).

The COVID-19 pandemic has brought into focus the need for alternative treatments, particularly alternative treatments that can be delivered remotely. The pandemic posed not only great difficulties that challenge the nature of AD/HD (e.g. physical distancing for patients with AD/HD, Cortese et al., 2020) but also compromised clinical services for mental health disorders in general due to the public health

\* Corresponding author at: Department of Psychology, Yangzhou University, Yangzhou 225000, China.

E-mail address: [dawei.zhang@monash.edu](mailto:dawei.zhang@monash.edu) (D.-W. Zhang).

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guidance, e.g., staying at home (Moreno et al., 2020). Thus, developing remote treatment options has been of interest in research (Lattie et al., 2022; Wright and Caudill, 2020).

Remote alternative treatments for reducing the symptoms of AD/HD have progressed substantially in recent times and garnered considerable attention. In 2020, the U.S. Food and Drug Administration permitted the marketing of gamified cognitive training called EndeavorRx for treating children with AD/HD (FDA, 2020), about a year after the debut of the first FDA-approved medical device called Monarch eTNS for at home treatment (FDA, 2019). Compared to current clinical practice, the two approved interventions offer several advantages, such as minimal long-term side effects and relatively low costs. The two interventions also share some similarities. In both cases, neurocognitive deficits in AD/HD are addressed with software and accessible hardware. These features suggest the potential of remote interventions for the treatment of AD/HD.

Due to the growing need for accessible interventions and recent progress in this area, here we synthesized the current evidence for remote neurocognitive interventions. The interventions reviewed here met the following criteria. Firstly, the interventions were described as approaches that are specifically designed to address neurocognitive deficits in AD/HD. The definition distinguishes neurocognitive interventions from other interventions with broader aims that may also benefit neurocognitive abilities in AD/HD, such as meditation (Zylowska et al., 2008) and aerobic exercise (Ludyga et al., 2017). Secondly, the interventions are cost-effective and can be delivered in remote settings (e.g. at home and in schools) with minimal professional guidance. For this reason, some promising interventions, such as fMRI-based neurofeedback training (Rubia et al., 2019) and transcranial magnetic stimulation (Alyagon et al., 2020), were excluded due to their high cost and high level of professional guidance during intervention delivery. Thirdly, the neurocognitive interventions reviewed here are evidence-based, including (1) those that have been remotely delivered and

improved neuropsychological functions or symptoms in patients with AD/HD and (2) those that showed benefits for AD/HD only in clinical or laboratory settings but are technically feasible for remote delivery.

To our knowledge, this is the first review highlighting the potential of remote neurocognitive interventions for the treatment of AD/HD. We begin with an overview of neurocognitive deficits in AD/HD to identify the targets for developing interventions. The role of neuroplasticity is then highlighted, as it is essential to facilitating neuropsychological adaptations. Next, the section on each intervention discusses the critical details of the intervention protocols, the role of neuroplasticity, and the available evidence. Finally, we offer suggestions for future directions and studies. Table 1 summarizes the reviewed interventions.

## 2. AD/HD and its neurocognitive deficits

The symptoms of AD/HD can appear in two dimensions, namely inattention and hyperactivity/impulsivity (American Psychiatric Association, 2013). Inattention is associated with shy and passive social behavior, impaired adaptive functioning, and impaired academic functioning, whereas hyperactivity-impulsivity symptoms are more strongly linked to overt rejection by peers, relational aggression, and injuries (Willcutt et al., 2012). In adolescence and young adulthood, hyperactivity/impulsivity tends to reduce, but inattention often persists (Faraoane et al., 2021). The etiology of the symptoms remains unclear, with possible mechanisms including genetic liability (e.g. polymorphisms in dopamine receptor genes), risky environmental factors (e.g. prenatal maternal distress), and gene-environment interactions (Nigg et al., 2020).

Several influential models attribute ADHD symptomatology to neurocognitive dysfunctions (Barkley, 1997; Sergeant, 2005; Sonuga-Barke, 2005). Neurocognitive functions refer to cognitive abilities that are deeply rooted in brain regions or neural networks. Neuropsychological dysfunctions, including but not limited to executive functions (EF),

**Table 1**  
A summary of the reviewed interventions.

	Aim	Variety	Protocol Parameter	Neuroplasticity*	Challenges
Cognitive training	Enhance cognitive skills associated with AD/HD symptoms via repetitive training	Inhibitory control training Working memory training Cognitive flexibility training Attention training	Targeted cognitive skills Difficulty Duration Delivery mode	Role 1	Optimal parameters: Strategies for determining the best parameters for each protocol  Long-term effectiveness/efficacy: Comparison of the long-term effectiveness and efficacy of promising protocols with existing treatments (e.g., medication therapies)
EEG Neurofeedback Training	Normalize brain oscillations implicated in AD/HD via behavioral learning with real-time feedback using portable EEG	Slow cortical potentials training Theta/beta ratio training Sensory motor rhythm training Alpha or beta training	Targeted brain oscillations Feedback type Feedback latency	Role 1 Role 2	Protocol combination: Approaches for combining different protocols based on their specific roles in neuroplasticity  Optimal number of sessions: The ideal number of intervention sessions to achieve short- and long-term effects for each protocol
Transcranial electrical stimulation	Modulate brain regions implicated in AD/HD by applying a weak current to the scalp	Transcranial direct current stimulation Transcranial alternating current stimulation Transcranial random noise stimulation	Electrical intensity Electrode placement Electrical frequency	Role 1 Role 2	Tailoring protocols: Customizing protocols based on individual demographic, behavioral, and brain profiles
Non-invasive cranial nerves stimulation	Modulate brain regions implicated in AD/HD by applying a weak current to the cutaneous distribution of cranial nerves	External Trigeminal nerve stimulation External Vagus nerve stimulation	Electrical intensity Electrode placement Electrical frequency	Role 1 Role 2	

*Note.* The following abbreviations are used in the text: Cognitive training – CT; Neurofeedback training – NFT; Slow cortical potentials – SCP; Theta/beta ratio – TBR; Sensory motor rhythm – SMR; Transcranial electrical stimulation – tES; Transcranial direct current stimulation – tDCS; Transcranial alternating current stimulation – tACS; Transcranial random noise stimulation – tRNS; Trigeminal nerve stimulation – TNS; Vagus nerve stimulation – VNS.

sustained attention or vigilance, reward motivation, and state regulation, have been frequently observed in the AD/HD population (Barkley, 1997; Sergeant, 2005; Sonuga-Barke, 2005; Nigg et al., 2020) (Barkley, 1997; Sergeant, 2005; Sonuga-Barke, 2005). Neuroimaging studies have enabled the identification of the brain mechanisms underlying neurocognitive dysfunctions. Cortical changes, particularly in the frontoparietal region, have been associated with cognitive dysfunction (Albajara Sáenz et al., 2019; Clarke et al., 2020; Rubia, 2018; Zhang et al., 2017; Zhang et al., 2018). Targeting the neurocognitive dysfunctions represents a promising avenue for developing alternative treatments.

### 3. Neuroplasticity and neuropsychological intervention

Neuroplasticity refers to the brain's ability to change structure and function in response to different forms of stimuli (Kolb and Whishaw, 1998) and is one mechanism that contributes to achieving the desired changes (Cramer et al., 2011; Merzenich et al., 2014). This dynamic process involves intricate mechanisms ranging from molecular levels to system levels (Ganguly and Poo, 2013).

It is important to note that neuroplasticity's exact role in neurocognitive interventions varies depending on whether neurocognitive interventions trigger neuroplasticity (role 1) or modulate its likelihood (role 2). In role 1, referred to as "neuroplasticity induction", neurocognitive interventions induce neural changes but do not affect the inherent malleability of the brain (i.e. the likelihood of neuroplasticity) (Lövdén et al., 2010). The evidence of role 1 can come from the brain changes at different levels after neurocognitive interventions. For example, one may examine the number of postsynaptic receptors, glial cells, and neurons varied at the deficit regions of AD/HD at the cellular level, while others may examine the change in terms of the brain volume and network connection from a system perspective. In role 2, referred to as "neuroplasticity modulation," neurocognitive interventions modulate the likelihood of neuroplasticity. In other words, the malleability of the brain is changed. Long-term potential (LTP) is a widely-studied form of neuroplasticity, and its successful induction acts on the binding of glutamate to NMDA receptors for the influx of calcium ions, which can occur more easily if the postsynaptic neuron is partially depolarized (Lisman, 2017). If a neurocognitive intervention can cause partial depolarization so that LTP can be induced easily or hyperpolarization for a harder LTP, the neurocognitive intervention is thought to play role 2. Interestingly, the modulatory effect may persist after the termination of the neurocognitive intervention. This long-term effect is defined as "metaplasticity" (Abraham, 2008). It should be noted that for role 2, neurocognitive interventions only cannot alter behavior, as they only modulate the likelihood of neuronal changes (defined as the malleability/neuroplasticity) but do not induce neuronal changes relevant to cognition. However, this modulatory effect indicates the possibility of combining it with interventions that induce neuronal changes in cognitive systems (e.g. neurocognitive interventions with role 1) for a

synergistic result.

## 4. Remote neurocognitive interventions in AD/HD

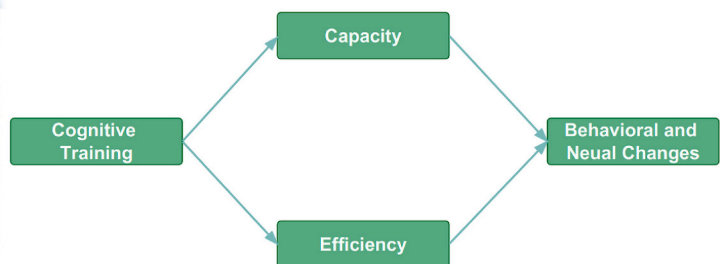
### 4.1. Cognitive training (CT)

#### 4.1.1. Brief introduction

Cognitive abilities, from perception to higher-order cognitive control, are malleable (Sauce and Matzel, 2018), leading to a "skill learning" perspective to explain cognitive development (Johnson, 2011; Jolles and Crone, 2012; Klingberg, 2014). This perspective echoes the quote, "Practice makes perfect", and forms the basis for computerized CT. As such, CT provides an environment that contains an array of opportunities for developing desired cognitive skills (For an example of CT, please see Fig. 1). A recent molecular genetic study suggests that CT may mimic the environment that elicits natural cognitive development in children (Sauce et al., 2021). A central assumption in CT is that cognitive abilities can be improved through practice, which is often analogous to physical training (von Bastion et al., 2022). The "capacity-efficiency" model (Fig. 1) has been suggested to explain the mechanisms of CT (von Bastion et al., 2022; Zhang and Sauce, 2023). Due to the availability of hardware (such as computers and smartphones) required for most CT, remote delivery is a viable option.

#### 4.1.2. Key parameters in CT

**4.1.2.1. Training content.** In AD/HD, CT usually focuses on deficient neurocognitive functions such as EF and sustained attention due to their association with symptoms. Here, we define EF based on a prevailing framework that includes inhibition, working memory, and cognitive flexibility (Diamond, 2013). Generally, CT trains these abilities by using the same task paradigms used for measuring them in research. The rationale is that such tasks intensively engage these cognitive processes. Note that there is a variety of tasks available (for representative tasks, please see Diamond, 2013, and the choice may affect training effects in AD/HD (e.g. Jones et al., 2020). Despite this, there has not been a systematic study of the effect of task selection on training effects. Another question in previous studies is about using uniform training content for all individuals, despite the marked heterogeneity of neurocognitive deficits in those with AD/HD (Nigg et al., 2020). A more effective approach may involve tailoring training content to individual neurocognitive profiles (for a comprehensive discussion on this topic, refer to Zhang, 2023). Further, although representative tasks present the best tools for taxing EF and sustained attention, they are also susceptible to task impurities; for example, each EF task includes non-EF cognitive processing (Miyake et al., 2000). Consequently, an increase in CT performance may be due to an improvement in non-EF cognitive processing rather than a change in desired cognitive processing, which may impede the transfer effect of training on symptoms associated with ADHD.



**Fig. 1.** An example of cognitive training and the capacity-efficiency model of cognitive training. The example was sourced from EndeavorRx, an FDA-permitted software application for improving inattention in children with AD/HD (FDA, 2020). The capacity-efficiency model, proposed by von Bastion et al. (2022), suggests two mechanisms underlying training-induced changes: a capacity mechanism that enhances overall cognitive resource capacity and an efficiency that optimizes performance within the existing capacity limit.

**4.1.2.2. Adaptive difficulty.** CT usually uses an adaptive algorithm to control the difficulty of tasks to provide trainees with a challenging training environment. For example, during working memory training, trainees who successfully remember three stimuli will then be required to recall four stimuli. Although adaptive training has become an essential condition for generating desired training effects (Diamond and Lee, 2011; Klingberg et al., 2005), little is known about optimizing the adaptive algorithm (Plass and Pawar, 2020).

**4.1.2.3. Duration.** Intensive practice is required to achieve training gains (Klingberg, 2010). As a rough approximation, studies with CT typically involve 1096 min of training spread over multiple training sessions (Veloso et al., 2020). Insufficient training may impair training effects (Zhang et al., 2021), and prolonged training may not result in a greater improvement (Wiemers et al., 2019). Further studies are needed to provide a nuanced relationship between duration and training effects.

**4.1.2.4. Delivery mode.** CT can be categorized as computerized CT or non-computerized CT (Veloso et al., 2020). The former method relies on software to deliver training content (e.g., computer games incorporating EF), whereas the latter method relies on instructors to provide training (e.g., card games incorporating EF). A computerized CT offers the advantages of precisely controlled training (e.g., training duration and adaptability) and is less labor-intensive. In contrast, non-computerized CTs are more cost-effective (Qian et al., 2017) and can involve social interaction, which may enhance the effectiveness of training (Studer-Luethi et al., 2022).

#### 4.1.3. Role of neuroplasticity in CT

Several studies have shown that CT can change brain regions or networks that are associated with targeted cognitive functions. This indicates Role 1 of neuroplasticity in CT. The brain mechanism associated with working memory training has been the most extensively examined, with changes frequently observed in the frontoparietal regions (e.g., medial frontal gyrus and intraparietal parietal cortex) that are critical for working memory performance (Constantinidis and Klingberg, 2016; Salmi et al., 2018). A similar effect was found for training sustained attention, inhibition, and cognitive flexibility – CT can change the brain processing related to the involved cognitive ability (Al-Shargie et al., 2019; Berkman et al., 2014; Olfers and Band, 2018).

The neuroplastic changes caused by CT may be manifested as an increase or a decrease in regional activation and brain networks (Berkman et al., 2014; Constantinidis and Klingberg, 2016). The directional difference suggests that CT may be governed by two different mechanisms. While the increase may indicate a higher level of resources available for relevant brain processing after CT, the decrease is explained by efficiency gains associated with relevant brain processing (Constantinidis and Klingberg, 2016). It is possible that CT will involve both mechanisms at the same time but in different brain regions or networks.

#### 4.1.4. CT in AD/HD

Since a seminal study conducted by Klingberg et al. (2005), several RCTs have investigated the effects of remote CT on neuropsychological functions and AD/HD symptoms. Klingberg et al. (2005) found that children with AD/HD who were trained on computerized visuospatial working memory tasks at home or school improved on untrained working memory tasks, inhibition, reasoning, and parental ratings of AD/HD symptoms. Computerized remote training has been successfully extended to train other cognitive functions associated with AD/HD symptoms, such as sustained attention (Rabiner et al., 2010), inhibition (Johnstone et al., 2010; Meyer et al., 2020), and cognitive flexibility (Kray et al., 2012). The landmark study on remote CT came from Kollins et al. (2020) where the authors, using a multi-center and double-blind RCT, reported that 4-week home-based CT involving attention and

inhibition training can alleviate the inattention symptom in children with AD/HD. The CT software used by Kollins et al. (2020) was then permitted by FDA (2020) and is the first digital therapeutic device for children with AD/HD.

Despite the positive outcomes demonstrated in these individual studies, CT has not been widely accepted as a treatment as its efficacy has not been verified at a synthesis level. Two influential meta-analyses suggested that CT may be beneficial for cognitive abilities associated with training content but had little effect on AD/HD symptoms rated by proximal assessors (Cortese et al., 2015; Sonuga-Barke et al., 2013). However, the meta-analyses are controversial. It has been argued that proximal ratings (often the teacher) are less sensitive to symptom changes and thus cannot reflect training gains (Arns et al., 2020). Also, the effect sizes estimated by the meta-analysis were derived from pooling different CT protocols, which is flawed because different CT protocols may differ in their effects on AD/HD (e.g. Jones et al., 2020). Future meta-reviews may examine the effect of CT on AD/HD symptoms by using reliable object measures (e.g. the attention performance index used by Kollins et al., 2020) and considering factors (e.g. training content) that may moderate its effect.

## 4.2. Neurofeedback training (NFT)

### 4.2.1. Brief introduction

NFT is a technique that enables trainees to volitionally regulate brain activity through learning by providing them with real-time feedback (Sitaram et al., 2017). Instrumental learning is commonly regarded as a mechanism of NFT (Sherlin et al., 2011; Sitaram et al., 2017). In this scenario, the targeted brain activity is viewed as a “behavior” that can be reinforced by providing positive feedback. Considering the purpose of this review, we only focus on a portable and cost-effective form of NFT - EEG-based NFT. Recently, portable EEG devices have been developed and can be used to obtain reliable EEG signals conveniently and cost-effectively (Lau-Zhu et al., 2019). This development has made it possible to conduct NFT in remote settings. There are two key components to NFT: hardware that collects real-time brain activity and software that analyzes real-time brain activity and presents it as sensory information (Fig. 2).

### 4.2.2. Key parameters in NFT

**4.2.2.1. Targeted brain activity.** EEG measures electrophysiological changes on the scalp over time. One research line focuses on slow cortical potentials (SCP), which refer to changes in voltage that occur over several seconds to minutes. In most studies, EEG data are transformed into the frequency domain due to the correlation between EEG frequencies and symptoms of AD/HD (Clarke et al., 2020). The frequency-domain NFT in AD/HD initially used the sensory motor rhythm (SMR), but more popular methods involve decreasing slow frequencies and increasing fast frequencies – for example, the theta/beta ratio (TBR) protocol (Enriquez-Geppert et al., 2019). Besides, there have been some studies that use multiple frequencies as feedback signals simultaneously. As an example, focus-state NFT involves an EEG pattern characterized by a dominant beta pattern along with several other frequencies (Johnstone et al., 2017). Moreover, researchers have recently developed multivariate pattern analysis based NFT (Sitaram et al., 2017). Following this approach, future studies may first use multivariate pattern analysis to decode the EEG pattern that differs between AD/HD and controls and then factor that pattern into NFT as the targeted brain signal.

**4.2.2.2. Types of feedback.** Feedback is a key feature of NFT, as it is used to display simplified EEG data and contributes to the reinforcement of desired brain activity. Previous research primarily employed visual, auditory, and haptic modalities for delivering feedback, with visual

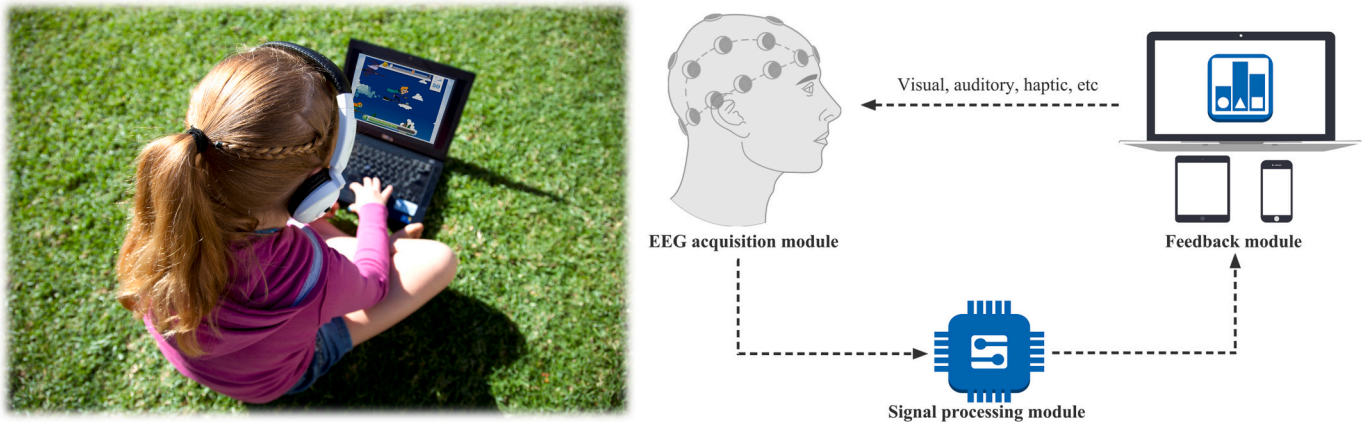


Fig. 2. An example of EEG neurofeedback along with a diagram introducing its essential modules. Purpose designed training software is presented on a laptop, with a wireless EEG device used to provide real-time EEG input linked to software elements.

feedback being the most used. While haptic feedback has been found to be as effective as visual feedback (Shabani et al., 2021), visual feedback appears to induce better learning outcomes than auditory feedback (Hinterberger et al., 2004). One of the confounding factors in the comparative studies was the desire for different modalities of sensory feedback. For those who are motivated by pleasing auditory stimuli, auditory feedback can also be effective. Essentially, regardless of the type of feedback, the feedback should be positive and easy to extract to enable a clear response-reinforcer association (Belinskaia et al., 2020; Sherlin et al., 2011).

**4.2.2.3. Feedback latency.** Feedback latency refers to the time between the response and the feedback. This timing parameter can significantly influence the learning process of NFT, with short-delayed feedback causing a faster learning process (Belinskaia et al., 2020; Sherlin et al., 2011). This feature imposes some hardware requirements for conducting NFT in remote settings. Hardware should have sufficient computing power to provide feedback as quickly as possible and provide consistent feedback latency across training trials. Otherwise, NFT may become a delayed and variable-interval schedule that is detrimental to learning efficiency. However, the delayed feedback can be beneficial in some circumstances. To increase the transferability of NFT, trials involving long-delayed feedback can be introduced after the desired response has been learned (Sherlin et al., 2011; Zuberer et al., 2015).

#### 4.2.3. Role of neuroplasticity in NFT

Numerous studies have shown neuroplastic changes following EEG-based NFT in animals and humans (Gruzelier, 2014; Sitaram et al., 2017), which suggests NFT is an effective method of inducing neuroplasticity (role 1). The specificity of NFT, however, has been questioned - neuroplastic changes are not limited to the targeted brain regions and frequency bands. For example, a frontal alpha NFT also affects on posterior alpha and frontal beta in children with AD/HD (Zhang et al., 2021). Due to issues related to spatial and frequency specificity, it becomes difficult to infer the brain mechanism underpinning NFT's therapeutic effect (Zuberer et al., 2015; Kvamme et al., 2022).

Neuroplasticity may also be modulated by NFT (role 2). Using transcranial magnetic stimulation in conjunction with motor-evoked potentials, Ros et al. (2010) demonstrated that alpha-based NFT increases cortical responses to external stimuli, indicating an increase in neuroplasticity. The increased neuroplasticity after NFT is also evident in studies pairing NFT with behavioral learning. Several studies have demonstrated that alpha-based NFT can accelerate implicit motor learning, perceptual learning, and visuospatial recovery (Ros et al., 2014, 2017; Parsons and Faubert, 2021). A possible explanation lies in the correlation between cortical alpha activity and gamma-

aminobutyric acid (GABA), the neurotransmitter vital to neuroplasticity; thus, modulating alpha with NFT impacts neuroplasticity (Ros et al., 2010).

#### 4.2.4. NFT in ADHD

There have been several decades of use of NFT in AD/HD research, primarily with SCP, SMR, and TBR protocols (Enriquez-Geppert et al., 2019). In 2016, the European ADHD Guidelines Group conducted a meta-analysis to examine the efficacy of NFT in treating AD/HD (Cortese et al., 2016). Similar to CT, they found a limited effect of NFT on AD/HD symptoms when considering proximal assessors' ratings. However, as mentioned above, the method of rating AD/HD symptoms has been questioned (Arns et al., 2020). A recent study by Arns et al. (2020) reevaluated the efficacy of NFT in AD/HD using a more rigid version of the "Empirically Supported Treatments" framework. Briefly, the review (1) relied on multiple-center RCT and meta-analyses and (2) considered the remission rate as well as short- and long-term effects. Using this evaluation framework, Arns et al. (2020) concluded that NFT has "a well-established treatment with medium to large effect sizes and 32–47% remission rates after 6–12 months". A follow-up review indicates that personalized NFT - in which NFT protocols are tailored to an individual's baseline profile - may result in a better treatment outcome (Pimenta et al., 2021). It should be noted that the conclusion is based on SCP, SMR, and TBR protocols. Although NFT based on complex EEG features also shows significant effects in AD/HD (e.g. Johnstone et al., 2017; Luo et al., 2022; Zhang et al., 2021), its effect has not been evaluated by this framework.

Multiple studies have taken advantage of portable EEG devices and delivered NFT in remote settings. The extensive training sessions required by clinic-based NFT can adversely affect the adherence of patients (Bussalb et al., 2019). This problem can be resolved by NFT training software using portable EEG devices. Remote NFT for AD/HD has been available since 2004 as tele-neurofeedback from clinics in the Netherlands using a wireless Bluetooth-based neurofeedback system (Brainquiry PET) - this method was also successfully used in a remote NFT study for insomnia using SMR tele-neurofeedback (Cortoos et al., 2010). Steiner et al. (2014) conducted the first RCT to examine the efficacy of remote NFT in children with AD/HD. A 40-session TBR-based NFT was run on in-school computers with EEG sensors mounted on bicycle helmets. Compared with a CT condition and a waitlist control, the NFT protocol significantly reduced ADHD symptoms rated by parents, the effect of which was maintained for 6 months after training (Steiner et al., 2014). The efficacy of in-school NFT was further confirmed with SCP and SMR protocols (Minder et al., 2018; Rajabi et al., 2020). Interestingly, Minder et al. (2018) found that the effect of NFT conducted in schools did not differ from that of NFT conducted in outpatient

clinics (Minder et al., 2018), which alleviates the concern about the quality of NFT in remote settings. While NFT has shown promise in home settings as well (Johnstone et al., 2017; Luo et al., 2022; Zhang et al., 2021), a recent large-scale noninferiority study found that at-home NFT may be less effective than front-line methylphenidate treatment in improving AD/HD symptom scores rated by clinicians (Purper-Ouakil et al., 2022). It should be noted that this study only examined the immediate effect after NFT but not the long-term effect. An earlier review reported that NFT is superior to methylphenidate in the long-term effect (Pimenta et al., 2021). These results open the discussion regarding the role of NFT at home in treating AD/HD. Together, while the efficacy of remote NFT has been demonstrated, further studies may compare its effectiveness with existing therapies and determine the optimal way of using remote NFT.

### 4.3. Transcranial electrical stimulation (tES)

#### 4.3.1. Brief introduction

Electrical stimulation has been used for treating aberrant behavior for many years (Butler et al., 2008). Interest has dramatically increased since the beginning of this century about whether or not weak currents applied to the scalp impact intracellular functioning, thereby affecting behavior (Nitsche and Paulus, 2000) - a technique called transcranial electrical stimulation (tES). Several variants of tES have been classified based on the current applied to the scalp, including transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS) (for more information, see Bikson et al., 2019). tDCS delivers anodal or cathodal direct current to targeted brain regions, whereas tACS and tRNS utilize alternating current. In contrast to tACS, which delivers a current with a specific frequency, tRNS delivers currents across a range of frequencies (e.g. between 0.1 Hz and 640 Hz in a typical full-spectrum protocol). Fig. 3 illustrates the difference between the three forms of tES. These different forms of tES modulate brain activity in different ways. While tDCS induces subthreshold changes in membrane potential, tACS trains cortical rhythmic activity to external driving frequency, and tRNS imposes random noise on neuronal processing (Bikson et al., 2019). Despite their differences, the three forms of tES share some common characteristics, such as being noninvasive, cost-effective, and portable, making them promising tools for neuropsychiatric rehabilitation (Grover et al., 2021). In light of these advantages, there have been clinical trials evaluating home-based tES treatments (e.g. Martens et al.,

2018; Park et al., 2019).

#### 4.3.2. Parameters in tES

**4.3.2.1. Intensity.** The selection of stimulation intensity is influenced by safety and efficacy. Ideally, stimulation intensity should be able to modulate neurons while causing negligible adverse effects. Conventional tES protocols use an intensity of  $\leq 4$  mA with a stimulation charge of  $\leq 7.2C$ , and while these settings do not result in reports of irreversible injury (Bikson et al., 2016), there may be possible mild adverse events, including headache, fatigue, and skin issues (Antal et al., 2017; Bikson et al., 2016). To increase tolerability, current protocols commonly use intensity from 1 mA to 2 mA (Antal et al., 2017; Bikson et al., 2016). In terms of efficacy, the evidence is less clear. Although stimulation intensity as low as 1 mA can alter membrane polarization (Herrmann and Strüber, 2017), this finding was based mostly on animal research, and the complex structure of the human brain (e.g., highly gyrated cortices) may limit a direct translation (Liu et al., 2018; Beliaeva et al., 2021). Using tACS, a lower intensity may produce a modulatory effect if the stimulation frequency matches the brain's intrinsic frequency and vice versa (Herrmann and Strüber, 2017; Liu et al., 2018). As stimulation intensity increases with tRNS, the efficacy follows an inverse U shape (Harty and Cohen Kadosh, 2019; van der Groen and Wenderoth, 2016).

**4.3.2.2. Electrodes.** Electrode placement determines the brain areas upon which the protocol will work. While the therapeutic use of tES appears straightforward - place electrodes above the brain regions which contribute to disorders - the shunting effect of current (i.e. current flowing through a low-resistance path such as skin and subcutaneous tissue) means we can only deliver a small amount of current to the targeted areas (Liu et al., 2018). Consequently, researchers tend to simulate the electrical field generated by a to-be-implemented protocol, using tools like ROAST (Huang et al., 2018) and SimNIBS (Saturnino et al., 2019) to optimize electrode placement. It is possible in some toolboxes to guide how electrodes are used to stimulate the desired regions (e.g. ROAST). In addition, more electrodes are used in protocols (also known as high-density tES) so that the current can be delivered more focally (Alam et al., 2016).

**4.3.2.3. Frequency.** A tES protocol involving alternating current, typically a sinusoidal waveform, should also consider frequency. The frequency can be selected in two ways: by individual-tuning and by fixed-

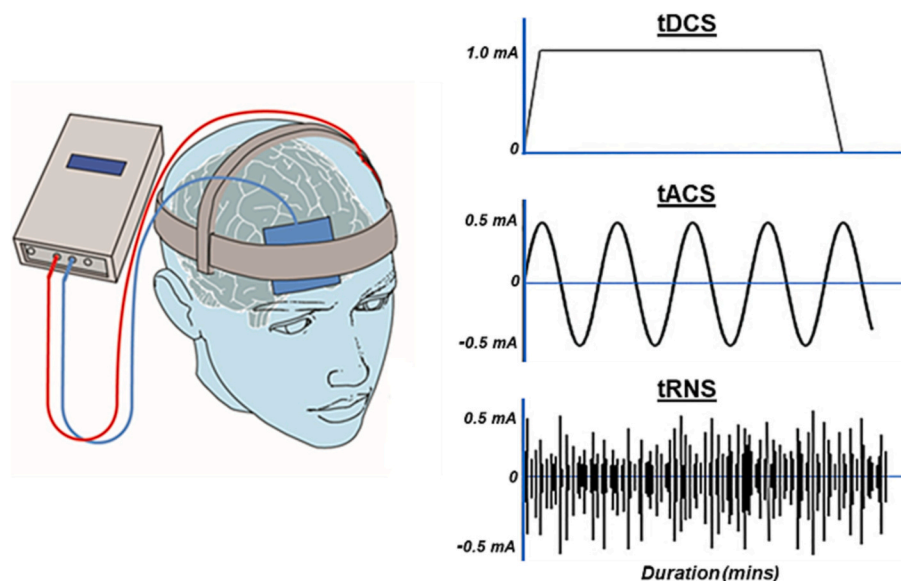


Fig. 3. A tES set-up and the electrical waveforms generated by different types of tES.

tuning. Individually-tuned stimulation involves adjusting the stimulation frequency based on the intrinsic frequency of an individual. As discussed above, even a low-intensity following this approach can have modulatory effects (Herrmann and Strüber, 2017). The frequency of stimulation, on the other hand, can be fixed across participants by convention or by a theoretical perspective. For example, a recent study used 4 Hz to slow theta activity to improve working memory (Wolinski et al., 2018). Although few studies have compared the two methods of frequency selection, a recent study suggests that individual tuning is more effective than fixed tuning with a typical intensity of 1 mA (Zhang et al., 2022). Instead of selecting a frequency, tRNS protocols should consider spectrum range: low spectrum (0.1-100 Hz), high spectrum (101-640 Hz), or full spectrum (0.1-640 Hz). Although the cutoff point of 100 Hz is arbitrary, selecting different spectrum ranges can result in distinct behavioral outcomes. Specifically, the high-spectrum tRNS appears to be more effective in enhancing cortical excitability, yet the critical difference between high- and low-spectrum tRNS may lie not in the frequencies themselves but rather in the width of the frequency band (Moret et al., 2019).

#### 4.3.3. Role of neuroplasticity in tES

Neuroplasticity is mainly modulated by tES during stimulation - role 2 - but in different ways. The membrane potential shifts to depolarization or hyperpolarization when anodal or cathodal current is delivered by tDCS. The result is that LTP or LTD can be induced more easily, which is mediated by a range of biochemical changes, such as changes in glutamate receptors, monoamine neurotransmitters, and neurotrophic factors (Yamada and Sumiyoshi, 2021). However, it remains unclear whether this modulation works on all stimulated neurons, state-dependent neurons, or network activity (Fertonani and Miniussi, 2017). As with anodal tDCS, tRNS is believed to enhance neuronal excitability (Antal and Herrmann, 2016). Potential mechanisms include voltage-gated Na<sup>+</sup> channels (Chaieb et al., 2015), GABA receptors sensitivity (Chaieb et al., 2015) and levels (Sánchez-León et al., 2021), stochastic resonance (van der Groen and Wenderoth, 2016), and the excitation/inhibition ratio (van Bueren et al., 2022). Although there is no clear understanding of the mechanism of tACS, it is widely accepted that tACS generates the tendency for depolarization or hyperpolarization according to the stimulation phase (Liu et al., 2018). Further, tACS modulates neuroplasticity by simulating GABAergic neurons at 40 Hz (Guerra et al., 2018).

The effects of tES can outlast the period of stimulation, during which both role 1 and role 2 are involved. Regarding role 1, an in-depth review has summarized the effect of after-stimulation on inducing LTP or LTD directly (Korai et al., 2021). However, LTP or LTD induced by the after-stimulation effect may differ from that induced by typical learning-induced LTP or LTD (Pell et al., 2011). After-stimulation tES also modulates neuroplasticity—role 2. The evidence for this mainly stems from tDCS studies where a priming excitatory tDCS protocol (e.g. anodal stimulation), intended to facilitate cortical response, inhibited the later response to tDCS or transcranial magnetic stimulation instead and vice versa (Hurley and Machado, 2017). The pattern can be explained by homeostatic metaplasticity (Cooper and Bear, 2012) - the priming excitatory (inhibitory) tDCS increases (decreases) the threshold for excitation, reducing (increasing) the likelihood of subsequent stimuli causing excitation.

#### 4.3.4. tES in AD/HD

Most studies examined the efficacy of tES in AD/HD in clinical or laboratory settings, mainly using tDCS. There have been two recent meta-analyses of the effect of tDCS on AD/HD (Salehinejad et al., 2020; Westwood et al., 2021a). The key finding was that anodal tDCS had a small effect size on most neuropsychological functions, including inhibition, working memory, and processing speed. However, several factors limit the effect size. Considering that empirical tDCS studies measured neuropsychological functions differently, a practical strategy to

synthesize an overall effect is to pool the effect sizes derived from different cognitive tasks, which may cause heterogeneity and underestimate the effect size (Chhatbar and Feng, 2015). Most prior research stimulated the left dorsolateral prefrontal cortex (dlPFC), yet such an approach is not effective in improving the deficient response inhibition and spatial working memory in AD/HD, which predominantly implicate the right inferior frontal cortex (Aron et al., 2004) and right dlPFC (Constantinidis and Klingberg, 2016), respectively. Interestingly, a recent study stimulated the right dlPFC and reported that tDCS resulted in fewer impulsive decisions in children with AD/HD (Nejati et al., 2022). In terms of the effect on clinical symptoms, although there has been evidence of reducing inattention by tDCS (Cachoeira et al., 2017; Soff et al., 2017), the small number of studies causes the difficulty in estimating a reliable overall effect (Westwood et al., 2021a).

One recent study extended tDCS to a home setting in adults with AD/HD (Leffa et al., 2022). To our knowledge, this is the first home-based tDCS RCT for AD/HD. The tDCS treatment consisted of 28 sessions (30 mins/session and 1 session/day) and exciting the right dlPFC with 2-mA direct current. Compared to a sham condition, the treatment group improved on inattention with a Cohen *d* of 1.23 95% CI [0.67, 1.78]. Meanwhile, the treatment group experienced manageable adverse events (e.g. tingling) and showed high adherence (25 completed, 3 dropped due to pandemic restrictions, 1 dropped due to depressive symptoms, 1 dropped for unknown reasons). These results suggest that tDCS is a promising remote treatment option for AD/HD, and further studies are needed to examine the effect of tDCS parameters (e.g. stimulation intensity and electrodes placement) to enhance the effectiveness/efficacy of the training protocol (Cosmo et al., 2020; Leffa et al., 2022).

Promising results also have been reported from the few studies using alternating currents stimulation in AD/HD. Patients with AD/HD often show a reduction in the P300 component of the event-related potential (ERP), which may indicate a deficit in attentional allocation (Johnstone et al., 2013). P300, a temporal domain feature of brain activity, can be translated into a frequency domain, falling within 0-8 Hz, thus allowing stimulation by tACS. Following this rationale, Dallmer-Zerbe et al. (2020) tested the effects of tACS on adults with AD/HD. They reported that tACS resulted in a larger P300 and fewer behavioral errors in a visual detection task (Boetzel and Herrmann, 2021). Another promising alternating-current protocol comes from Berger et al. (2021), in which a tRNS protocol targeting bilateral dlPFC improved working memory and reduced symptoms in children with AD/HD, even compared to the tDCS-dlPFC protocol, suggesting that the tRNS protocol is more effective than the commonly used protocol.

Together, the home-based tDCS trial demonstrated the feasibility of administering tES remotely and its effectiveness in treating AD/HD (Leffa et al., 2022). Meanwhile, with the promising outcomes of alternative tES methods in laboratory settings for helping AD/HD (Berger et al., 2021; Boetzel and Herrmann, 2021; Dallmer-Zerbe et al., 2020), future studies could compare the efficacy and effectiveness of home-based tDCS with other forms of tES forms. Moreover, advanced tES protocols have been developed for delivering stimulation more precisely (Alam et al., 2016), stimulating networks with high-density protocols (Saturnino et al., 2017), and targeting deep brain structures (Grossman et al., 2017), so the effect of these advanced tES protocols should be considered for treating AD/HD. Section 5.4 suggests a workflow for testing novel protocols.

### 4.4. Non-invasive cranial nerves stimulation

#### 4.4.1. Brief introduction

As part of the peripheral nervous system, cranial nerves transmit information between the brain and the rest of the body. Cranial nerves are unique in that they have direct connections with the brain and can transmit information directly. As a result of this unique feature, bottom-up neuro-modulation can be achieved by modulating the brain via

stimulation of the cranial nerves (Adair et al., 2020). Electrodes are typically attached near cranial nerves or to the cutaneous distribution of cranial nerves to deliver a low-intensity electrical current noninvasively. While there are 12 cranial nerves, this review mainly focuses on the cranial nerve stimulation that has been used for AD/HD - trigeminal nerve stimulation (TNS) – with other types of promising cranial nerve stimulation discussed below. Given the purpose of this review, TNS here only refers to transcutaneous TNS or external TNS. Fig. 4 shows an external TNS system.

Trigeminal nerves originate from the brainstem and have three afferent branches: ophthalmic, maxillary, and mandibular. The ophthalmic branch is usually targeted to deliver TNS (Regenold et al., 2022). The therapeutic use of TNS was introduced initially to treat craniofacial pain disorders and epilepsy. Due to its ability to modulate broader brain regions, it has recently been found to be useful in treating patients with higher-order cognitive dysfunctions (Adair et al., 2020; Shiozawa et al., 2014; Regenold et al., 2022). It has been hypothesized that the ophthalmic branch passed the stimulation into the brain stem, from which monoamine neurotransmitters are released, causing the “bottom-up” modulation (Adair et al., 2020; De Cicco et al., 2018). A standard external TNS device consists of a battery-powered generator connected to a set of skin electrodes delivering electrical impulses of adjustable amplitude, frequency, and duration.

#### 4.4.2. Parameters in TNS

Only limited research has been done on the effect of different TNS parameters on treatment. In this section, we present parameters of TNS generally used in clinical settings, followed by parameters used specifically for AD/HD.

Despite diverse therapeutic purposes, two TNS electrodes are often attached bilaterally to the forehead to stimulate the left and right ophthalmic branches of the trigeminal nerve. TNS generates current as a periodic bipolar-pulse train with a range of intensities (in mA), pulse frequencies of 1-200 Hz, and pulse widths of 50-250  $\mu$ S (Adair et al., 2020). As TNS can activate cutaneous A $\delta$  and C fibers to cause uncomfortable symptoms (such as pin-prick and burning pains), protocols usually allow users to adjust intensity. The effect of a high frequency may differ from that of a low frequency. Animal subjects only responded to frequencies greater than 100 Hz, which informed the design of a human study that utilized a high frequency of 120 Hz for the experimental group and a low frequency of 1 Hz for the active-control group (DeGiorgio et al., 2013). The pulse width of 250  $\mu$ S is popularized in TNS studies, which is based on the observation that this pulse width is optimal for inducing modulatory effects in adults (Lauritsen and Silberstein, 2019).

The TNS protocol for AD/HD is administered using the same parameters as for treating epilepsy and major depression disorder - bilateral pulse stimulation of the ophthalmic branch, 2-4 mA intensity, 120

Hz frequency, 250 S width, a duty cycle ratio of 1:1, for about 8 h per night over four weeks (McGough et al., 2019a). The rationale behind this protocol is that it may improve attention and brain regions implicated in ADHD (McGough et al., 2019a). While the multiple-session and overnight stimulation raised safety concerns (Schutter et al., 2019), the original research did not find any adverse effects on sleep (McGough et al., 2019b), and no serious events or cognitive loss were reported after long-term TNS in adults (Gil-López et al., 2020). Due to the paucity of direct evidence for the use of TNS in AD/HD, future studies may systematically examine if there are any side effects (e.g. potential excitation-inhibition disturbances suggested by Schutter et al., 2019).

#### 4.4.3. The role of neuroplasticity in TNS

While exact TNS mechanisms are poorly understood, there is evidence that TNS can directly induce neural changes (role 1). Cell proliferation assays were used to test the effects of TNS on brain sections cut from rats going through a 3-h TNS session (Mercante et al., 2017). Compared with a sham group, the experimental group experienced increased hippocampal cell proliferation, possibly due to an increased synaptic level of noradrenaline due to TNS on the locus coeruleus. The role 1 of TNS is also suggested by a study with human participants in which TNS-induced LTD-like plasticity at the brainstem is indexed by the blink reflex (Pilurzi et al., 2016).

The role of neuroplasticity in TNS can also be informed by studying vagus nerve stimulation (VNS). Both TNS and VNS interface with brainstem regions like the locus coeruleus, explaining their similar modulatory behavior (Adair et al., 2020; De Cicco et al., 2018). Numerous studies have shown that VNS can increase levels of neurotransmitters that modulate neuroplasticity (role 2) – noradrenaline and GABA – by activating noradrenergic neurons in the locus coeruleus and GABAergic neurons in the nucleus of the solitary tract (Adair et al., 2020; Colzato and Beste, 2020; De Cicco et al., 2018). The increased neurotransmitters were observed in subcortical structures (e.g. brainstem and amygdala, Hassert et al., 2004) and cortices (e.g. frontal and frontotemporal areas, Marrosu et al., 2003). As predicted by the proposed mechanism, VNS has successfully enhanced neuroplasticity to facilitate rehabilitation in patients (Meyers et al., 2018, 2019).

#### 4.4.4. TNS in AD/HD

In 2019 the FDA in the USA approved the marketing of a TNS device for treating children with AD/HD (FDA, 2019). The approval was based primarily on a double-blind, sham-controlled trial run with children with AD/HD (McGough et al., 2019a). Children with AD/HD were required to wear a TNS device at home while sleeping for four weeks. A description of the TNS protocol is given above. The results showed that AD/HD symptoms were significantly decreased in the experimental group with a medium effect size. The degree of reduction was significantly correlated with individual frontal EEG changes. Also, the study evaluated the impact of the treatment on patient ratings of EF, but no distinction was observed. However, this outcome could have been mitigated by the placebo effect in the sham group. Further, no serious adverse events were reported in the TNS study, and only two out of 62 participants dropped out, suggesting the protocol had a high level of tolerance and compliance. It is interesting to note that the effect size found by McGough et al. (2019a) is similar to that reported for non-stimulant medications (Faraone, 2009). The similar effect sizes could be attributed to the fact that non-stimulant medications also impact noradrenaline, one of the proposed mechanisms of TNS (Michelson et al., 2003). These results suggest the efficacy of a home-based TNS protocol for treating AD/HD, although its exact mechanism is not known. Note that this is the only TNS trial run in AD/HD, and the results should be replicated. In addition, it is unknown if the parameters used in the study are ideal and the long-term effect of the protocol. Moreover, a follow-up study showed that participants with lower EF at baseline responded better to TNS treatment, suggesting individual differences (Loo et al., 2021).

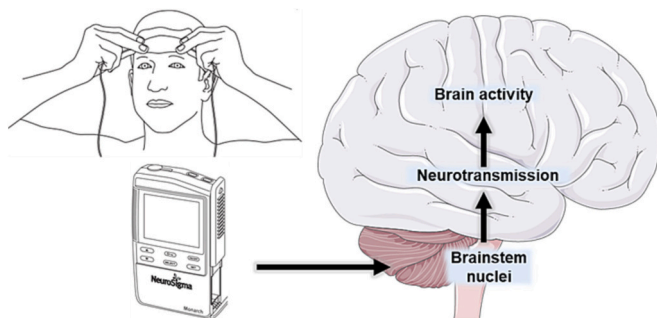


Fig. 4. An external TNS system and its possible mechanism. The system called Monarch eTNS is an FDA-approved medical device for treating children with AD/HD (FDA, 2019). The electrode is attached around the facial distribution of the trigeminal nerve. The external TNS might modulate brain activity via stimulating the brainstem nuclei – a bottom-up modulation (Adair et al., 2020).



Besides TNS, other types of cranial nerve stimulation may also benefit AD/HD patients. TNS is the only cranial nerve stimulation used to treat AD/HD to date, but transcutaneous VNS treatment has been highlighted for use in AD/HD (Zaehle and Krauel, 2021). Transcutaneous VNS and TNS share common features such as noninvasiveness and portability, use of a similar current generator, and possible use of a similar mechanism. Despite this, their effects on AD/HD may differ in efficacy since different afferent nerves are involved in stimulation. In addition, there have been other forms of noninvasive cranial nerve stimulation that can modulate the abnormal brain regions in AD/HD; for example, olfactory nerve stimulation modulates the prefrontal cortex (Adair et al., 2020), which deserves further consideration in the future research.

## 5. General discussion

### 5.1. Remote $\neq$ "DIY"

In light of the advancement in neurocognitive interventions and the demand for more accessible interventions in AD/HD, this paper reviewed neurocognitive interventions that can be conducted in remote settings (e.g. at home and in schools). It should be noted that "remote" does not imply DIY (i.e. "do it yourself"). In fact, two FDA-approved alternative treatments are prescribed. Several interventions described here seem to be easy to obtain. Searching the internet for terms like "cognitive training" or "tDCS" can lead to multiple commercial products or even manufacturing manuals. Nevertheless, the same technique can be employed with various protocols, resulting in null or adverse effects (Stojanoski et al., 2021; Wurzman et al., 2016). Additionally, even when experiencing the same protocol with the same device, individuals may respond differently (Loo et al., 2021; Wiemers et al., 2019).

### 5.2. One size does not fit all

The effectiveness of remote neurocognitive interventions may vary among individuals. Although the FDA-approved TNS showed a medium effect size on improving AD/HD symptoms at the group level (McGough et al., 2019a), a later 'responder analysis' indicated that only those with poor neurocognitive performance and higher levels of abnormal EEG power will be more likely to benefit from the TNS protocol (Loo et al., 2021). Even though the RCT study which underpins the FDA's permit for cognitive training in AD/HD is not available for such analysis due to its subsampling, relevant research in other populations has indicated that individuals respond differently to cognitive training (e.g. Wiemers et al., 2019), suggesting that there might be individual differences to the treatment effects of cognitive training in AD/HD. The individual difference may also be true for other forms of neurocognitive training, for example, NFT (Arns et al., 2012; Su et al., 2021), VNS (Brázdil et al., 2019), and tES (Chew et al., 2015; Lipka et al., 2021).

To address these individual differences, pre-intervention neuropsychological and brain measures can be used to identify individuals most likely to benefit from remote neurocognitive interventions. AD/HD is characterized by heterogeneity in neuropsychological and brain profiles (Nigg et al., 2020). Combining neuropsychological with brain measures has shown promise in revealing the nature of the disorder (e.g. Jacobs et al., 2021; Johnstone et al., 2021; Lipka et al., 2021). Similarly, both measures have demonstrated their unique value in predicting intervention effects (Michellini et al., 2022; Nemmi et al., 2016; Harty and Cohen Kadosh, 2019). It is worth noting that significant efforts have been made to measure neuropsychological and brain measures using mobile recording approaches in AD/HD (Marzena Oliveira et al., 2023; Lau-Zhu et al., 2019; Johnstone et al., 2021). This progress motivates future studies to explore the potential of turnkey solutions that combine a predictive module based on remote neuropsychological and brain recording with a remote intervention module in the direction of personalized remote neurocognitive interventions.

The demographic background of individuals can also be used to personalize treatment protocols. The manifestation of AD/HD can vary depending on age, gender, and culture (American Psychiatric Association, 2013). Such differences may indicate specific situations where remote neurocognitive interventions can be particularly beneficial. For example, since inattention is more prominent in adulthood (Faraone et al., 2021), in females (Biederman et al., 2002), and in Eastern individuals (Davis et al., 2012), remote neurocognitive training focused on attention might be more effective in such cases. Thus, future studies could also consider incorporating demographic variables in 'responder analyses' to further inform the circumstances under which remote neurocognitive interventions are most effective.

The methodology for 'responder analyses', however, deserves attention. A commonly used approach involves regressing the change in an outcome (e.g., the pre-post difference in AD/HD symptoms) on predictive variables (e.g., the patient's pre-intervention cognitive profile). In one variation of this approach, the continuous change is categorized, and the difference between the pre-post intervention change and the post-intervention change is compared between "responders" and "non-responders" (e.g. the top 30% against the bottom 30%). The regression to the mean caused by measurement errors may compromise the approach and result in false negative predictions – the worse gets better (Smoleń et al., 2018; Tidwell et al., 2014). To avoid false prediction, one may consider the residualized model, for example, regressing the post-intervention symptom on the pre-intervention symptom and the cognitive profiles. However, the approach may suffer from collinearity and underestimate the predictive value of the variable of interest (for additional discussion and suggestions, please see Castro-Schilo and Grimm, 2018).

Another approach to be considered is stratified psychiatry (Arns et al., 2022), where patients are stratified between a range of active treatments (such as the treatments covered in this review) based on a biomarker. In this case, since patients will always be stratified to an active treatment, lower sensitivity and specificity are required. This approach was recently successfully demonstrated to stratify AD/HD patients between NFB and Methylphenidate, confirmed after blinded out-of-sample validation (Voetterl et al., 2022).

### 5.3. Combined approach and neuroplasticity

A feature of the current review is highlighting the role of neuroplasticity in remote neurocognitive interventions. While some interventions rely on neuroplasticity so that abnormal brain activity can be rectified, others can enhance neuroplasticity. It seems, therefore, that combining the two types of interventions may result in a more effective protocol.

Developing a valid combined intervention, however, requires a clear understanding of the role that neuroplasticity plays in each elemental intervention, particularly when elements of interventions involve multiple roles for neuroplasticity (e.g. NFT, tES, and external TNS). Examining the combination of tES and CT, for instance, a popular hypothesis suggests that tES can enhance the neuroplasticity necessary for CT to function. However, things are more complicated. One study combining tES with CT found that the effects were a function of stimulation intensity with an inverse-U shape (Ehrhardt et al., 2021). Moreover, despite the suggestion that both tRNS and tDCS enhance cortical excitability, inconsistent effects have been reported when they are combined with CT. – While CT combined with tRNS elicited larger gains in AD/HD (Dakwar-Kawar et al., 2022), CT combined with tDCS reduced training gains in normal and AD/HD populations (Au et al., 2021; Westwood et al., 2021b). The inconsistent results may be caused by the complex role of neuroplasticity in tES. According to Section 4.3.4, tES can trigger and modulate neuroplasticity, thus leading to alternative effects, such as a null effect when the protocol of tES only trigger the overlapping neuroplasticity as CT does, or a negative effect when the protocol of tES also causes homeostatic metaplasticity, which negatively affects the

memory consolidation stage of CT. Considering that the roles of neuroplasticity may vary on parameters in tES protocols, future studies should provide a clear picture mapping between the roles and the parameters, thereby facilitating the design of an effective combination.

#### 5.4. From pilot to evidence-based practice

Most of the interventions considered are in their infancy. In addition, the combined approach may inspire more studies that take advantage of each elementary intervention in its entirety. Based on the methodological agreement on behavioral interventions (Shawn Green et al., 2019) and evidence-based practice (Southam-Gerow and Prinstein, 2014; Tolin et al., 2015), we highlight some relevant considerations when developing evidence-based remote neurocognitive interventions for future studies.

There are four kinds of interventional research - feasibility, mechanistic, efficacy, and effectiveness (Shawn Green et al., 2019). Our discussion is not concerned with mechanistic studies, as the mechanism may have been investigated in other situations. Instead, we aim to determine if the effect can be achieved via remote delivery. Therefore, the following is only concerned with the other types of studies. The development of a new intervention often begins with feasibility studies (also known as pilot studies). Differing from different types of studies, studies of feasibility do not require a control group and a precise estimate of sample size, since their goal is to prove the feasibility of a project by collecting data on practical measures (e.g. dropping out rate and reasons, tolerance, and user experience), as well as the clinical outcomes that are of interest (e.g. neurocognitive functions). This type of research is generally regarded as unpublizable due to its preliminary nature. Journals, however, become increasingly friendly to feasibility studies (Shawn Green et al., 2019), such as for neurocognitive training through remote control (Ha et al., 2022), as they can also contain information that researchers might be interested in (e.g. if children with AD/HD can complete the intervention at home with minimal help).

In the case of positive feasibility results, it is possible to move on to efficacy and effectiveness studies. Efficacy studies are usually conducted before effectiveness studies to ensure that observed effects are caused by the core manipulation in the intervention but not by non-experimental factors (e.g. nature development during intervention sessions and participants' expectations about the use/effectiveness of high-tech products). Thus, in addition to measuring the outcome of interest, selecting an appropriate control group is particularly important (Singal et al., 2014; Shawn Green et al., 2019). An established efficacy may direct research attention to investigate the real-world impacts of an invention through an effectiveness study. In comparison to efficacy studies, effectiveness studies have higher external validity and generalize better to clinical settings because they recruit unconstrained participant samples (e.g. children with AD/HD with comorbidities) and have fewer restrictions on how interventions are conducted (e.g. scheduling interventions as one sees fit). Furthermore, effectiveness studies often compare a new intervention to an existing intervention, such as comparing a remote neurocognitive intervention with Ritalin in AD/HD.

Despite the difference, efficacy and effectiveness studies are similar in measuring and analyzing the interventional effect. In our case, both types of studies measure symptoms of AD/HD as well as neurocognitive functions. Additionally, it should be noted that quality of life has been emphasized increasingly in AD/HD research (Coghill et al., 2009) as well as remission instead of response (Arns et al., 2020). Considering that remote neurocognitive interventions may provide patients with greater convenience, future research may examine whether this can be an advantage. Effectiveness and efficacy studies typically involve group-level statistics. We suggest that future studies may consider a follow-up responder analysis, as discussed in Section 5.2, to examine individual differences in response to interventions. Ideally, this analysis can be conducted directly from efficacy and effectiveness studies; however, this requires researchers to design their studies so that all the measures

needed for the responder analysis are collected simultaneously.

With increasing research, remote neurocognitive interventions can be assessed further based on evidence-based practice to inform patient care decisions. A framework proposed by the American Psychological Association laid the foundation for synthesizing evidence (Chambless and Hollon, 1998), but has been criticized (Southam-Gerow and Prinstein, 2014; Tolin et al., 2015). Recommendations, such as not only focusing on symptom reduction but also effect size and using systematic and meta-reviews but not independent studies, are made to rate evidence more strictly (Southam-Gerow and Prinstein, 2014; Tolin et al., 2015). The remote neurocognitive interventions reviewed here, including those permitted by the FDA, have not been subjected to such an assessment, and this might be done in the future if conditions (e.g. the number of independent studies) are met.

#### Declaration of Competing Interest

None.

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