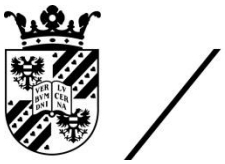
Neuroscientific insights into *executive functions*

From brain waves to behavioral improvements through neurofeedback

Diede Smit



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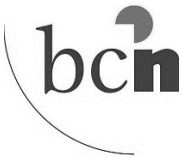

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Chapter 1

General introduction

GENERAL INTRODUCTION

Humans possess a remarkable capacity for adaptive, self-directed, and goal-oriented behavior. We can evaluate ideas and risks, formulate goals, plan and prioritize our actions, initiate and shift between tasks, solve problems, control our emotions and impulses, and adapt flexibly to changing circumstances or new situations. These capacities are known as executive functions (EFs), which encompass a wide range of separable but interconnected higher cognitive functions (Karr et al., 2018; Barkley, 2012; Lezak et al., 2012). EFs can override well-learned automatic or instinctive behavior in favor of more effortful non-routine behavior based on plans or intentions (Norman & Shallice, 1986; Diamond, 2013). When EFs are intact, individuals can have different sensory, motor, and/or cognitive impairments, and still be able to display self-serving, creative, and socially constructive behavior in daily life (Lezak, 1982). Unfortunately, difficulties regarding EFs are frequently self-reported in both the working population (Stenfors et al., 2013) and elderly population (Slavin et al., 2010), and EF impairments are seen as a transdiagnostic feature of psychopathology (Snyder et al., 2015; Abramovitch et al., 2021) and neurological conditions (e.g., Chiaravalloti & DeLuca, 2008; Muslimović et al., 2005). Individuals with impairments in EFs may show problems with tasks that require planning, organizing, and completing complex activities, such as multi-step work assignments or managing finances (Brown, 2009), as well as difficulties with for instance impulse control, problem solving, and activities that require flexibility, such as changing plans or adapting to new situations (Roth et al., 2005). Impairments in EFs tend to be supramodal, meaning they can have significant consequences in different areas of life, including school dropout, occupational problems, poorer interpersonal relationships, criminal behavior, poorer mental and physical health, and lower quality of life (Low et al., 2021; Diamond, 2013; Williams & Thayer, 2009). The impact of such consequences is profound and impose high direct and indirect costs on society, such as social welfare benefits, court cases and criminal convictions, hospital admissions, and prescription drugs (e.g., Richmond-Rakerd et al., 2020). Therefore, effective interventions are needed that can alleviate impairments in EFs as well as optimize EFs throughout the general population, yielding benefits for both individuals and wider society.

Treatment of executive function impairments

Currently, there are no widely accepted standardized protocols or guidelines for the treatment of EF impairments. There are some treatment options available, but their effectiveness varies. One possible intervention is Goal Management Training (GMT), which is designed to teach individuals to be aware of their deficits and improve EFs in daily life (Levine et al., 2000). GMT typically involves psychoeducation, real-life examples, mindfulness exercises, and other assignments. Studies have shown that GMT can lead to small to moderate improvements in (everyday) EF task performance and self-report ratings of EFs, which can be maintained during follow-up evaluations (Stamenova & Levine, 2018). Another intervention is cognitive-

behavioral therapy (CBT), which focuses on addressing specific cognitive and behavioral patterns associated with EF impairments. CBT can help individuals to learn coping strategies and skills to manage their EF difficulties in daily life (e.g., Ramsay, 2007; Solanto, 2011; Ellis et al., 2022), however, more systematic research is needed to establish its effectiveness. Computer-based cognitive training is another treatment option that involves the repeated stimulation of the affected EF, such as working memory training (Melby-Lervåg & Hulme, 2013). However, there is limited evidence for the effectiveness of this treatment for EF impairments (Van de Ven et al., 2016). Other interventions for EF impairments include, among others, physical exercise, mindfulness meditation, and pharmacological treatments, however, their effectiveness is not (yet) fully established. In general, it appears that most interventions aimed at enhancing EFs yield only immediate, specific effects (e.g., only improvement in specific types of tasks) that do not generalize to other domains or daily life (Diamond & Ling, 2016).

In recent decades, interest has grown in using neuroscientific interventions to directly target the underlying (pathophysiological) neural mechanisms of cognition and behavior, including techniques such as neurofeedback (NF), transcranial direct current stimulation, and transcranial magnetic stimulation (Clark & Parasuraman, 2014; Enriquez-Geppert et al., 2013a). Among these interventions, NF is particularly promising because of its active approach involving learning, potentially leading to more sustainable long-term effects. Before delving deeper into NF as a neuroscientific intervention to improve EFs, it is important to first explain more about the assessment of EF impairments and how the brain implements EFs.

Assessment of executive function impairments

There is generally agreement that EFs can be defined as a complex set of cognitive processes that: (i) serve to guide action and behavior essential to learning and everyday performance, (ii) involve monitoring and regulation, and (iii) are not limited to the cognitive domain, but extend to the socioemotional and behavioral domains of human performance (Baggetta & Alexander, 2016). However, identifying impairments in EFs is challenging due to the complexity of the construct and heterogeneity in EF conceptualizations and operational definitions. This leads to variation in how EFs are assessed and measured, making it difficult to compare findings across studies.

In this thesis, the model by Miyake and colleagues (2000b) is adopted in which three core EFs are distinguished: set-shifting (i.e., shifting between tasks, operations, or mental sets), working memory updating (i.e., monitoring incoming information, determining its relevance, and updating outdated or irrelevant information with new and more pertinent information), and response inhibition (i.e., inhibition of dominant, automatic, or prepotent responses). Based on follow-up studies (e.g., Enriquez-Geppert et al., 2010), a fourth core EF is added: conflict monitoring (i.e., detection of conflicts in information processing). This model of EFs was adopted because these are the most independent and representative EFs that are highly

specific and can be accurately defined. Furthermore, behavioral and imaging studies have consistently separated them based on underlying neural and functional mechanisms, even though they do share some underlying commonality (e.g., Friedman & Miyake, 2017; Enriquez-Geppert et al., 2010). In turn, these four core EFs support more complex higher-order EFs, such as reasoning, planning, and problem solving (Diamond, 2013), and control and coordinate primary cognitive processes such as attention and memory (e.g., Friedman & Miyake, 2017).

In clinical practice, EFs are often measured using standardized objective tests, like the Trail Making Test, Tower of London task, or Wisconsin Card Sorting Test. However, relying solely on such tests can be problematic as individuals with EF impairments may perform normally in highly structured and formal examination settings (e.g., with clear instructions, well-specified goals, etc.), despite experiencing challenges in their daily lives (Lezak, 1982). One issue with using such complex standardized or "frontal" tests is that they involve multiple core and/or higher-order EFs as well as non-EF cognitive processes, resulting in what is called task impurity (Randolph & Chaytor, 2022; Suchy et al., 2017). Additionally, individuals may successfully compensate for their impairments, leading to inaccurate assessment results. Furthermore, these tests have low reliability and construct validity, lack ecological validity, and may have insufficient sensitivity and specificity to detect more subtle EF impairments (Miyake et al., 2000a).

Although more sensitive computerized tasks with better construct validity exist that can assess specific core EFs (e.g., Flanker, Simon and Stroop tasks for conflict monitoring), these are typically only used in research settings and not widely applied in clinical practice. This is probably because there is no established normative data available to determine cut-off scores or percentile scores for these tests based on the individual's demographics, such as age, gender, educational level, and ethnicity, which are needed to estimate current and premorbid level of functioning (Suchy et al., 2017). As a result, these objective tests are not ideal for assessing EF impairments in clinical settings. However, they can be useful to track changes in EFs over time in individuals when repeated assessments are conducted, and can be used in combination with neuroimaging techniques such as electroencephalography (EEG) or functional magnetic resonance imaging.

In conjunction with objective EF tests that aim to measure the best possible performance, EF impairments can be assessed using self-report measures of experienced problems in daily life. Subjective self-report EF measures offer the advantage of providing insight into an individual’s own perspective of their average or typical EF functioning in everyday life. As such, they are considered as an indispensable tool for the assessment of everyday cognition (Rabbitt et al., 1995). Self-report measures may be more sensitive in detecting mild EF impairments, which often manifest as sporadic functional lapses occurring intermittently amidst apparent normal functioning (Suchy et al., 2017). Furthermore, self-report ratings of EFs during childhood

appear to be better predictors of impairment in major life activities and occupational functioning during adulthood than standardized objective EF tests (Barkley & Fischer, 2011). However, psychological factors may contribute to the subjective experience of EF complaints. For example, certain personality traits (Koller et al., 2019; Slavin et al., 2010), negative affective states such as depressive symptoms, anxiety, and stress (Van Patten et al., 2022; Rönnlund et al., 2013), and self-efficacy (Facal et al., 2020). Hence, self-reported EF complaints in daily life do not necessarily correspond to objective measurable EF impairments on standardized tests (e.g., Buchanan, 2016; Meltzer et al., 2017; Burmester et al., 2016). This latter could also be partly explained by lack of disease insight in individuals with more severe EF impairments (Raffard et al., 2009).

Taken together, the complexity of assessing the EFs construct calls for a more holistic approach, taking into account that EFs are the result of a dynamic interaction between biological, psychological, and social factors (Havelka et al., 2009; Engel, 1980). Such a biopsychosocial model suggests that EFs are shaped by a complex interplay of factors such as genetics, brain development, health status, emotions, motivation, attitudes and beliefs, education and occupation, support network, and cultural factors. Therefore, this conceptual model (see Figure 1) offers a more comprehensive and integrated approach to understanding and assessing both subjective self-reported EF complaints and objective impairments in EFs.

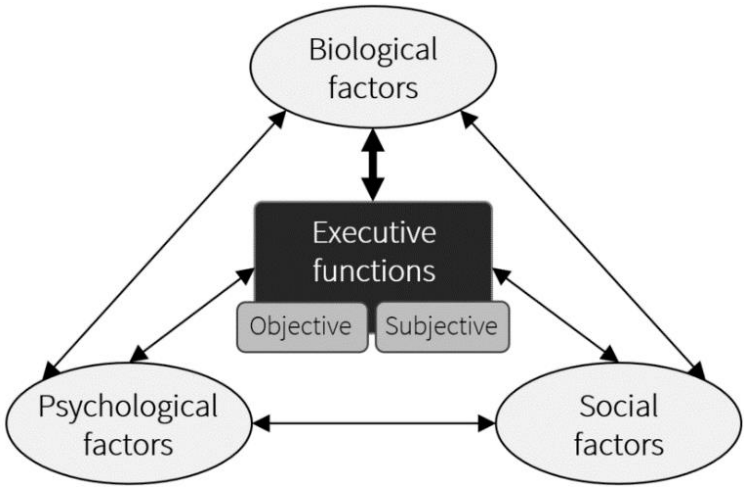

Figure 1. Biopsychosocial model of executive functions (after Havelka et al., 2009).

Neural underpinnings of executive functions

Despite the complex interplay of various biological, psychological and social factors contributing to EFs, this thesis considers efficient underlying neural mechanisms as the primary biological determinant or prerequisite for adequate EFs in daily life. Understanding the fundamental neural mechanisms that underlie EFs can provide valuable insights into their

nature and give important directions for the development and adaptation of interventions aimed at directly addressing the underlying (pathophysiological) mechanisms to potentially alleviate EF impairments and optimize EFs in healthy individuals.

The concept of EFs first emerged from impairments observed in patients with frontal lobe lesions, such as the famous case of Phineas Gage (e.g., Damasio et al., 1994). With the advent of functional neuroimaging, it has become clear that EFs depend on distributed neural networks encompassing the prefrontal cortex as well as several other interconnected brain regions. One of the largest meta-analyses to date by Niendam and colleagues (2012), including 193 functional neuroimaging studies of 2832 healthy adults, demonstrated that a broad range of EFs rely on a superordinate cognitive control network including the midcingulate cortex (MCC; widely referred to as dorsal anterior cingulate cortex [Vogt, 2016]), dorsolateral prefrontal cortex (DLPFC), and parietal cortex. The highly connected MCC supports monitoring and detecting of conditions, such as conflicts in information processing, that require cognitive control (Cavanagh & Frank, 2014), and relays this information to the parietal cortex and DLPFC (Niendam et al., 2012). Based on the information from the MCC, the parietal cortex updates task representations and biases relevant stimulus-response associations (Brass et al., 2005), and in turn informs the DLPFC about stimulus salience and learned stimulus-response pairings (Niendam et al., 2012). The DLPFC is involved in directing attentional focus to the demands of the task and enhancing the processing of target information, making it a crucial controller (Egner & Hirsch, 2005; Smith et al., 2019). Depending on the specific requirements of the EF task at hand, the brain regions in this superordinate network may be differentially engaged and additional cortical and subcortical regions may also be recruited (Niendam et al., 2012). For instance, the right inferior frontal cortex plays an important role in response inhibition (Aron et al., 2014).

The synchronization of neural oscillations is one fundamental mechanism by which brain networks communicate and enable various cognitive processes (Voytek & Knight, 2015; Fries, 2005). Neural oscillations, or brain waves, refer to the rhythmic or repetitive patterns of electrical activity generated in the central nervous system (Buzsáki & Draguhn, 2004; Donoghue et al., 2022). When faced with an unforeseen change in the environment and the habitual neuronal responses are insufficient to support goal-directed behavior, our neurons adapt by coordinated joint firing of action potentials in a synchronized rhythm. As a result, a large number of neurons (i.e., neuronal assemblies) form a functional network throughout the brain, allowing us to make necessary behavioral adjustments. In response to events requiring EFs (e.g., novelty, conflict, or errors), theta (θ) oscillations are generated, amongst others, in the MCC at a frequency between 4 and 8 Hz (Cavanagh & Frank, 2014; Eisma et al., 2021). This phasic task-related modulation in theta can be dissociated from tonic theta oscillations present at rest, and is widely regarded as a general mechanism reflecting the implementation of cognitive control for optimally adjusting behavior (Mitchell et al., 2008).

Two neurophysiological markers of EFs related to theta oscillations have been identified:

1. *Theta power at the frontal-midline (FM)*
   Tasks requiring EFs are accompanied by increases in FM theta power, reflecting the synchronization of neurons belonging to FM theta source regions such as the MCC (Cavanagh et al., 2012; Cooper et al., 2017). Higher levels of FM theta power are related to enhanced neuronal spike-field coupling within the theta band and the phase of the population theta cycle, and provide temporal windows for segregating cortical populations in order to separate information intake (Helfrich & Knight, 2016; Cavanagh & Frank, 2014). In turn, healthy individuals showing such an increase in FM theta power perform better on tasks that assess the core EFs: set-shifting (Cooper et al., 2017), working memory updating (Itthipuripat et al., 2013), response inhibition (Nigbur et al., 2011), and conflict monitoring (Eschmann et al., 2018).
2. *Functional theta connectivity within the superordinate network*
   Depending on the specific demands of the EF task, brain regions within the superordinate cognitive control network and complementary brain regions are activated simultaneously and synchronize, allowing control mechanisms to be executed efficiently (Womelsdorf et al., 2010; Cavanagh & Frank, 2014). This phase synchronization reflects functional connectivity or communication between cortical hubs (Cooper et al., 2017), which plays an important role in uptake, processing, and exchange of information between different brain regions within neural networks (e.g., Fries, 2015). Healthy individuals show increased functional theta connectivity in fronto-parietal brain regions during EF tasks assessing set-shifting (McKewen et al., 2021), working memory updating (Mizuhara & Yamaguchi, 2007), response inhibition (Harmony et al., 2009), and conflict monitoring (Cohen, 2014a).

According to a review by McLoughlin and colleagues (2021), task-related theta oscillations are affected in a range of disorders with known impairments in EFs, such as attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder, and substance abuse. Both disturbances in upregulating FM theta power and functional theta connectivity in the superordinate network can lead to inefficient recruitment of cognitive control processes resulting in impaired EFs (e.g., Ryman et al., 2018; Missonnier et al., 2013; Michelini et al., 2019). The role of FM theta oscillations in the implementation of EFs, along with the relationship between changes in these oscillations and EF impairments, highlights FM theta as a promising target for enhancing and optimizing EFs. Neuroscientific interventions, such as NF, can specifically address these underlying (pathophysiological) FM theta oscillations, providing a direct means of intervention.

Neurofeedback as intervention to improve executive functions

NF is a non-invasive neuroscientific approach that uses a closed-loop brain-computer interface consisting of a five-element processing pipeline (Enriquez-Geppert et al., 2017). As Figure 2 shows, the participant's brain activity is measured (Step 1) and pre-processed online

(Step 2). Next, specific brain features, such as a frequency band, are extracted (Step 3) and translated into signals that are fed back to the user in real-time (Step 4), for instance visual or auditory, making these brain features perceivable for the participant. This feedback guides the participant in learning to self-regulate those brain features (Step 5), with the end goal of directly altering the underlying neural mechanisms of cognition and behavior (Marzbani et al., 2016; Batail et al., 2019; Loriette et al., 2021). It is assumed that the learning mechanisms of NF are based on principles of operant (or instrumental) conditioning, skill learning, and motor learning (Sitaram et al., 2017; Enriquez-Geppert et al., 2017). Consequently, NF training is expected to induce neuroplasticity (Ros et al., 2014), which could lead to more long-term persistent effects (Van Doren et al., 2019; Garcia Pimenta et al., 2021).

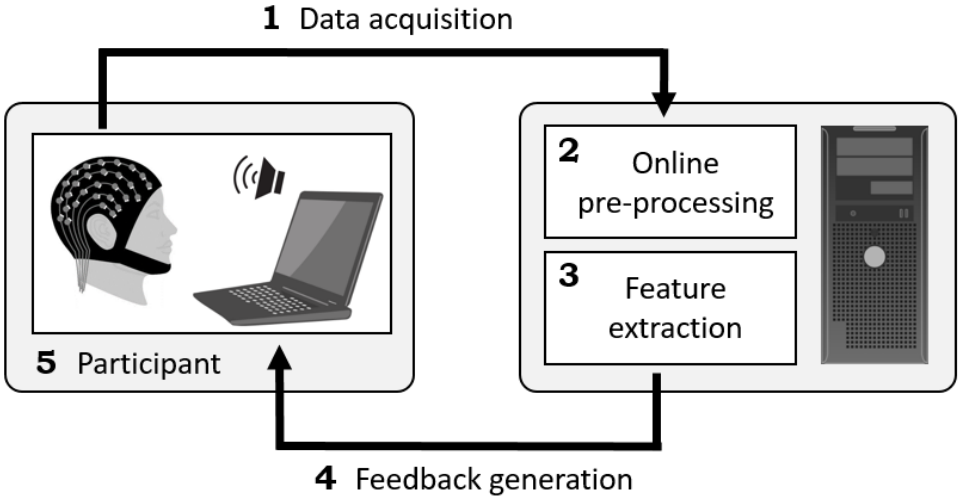

Figure 2. Neurofeedback processing pipeline.

According to a recent systematic review by Viviani and Vallesi (2021), NF is promising in effectively improving EFs in healthy adults, especially when applying a FM theta power protocol. To date, four published studies have specifically evaluated the effect of upregulating FM theta power through multiple sessions of NF on EFs in both healthy young and older adults, including Eschmann and Mecklinger (2022), Brandmeyer and Delorme (2020), Enriquez-Geppert and colleagues (2014a), and Wang and Hsieh (2013). In all these studies, the experimental NF group showed a significantly greater increase in FM theta power than the active control group during the NF training. Importantly, immediately after the NF training, they also found behavioral improvements on objective EF tests building mainly on proactive cognitive control, a preparatory process that anticipates and prevents interference from occurring (Braver, 2012). Reactive cognitive control, on the other hand, refers to transient control processes carried out after the perception of a stimulus, such as a high interference event, seems less affected by FM theta NF. The results of these studies suggest that FM theta

NF can effectively improve objective EFs in healthy adults immediately after training, paving the way for further research into its (long-term) potential as an alternative intervention for EFs in (sub)clinical samples.

Aims and outline of the thesis

The main goals of this thesis are to deepen our understanding of EFs, examining both objective and subjective aspects, with a specific emphasis on adults who self-report EF complaints in their daily lives, and explore the effectiveness of NF. Following the biopsychosocial model (Havelka et al., 2009), EFs are conceptually considered to be the result of a complex dynamic interplay of various biological, psychological, and social factors. The first chapter focuses on the biological aspect and evaluates the neurophysiological markers underlying EFs in adults self-reporting EF complaints. As a next step, the subsequent two chapters focus on assessing the effects of NF as a neuroscientific intervention method that directly targets the underlying neurophysiological marker FM theta power. This assessment involves examining the effects of FM theta NF training on objective and subjective EFs in a (sub)clinical population self-reporting EF complaints as well as the overall effectiveness of the FM theta NF protocol in upregulating FM theta power across multiple studies. In the final chapter, the focus shifts from the biological factors underlying EFs to the evaluation of its self-reported psychological predictors in the general population. A more detailed description of each chapter is provided below.

In Chapter 2, we investigate theta power and functional theta connectivity as neurophysiological markers of the four core EFs. We study these markers in three groups: adults self-reporting EF complaints with a diagnosis of ADHD, adults self-reporting EF complaints without a diagnosis, and controls who do not report any complaints regarding EFs.

In Chapter 3, the immediate and long-term effects of an individualized eight-session FM theta NF training on objective and subjective EFs are assessed in a sample of adults self-reporting EF complaints in daily life with or without a psychiatric disorder.

In Chapter 4, a mega-analysis is conducted combining raw data from multiple studies applying FM theta NF in healthy or (sub)clinical samples in order to evaluate its overall effectiveness on the upregulation of FM theta. Additionally, predictors of FM theta upregulation success and differences between NF responders and non-responders in terms of demographics are assessed.

In Chapter 5, it is explored which psychological factors best predict self-reported EFs in daily life (as well as self-reported functioning in the cognitive domains of memory and attention). The study considers factors such as personality traits, negative affective states, and demographic information in a large community sample of adults.

In Chapter 6, the main findings of this thesis and implications for research and practice are discussed.

Chapter 2

Theta power and functional connectivity as neuro-physiological markers of executive functions in individuals with self-reported executive function complaints in daily life

Smit, D., Trevino, L., Mohamed, S. M., & Enriquez-Geppert, S. (2023). Theta power and functional connectivity as neurophysiological markers of executive functions in individuals with cognitive complaints in daily life. *Biological Psychology, 178, 108503.*
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ABSTRACT

Impairments in executive functions (EFs) are common across psychological disorders. Research into the neural oscillations underlying EFs has the potential to help understand these impairments and contribute to the development of interventions. The aim of this study is to assess theta power and functional theta connectivity in the sensor space of the regions of the superordinate network for the core EFs: conflict monitoring, response inhibition, set-shifting, and working memory updating. We recruited adults with self-reported everyday EFs complaints and formed two groups: one with attention deficit hyperactivity disorder (ADHD) (n = 27) and another without any diagnosis (n = 22), and compared them to controls (n = 21) on the Stroop, Stop-signal, Switching, and N-back task using EEG. Power and functional connectivity analyses were conducted for four regions of interest: frontal-midline, frontolateral left and right, and parietal region. For all four EFs, the groups showed a dynamical increase in theta power over time in the four regions of interest, as well as in functional theta connectivity between these regions. Group differences were found especially for conflict monitoring, with differences in theta power in the frontal-midline and frontolateral right region. These neural markers are also associated with behavioral performance and complaints in daily life. For set-shifting, group differences were less pronounced and for response inhibition and working memory updating no group differences were observed.

1. INTRODUCTION

Cognitive impairments occur across various psychological disorders (Abramovitch et al., 2021) and are associated with disturbed neural oscillations in underlying brain networks (Başar & Güntekin, 2008; Uhlhaas & Singer, 2006). Executive functions (EFs) are particularly affected and are considered a transdiagnostic dimensional feature and a key impairment across psychological disorders (Snyder et al., 2015). EFs is an umbrella term encompassing a broad range of separate, but interrelated higher mental processes (Friedman & Miyake, 2017; Karr et al., 2018). EFs enable us to successfully engage in adaptive, independent, and goal-driven behavior (Diamond, 2013; Friedman & Miyake, 2017). Despite their broad nature, four core EFs have been established: conflict monitoring, response inhibition, set-shifting, and working memory updating (Miyake et al., 2000b; Enriquez-Geppert et al., 2010). EFs are frequently referred to as cognitive control processes, as they facilitate other cognitive functions, such as memory and attention (e.g., Friedman & Miyake, 2017). Intact EFs are needed to set goals and adapt flexibly to changing circumstances (Burgess & Simons, 2005). Therefore, impaired EFs can greatly affect independence in daily life, functional outcomes, and quality of life (e.g., Vaughan & Giovanello, 2010; Zhang et al., 2021; Mohamed et al., 2019).

The largest meta-analysis to date by Niendam and colleagues (2012) shows that EFs rely on a superordinate fronto-cingulo-parietal network involving the midcingulate cortex (MCC; widely referred to as dorsal anterior cingulate cortex [Vogt, 2016]), dorsolateral prefrontal cortex (DLPFC), and parietal cortex. Other very similar and overlapping networks have been described in the literature (e.g., Duncan, 2010; Camilleri et al., 2018; Cole & Schneider, 2007; Vincent et al., 2008), and recently Menon and D'Esposito (2022) have identified six networks that play a role in EFs, confirming the relevance of these brain areas. In general, the highly interconnected MCC monitors and detects conditions that require cognitive control and signals this information to the parietal cortex and DLPFC (Niendam et al., 2012). The parietal cortex updates relevant stimulus-response associations and task representations (Brass et al., 2005) and provides the DLPFC with information about stimulus salience and learned stimulus-response associations (Niendam et al., 2012). Additionally, the parietal cortex in its turn also modulates the MCC during multisensory action monitoring (Vogt, 2016). The DLPFC interconnects neural networks to nearly all cortical sensory systems, motor systems, and many other subcortical structures (Miller & Cohen, 2001), and is involved in directing attention to task demands and reinforces processing of target information (Egner & Hirsch, 2005). As such, the MCC can be seen as a monitor and the DLPFC as a controller (Smith et al., 2019). In addition, depending on the

specific task demands and required EFs, other brain areas also contribute to the superordinate network (Niendam et al., 2012), for example the right inferior frontal cortex in case of response inhibition (Aron et al., 2014).

Coordinated activity in networks of the brain during normal functioning is enabled by neural oscillations (Buzsáki & Draguhn, 2004; Buzsáki, 2006). Via oscillatory synchronization, information can be processed locally within a neuronal assembly and contemporaneously exchanged between different neuronal assemblies in a network (Fries, 2005). Regarding EFs, theta oscillations (4-8 Hz) are of particular interest, and can be measured using electroencephalography (EEG). In response to events requiring EFs, theta oscillations are amongst others generated in the MCC (Cavanagh & Frank, 2014) and represent a phasic, task-related modulation of the background EEG (Mitchell et al., 2008). As such, theta oscillations can be considered as the neural 'working language' of EFs (Cavanagh & Frank, 2014).

Theta power and functional theta connectivity within the superordinate network are two potential neurophysiological markers of efficient EFs. First, increases in theta power are associated with stronger neuronal spike-field coupling within the theta band, which provides temporal windows for coincident neural activity that contribute to EFs (Cavanagh & Frank, 2014; Helfrich & Knight, 2016). In studies on healthy individuals, upregulation of theta power at the frontal-midline (FM) during EF tasks reflected the amount of cognitive control recruitment and was associated with better performance on conflict monitoring (e.g., Eschmann et al., 2018), response inhibition (e.g., Nigbur et al., 2011), set-shifting (e.g., Cooper et al., 2017), and working memory updating (e.g., Itthipuripat et al., 2013). Second, functional connectivity as measured by phase synchronization enables efficient information intake, processing, and exchange of information between regions in neural networks (Fries, 2015; Fell & Axmacher, 2011). Depending on the specific EF task, neuronal assemblies in different brain regions within the superordinate network (and additional regions) synchronize, thereby serving control mechanisms more efficiently (Cavanagh & Frank, 2014). In healthy individuals, increased theta functional connectivity has been observed in fronto-parietal brain regions during conflict monitoring (e.g., Cohen, 2014a), response inhibition (e.g., Harmony et al., 2009), set-shifting (e.g., McKewen et al., 2021), and working memory updating (e.g., Mizuhara & Yamaguchi, 2007). The distinction between the two neurophysiological markers is important, because an increase in power is considered to reflect engagement of a cortical region, whereas functional connectivity (i.e., phase synchronization) is thought to reflect communication between cortical hubs (Cooper et al., 2017).

Disturbed theta oscillations in the superordinate network (e.g., disrupted upregulation of theta power or disturbances in functional theta connectivity) can contribute to EFs impairments in various disorders (e.g., McLoughlin et al., 2021; Ryman et al., 2018). For instance, several studies in adults with attention deficit hyperactivity disorder (ADHD) have shown disturbances in task-related theta oscillations of EF (Cowley et al., 2022; Buyck & Wiersema, 2015; Missonnier et al., 2013). However, most studies assess one specific EF and focus on a single neurophysiological feature in patients from a specific diagnostic category. Consequently, the knowledge about the neural basis of EFs and the changes in theta oscillations associated with psychological disorders is still limited. Characterizing the neural basis of different EFs tasks using multiple neurophysiological markers in individuals reporting EFs problems in daily life, regardless of diagnostic category, has the potential to contribute to understanding these impairments. In addition, this knowledge could support the development of new interventions that target the underlying pathophysiological mechanisms, such as neurofeedback, transcranial alternating current stimulation, and other neuroscientific approaches, enabling timely clinical treatment.

The aim of the current study is to take an integrative approach and systematically assess both theta power and functional theta connectivity in the sensor space of different regions of the superordinate network for the four core EFs (i.e., conflict monitoring, response inhibition, set-shifting, and working memory updating). We recruited participants with self-reported EFs complaints in daily life regardless of whether they had a psychological disorder or not. We then formed two groups, one with an ADHD diagnosis and one without any diagnosis, and compared them to controls without complaints. Our hypothesis is that individuals with subjective EF complaints and ADHD will have lower task-related increases in theta power and functional theta connectivity in the superordinate network, as well as poorer behavioral performance in the four core EFs tasks compared to controls. For the group with EF complaints without a diagnosis, we expect the neural measures of power and connectivity and behavioral performance to fall in between the other two groups.

2. METHODS

2.1. Recruitment and inclusion criteria

In this study, participants were recruited with self-reported EF complaints in daily life and a control group without EF complaints. Self-reported EF complaints were defined as a score in the 90th percentile or higher (i.e., high to very high/impaired range) on the Behavior Rating Inventory Executive Function-Adult version (BRIEF-A) total score (≥ 128) or in at least two of the following subscales: Task monitor (score ≥ 12), Inhibit (≥ 15), Shift (≥ 12), and/or Working memory (≥ 15). These subscales are considered to represent the four core EFs: conflict monitoring, response inhibition, set-shifting, and working memory updating, respectively. Exclusion criteria for this study were the presence or history of a severe neurological (e.g., brain tumor) or psychiatric disorder (e.g., schizophrenia) impairing functioning in daily life. Medication use was not an exclusion criterion.

2.2. Participants

The majority of the recruited participants with EF complaints reported a diagnosis of attention deficit hyperactivity disorder (ADHD) or no diagnosis. A small number of participants (n = 11) reported other types of diagnoses (e.g., autism spectrum disorder, eating disorder, mood disorder, post-traumatic stress disorder). To assess homogeneous and equally large groups, we formed the following three: participants with subjective EF complaints and ADHD (n = 27; mean age 30.0 years, *SD* = 7.3; ADHD group), participants with subjective EF complaints without any diagnosis (n = 22; mean age 35.0, *SD* = 10.5; No diagnosis group), and controls without subjective EF complaints (n = 21; mean age 32.0, *SD* = 12.1; controls), leaving the small number of participants with different reported diagnosis out. A total of 70 adults participated in this study.

In the ADHD group, 20 participants reported the predominantly inattentive subtype of ADHD (i.e., attention deficit disorder) and seven participants reported the combined ADHD subtype (i.e., attention deficit hyperactivity disorder). For most participants, their general practitioner confirmed the diagnosis through a mental health care organization. However, for six participants, the diagnosis was not officially confirmed because we had not received their permission to obtain this information. Before the start of the study, all participants gave written consent to the protocol. Participation was voluntary and there were no rewards provided. The study was approved by the Ethical Committee Psychology of the University of Groningen and conducted in accordance with the Declaration of Helsinki.

2.3. Procedure

Participants were recruited through personal contacts of the researchers and appeals in social media (i.e., Facebook and LinkedIn). First, the participants filled out the questionnaires during which the EEG cap was placed. Followed by an EEG resting state measurement and administration of four computerized tasks (while EEG was measured) in a sound attenuated room. Conflict monitoring, response inhibition, set-shifting, and working memory updating were measured by the four tasks. In all tasks, the participant had to respond via a button press and had two answering options. A black background and white letters and symbols were used for all tasks unless otherwise stated. Two different lists were used, varying the task order and stimulus-response assignments. Before each task, participants received instructions and a short exercise to familiarize them with the task. All tasks were implemented using Presentation software (Neurobehavioral Systems version 14.8) and had a duration of ten to eighteen minutes. Between the tasks, there were rest breaks, if requested by the participant. Participants were instructed to sit still and blink as little as possible while performing the tasks. For the ADHD and No diagnosis groups this measurement served as a pre-measurement for a neurofeedback training.

2.4. Questionnaires

To assess eligibility to participate in the study, EFs in daily life were assessed by the BRIEF-A (Roth et al., 2005). Participants had to indicate on a 3-point scale (i.e., never to often) how often they experienced certain EF problems during the last month. The BRIEF-A consists of nine subscales, which together add up to a total score. In this study, the total score and the subscales Task Monitor, Inhibit, Shift, and Working Memory were used.

The presence of depressive symptoms was assessed using the Beck Depression Inventory II (BDI-II; Beck et al., 1996). Participants had to indicate which statements out of four options, referring to a specific symptom, best applied to them over the past two weeks. A total score of 0-13 is considered minimal, 14-19 mild, 20-28 moderate, and 29-63 severe.

To assess the presence of ADHD symptoms, the self-report questionnaire on attention problems and hyperactivity for adulthood and childhood (Dutch: Zelf-rapportage vragenlijst over aandachtsproblemen en hyperactiviteit voor volwassenheid en kindertijd [ZVAH]) was used. This is a rating scale based on the DSM-IV criteria for ADHD (Kooij et al., 2005). Participants had to indicate on a 4-point scale how often (i.e., rarely to very often) they showed certain behaviors in the past six months and during childhood. In this study, only the version for

adulthood was used, which assesses nine criteria for attentional symptoms and nine for hyperactivity symptoms. For adults, the DSM-IV gives no information about the exact cut-off score for ADHD, however, there is research indicating that the cut-off score in adulthood is lower than in childhood; four of nine criteria (Kooij et al., 2005).

2.5. Tasks and stimuli

To assess conflict monitoring, the Stroop task was used for which color words (i.e., red, yellow, blue, or green) were presented either in the same color as the color word (Congruent condition) or in a non-matching color of the word meaning (Incongruent condition). Using button presses, participants had to indicate the color of the color word. In total, there were 72 Incongruent trials and 72 Congruent trials. Every trial has an average length of 2700 ms and consists of a fixation cross presented for a random duration of 1200-1400 ms, followed by the presentation of the color word for 500 ms, and a second fixation cross presented for a random duration of 100-500 ms. Trials were separated by an inter-trial interval of a random duration of 400-800 ms. After every sixteen trials participants received feedback about their performance to stimulate fast and accurate responding. There were four types of feedback: (1) 'Respond more accurate', shown if less than fourteen trials were correct, (2) 'Respond faster', shown if the average RT was more than 500 ms, (3) 'Respond faster and more accurate', shown if both condition (1) and (2) were met, and (4) 'Keep it up', shown if conditions (1) and (2) were not met.

To assess response inhibition, a visual Stop-signal task was used. In this task, left- and rightward pointing arrows were presented in a fixed starting color that changed to a different color during their presentation (three color options). Participants had to press either the left or the right button according to the direction of the arrow immediately when the stimulus was displayed (Go condition). However, a change into a specific color indicated that the participant had to inhibit the initiated response (Stop condition). The timing of the color-change of the arrow was adjusted dynamically via a stop signal delay (SSD; Logan et al., 1997), to ensure that participants could stop their response in 50% of the stop-condition trials. In total, there were 300 trials, including 100 stop-condition trials. Every trial had a length of 2000 ms and started with a fixation cross with a random duration of 300-600 ms. Right after, an arrow was presented with an initial duration of 250 ms before the color changed. This duration was adjusted by the SSD, by adding 50 ms after every second correct trial or subtracting 50 ms after a failed stop trial. The color change remained on screen for another 200 ms. The trial ended with the presentation of a fixation cross.

To assess set-shifting, a Switching task was used, with number-letter pairs presented on a colored background. The task consisted of two parts. The first part, included two unmix-blocks in which participants were instructed to only classify the numbers (even or odd) or the letters (vowel or consonant). In the second part, a mixed-block, participants classify either the number or letter cued by the background color (red, pink, or orange vs. green, blue, or turquoise). This mixed-block includes a Switch condition where a switch between number and letter classification is required and a No switch condition where the classification category is the same as in the previous trial. Only the mixed-block was assessed in this study and consisted of 234 trials, including 70 switch trials. Trial length was 3000 ms and consisted of a fixation cross with the random duration of 250-500 ms, the presentation of the letter-number pair for 2200 ms, and the presentation of a black screen (i.e., filler period) for 300-550 ms to complete the total trial length.

To assess working memory updating, the N-back task was used with a No update condition (i.e., 0-back) and an Update condition (i.e., 3-back). In the No update condition, participants press a button each time a letter is presented that matches with a target letter presented at the beginning of the sequence. In all other cases, the participants do not have to react. In the Update condition, participants have to press a button each time a letter is presented that matches the letter presented exactly three positions earlier in the sequence. There were ten Update sequences and nine No update sequences, which were presented alternately. The total number of trials per sequence was 24, with each eight target letters. Every trial had a length of 2000 ms and started with a fixation cross for a duration of 1000 ms, followed by a letter presented for 1000 ms.

Mean accuracy (AC), reaction time (RT), and RT variability (RTV) were calculated for the correct trials of the four different tasks. For the Stop condition of the Stop-signal task, reaction times were estimated as the stop-signal reaction time (SSRT), which is an estimation of the time needed to inhibit a response that has already been initiated (Logan & Cowan, 1984). All tasks had a condition requiring EFs (i.e., Incongruent, Stop, Switch, and Update) and a control condition (i.e., Congruent, Go, No switch, and No update).

2.6. EEG recordings and processing

During the performance of the tasks, EEG was continuously recorded with a 64 Ag/AgCl electrodes Waveguard™ connect cap using an average reference Twente Medical Systems International B.V. (TMSi) REFA amplifier and Openvibe recording software (Renard et al., 2010).

The electrodes were placed in accordance with the extended version of the international 10-20 system. The amplifier provided 24-bit resolution EEG data with a sampling rate of 256 Hz. The electro-oculogram was measured with two vertical electrodes on the dominant eye and two horizontal electrodes. The impedance level of the electrodes was initially put below 10 kΩ and checked after one or two tasks, if necessary, action was taken to lower the impedance again.

EEG data was processed offline in MATLAB version R2019B using functions of the EEGlab toolbox (Brunner et al., 2013). Data was filtered with a 40 Hz low-pass and 0.1 Hz high-pass, down-sampled to 250 Hz, and re-referenced against two mastoid electrodes. Independent component analysis using the *runica* algorithm was applied to detect and correct for eye artifacts (i.e., blinks and horizontal eye-movements). Data was epoched from −1250 ms to 1250 ms with respect to stimulus onset, which is appropriate for time-frequency analysis focusing on theta (Cohen, 2014b). Remaining artifacts were discarded using a semi-automatic procedure with a threshold of 60 μV. Noisy electrodes were interpolated. In order to control for unequal numbers of correct trials between task conditions and to obtain a comparable signal-to-noise ratio, trials were randomly removed as necessary to allow a maximum difference of ten epochs between conditions in the same task for each participant. The minimum number of epochs required for a condition was 27. In the Stop-signal task, only twelve controls met the required number of correct epochs. Therefore, the minimum number of epochs for this task was reduced to 20 trials, resulting in four additional participants for the analysis. Table 1 shows the final sample sizes per group and task included in the EEG analyses. In order to reduce volume conduction effects in EEG sensor space, a spatial Laplacian filter was applied to transform the EEG data into estimates of scalp current density at each electrode. Scalp current density suppresses widespread EEG signals, while enhancing the sensitivity to focal activity in the cerebral cortex (Kayser & Tenke, 2006).

Table 1. Sample sizes per group and task included in the EEG analyses for theta power and functional theta connectivity.

Task	ADHD group (n = 27)	No diagnosis group (n = 22)	Controls (n = 21)
Stroop	27	22	21
Stop-signal	24	18	16
Switching	22	18	19
N-back	24	21	19

2.7. Time frequency analysis and data extraction

To decompose the EEG signal into frequency over time, event-related spectral perturbations (ERSPs) were calculated for the different conditions of the four EF tasks. ERSPs represent the log-transformed changes of power in dB relative to baseline (Delorme & Makeig, 2004). A Morlet wavelet transform was applied, with the number of cycles increasing in proportion to the frequency. The frequency range used was 2-30 Hz, starting with one cycle at 2 Hz and increasing by 0.5 cycles per 1 Hz increment, ending with fifteen cycles at 30 Hz. Single trial baseline correction was used to reduce the effect of potentially noisy trials. The average power across trials was divided by the frequency specific baseline values separately for each frequency in order to visualize power changes relative to the pre-stimulus activity. To assess the ERSP for each task condition, we automatically detect the maximum peak in power. Because FM theta power may also have a different time course in the group complaining of EFs compared to controls (Missonnier et al., 2013; Keute et al., 2019), we assess eight 200 ms time windows ranging from −100 ms to 800 ms after stimulus onset with a 50% overlap (i.e., sliding window). The average power in each time window was calculated for the maximum peak ± 50 ms and ± 1 Hz for four regions of interest (ROI) in the sensor space: frontal-midline (FM: Fz, FC1, FC2, Cz, FCz), frontolateral right (FLr: F8, FC6, F6, FT8), frontolateral left (FLl: F7, FC5, F5, FT7), and parietal (CP1, CP2, Pz, P1, P2) region. As a result of temporal leakage, the time windows can contain power outside this window.

2.8. Connectivity analysis and data extraction

In order to investigate oscillatory synchronization, while minimizing artificial interaction at the electrode level, an imaginary coherence analysis was performed (Stam et al., 2007). Coherence is defined as the normalized cross-spectral correlation between two time series. To calculate imaginary coherence, the cross-spectrum between single-trial ERSP at the electrodes (j, k) of the four ROIs was calculated for each participant, condition, time (t), and frequency (f) (Eq. 1). Here, $\bar{P}_k(t, f)$ is the complex of the power at electrode k.

$$S_{jk}(t, f) = P_j(t, f) * \bar{P}_k(t, f) \qquad (1)$$

To compute the coherence, the cross-spectrum between an electrode pair was divided by the root of the power of the auto-spectrum from each respective electrode (Eq. 2).

$$C_{jk}(t, f) = \frac{S_{jk}(t,f)}{\sqrt{S_{jj}(t,f) S_{kk}(t,f)}} \qquad (2)$$

To finally extract the imaginary coherence, the complex component of coherence was extracted of $C_{jk}(t,f)$ (see Cooper et al., 2015). To assess theta connectivity within the EFs network, the imaginary coherence for theta was averaged across the same eight sliding time windows for five ROI pairs in the sensor space: FM-FLr, FM-FLl, FM-parietal region, FLr-parietal region, and FLl-parietal region.

1.9. Data preparation and statistical analyses

The study sample was divided into three groups: ADHD, No diagnosis, and controls. Comparing the No diagnosis group with controls indicates the sole effect of subjective EF complaints on task performance and related theta power and connectivity. Comparing the No diagnosis with the ADHD group indicates the additional effect of an ADHD diagnosis next to subjective EF complaints, and comparing the ADHD group with controls indicates the combined effects of both subjective EF complaints and an ADHD diagnosis. In each group a winsorizing approach was used on the amplitude, connectivity, and behavioral data to minimize the influence of outliers by replacing outliers by a less extreme value (i.e., mean ± three * SD). For the amplitude and connectivity data, the mean per time window for each group was calculated and visualized in line charts, and for the behavioral data, the mean and standard error of the mean per group were calculated and visualized in bar plots.

Statistical analyses were only performed on the task conditions requiring EFs (i.e., Incongruent, Stop, Update, and Switch) in order to test our hypotheses and limit the number of tests. For the behavioral data, one-way ANOVAs were used to compare AC, RT, and RTV across the three groups. If significant, post-hoc comparisons were performed using Tukey's Honest Significant Difference (HSD) test. For the power and connectivity data, repeated measures (RM) ANOVAs were performed, with the within-subjects factor TIME (8 time windows) and between-subjects factor GROUP (3 groups). In case of violations of sphericity, the Greenhouse-Geisser correction was applied and corrected degrees of freedom and *p*-values were reported. For significant interaction effects, a post-hoc ANOVA was performed to compare the groups in Time window 4, as the effects of EFs are specifically expected 200 to 400 ms after stimulus onset. If significant, post-hoc Tukey's HSD tests were performed to determine the exact group differences. Finally, to explore the neurocognitive associations between the neurophysiological markers (i.e., power and connectivity) and behavior (i.e., AC, RT, RTV, and BRIEF-A questionnaire), Pearson correlation coefficients were calculated for all ROI (pairs).

For all tests, a *p*-value of ≤ .05 was used to identify significant differences. Because of the clear a priori hypotheses about the effects, multiple test correction was not applied for the RM ANOVAs and one-way ANOVAs. However, the interpretation and discussion of the results did take into account the higher Type I error rate resulting from multiple testing. For the explorative correlation analyses, the Benjamini-Hochberg adjustment with a false discovery rate of .05 was applied as a multiple comparison correction for each task and neurophysiological marker separately (Chen et al., 2017). The effect size (ES) for RM ANOVA was indicated by partial eta squared (η_p^2) and for one-way ANOVA by eta squared (η^2) and interpreted as: < .06 is small, ≥ .06 is medium, and ≥ .14 is large. Pearson correlations were interpreted as: < .3 is small, ≥ .3 is medium, and ≥ .5 is large. All analyses were carried out using SPSS (IBM Corp., 2019). According to an a priori power calculation (G*Power 3.1.9.4), eighteen participants per group would be sufficient to detect a medium effect (η_p^2 = .06, i.e., smallest ES of interest) for a within-between interaction in RM ANOVA (α = .05, β = .95, non-sphericity correction ϵ = .4).

3. RESULTS

3.1. Sample characteristics

Table 2 provides an overview of the demographics and questionnaire scores for the three groups. Educational level was rated on an 8-level scale and classified into low (i.e., primary education [1] or preparatory secondary vocational education [2]), intermediate (i.e., secondary vocational education [3], senior general secondary education [4], or pre university education [5]), or high (i.e., higher vocational education [6], university bachelor [7], or university master [8]). There were no significant differences between groups regarding age, education, and sex. As expected, the controls scored significantly lower on the BRIEF-A total score and subscales Task monitor, Inhibit, Shift, and Working memory, in comparison to the ADHD and No diagnosis group. There were no significant differences between the two latter groups regarding BRIEF-A outcomes. Regarding ADHD symptoms, the controls reported significantly less attentional symptoms as compared to both the ADHD and No diagnosis group. The two latter groups showed a similar number of attentional symptoms, both exceeding the cut-off score of four out of nine criteria. For hyperactivity symptoms, all groups differed significantly from each other. Here only the ADHD group exceeded the cut-off score. As to depressive symptoms, the controls scored significantly lower than the ADHD and No diagnosis group. The number of depressive symptoms was similar for the ADHD and No diagnosis group. On average, all groups scored in the minimal range (≤ 13).

Regarding medication intake, thirteen participants in the ADHD group reported taking methylphenidate and five participants dexamphetamine, on a daily basis or when needed. Two of them voluntarily discontinued intake during the study. The remaining nine participants in the ADHD group, all diagnosed with the inattentive subtype of ADHD, reported not taking any medication. One participant in the ADHD group also reported taking Pregabalin, which is an anticonvulsant and anti-anxiety medication that can have mild negative cognitive effects (Salinsky et al., 2010). Seven participants in the No diagnosis group suspected a diagnosis of ADHD, but this was not officially confirmed. One participant in the No diagnosis group reported taking an antidepressant (i.e., Citalopram). The remaining participants in this group and all controls reported not taking any medication that could affect cognition and did not suspect or had any confirmed psychological or neurological diagnosis.

Table 2. Demographic characteristics and questionnaire scores per group. Note: BRIEF-A = Behavior Rating Inventory Executive Function – Adult version, BDI-II = Beck Depression Inventory II, ZVAH = Self-report questionnaire on attention problems and hyperactivity for adult and childhood. * This information was not obtained for all participants; for the ADHD group information from five participants is missing (n = 22) and for the No diagnosis group information from one participant is missing (n = 21).

	ADHD group (n = 27)	No diagnosis group (n = 22)	Controls (n = 21)
Variables	n (%)	n (%)	n (%)
Education level (low / intermediate / high)	1 (3.7%) / 15 (55.6%) / 11 (40.7%)	0 (0%) / 9 (40.9%) / 13 (59.1%)	1 (4.8%) / 9 (42.9%) / 11 (52.4%)
Sex (female)	21 (78%)	14 (64%)	14 (67%)
Self-reported EFs (BRIEF-A)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Total score	162.7 (18.6)	154.7 (13.5)	97.0 (12.2)
Task monitor	15.7 (1.8)	15.0 (1.7)	9.0 (1.9)
Inhibit	17.3 (2.9)	16.7 (3.5)	11.4 (1.5)
Shift	13.4 (2.6)	12.5 (3.0)	8.7 (2.0)
Working memory	20.6 (2.4)	19.0 (2.5)	10.5 (2.1)
Depressive symptoms (BDI-II)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Total score	11.2 (7.2) *	8.7 (5.7) *	3.6 (3.2)
ADHD symptoms (ZVAH) (adulthood)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Number of attentional symptoms	6.6 (2.3) * Range: 1-9	4.0 (2.7) * Range: 0-8	0.1 (0.4) Range: 0-1
Number of hyperactivity symptoms	4.5 (2.9) * Range: 0-9	2.6 (1.9) * Range: 0-6	1.0 (1.2) Range: 0-4

3.2. Behavioral data

Figure 1 shows the mean AC, RT, and RTV of the correct responses on all conditions of Stroop, Stop-signal, Switching, and N-back task. In the following, the results of the one-way ANOVAs are described, for a full overview see Supplementary material Table 1.

Regarding the Incongruent condition of the Stroop task, an ANOVA demonstrated a significant difference in RT between the three groups ($F(2,67) = 3.206$, $p = .047$, $\eta^2 = .087$). Tukey's HSD test showed a significantly higher RT for the ADHD group ($M = 637$, $SD = 138$) compared to controls ($M = 550$, $SD = 116$; $p = .040$, 95% confidence interval: 3, 171). In the ADHD group, the RT of participants using stimulant medication (n = 16, $M = 644$, $SD = 159$) was similar to non-users (n = 11, $M = 627$, $SD = 105$). There were no significant differences in RT between the other groups. For RTV and AC there were no significant group differences on the Incongruent condition. For the Stop condition of the Stop-signal task, Switch condition of the Switching task, and Update condition of the N-back task, there were no significant group differences for any of the behavioral outcomes.

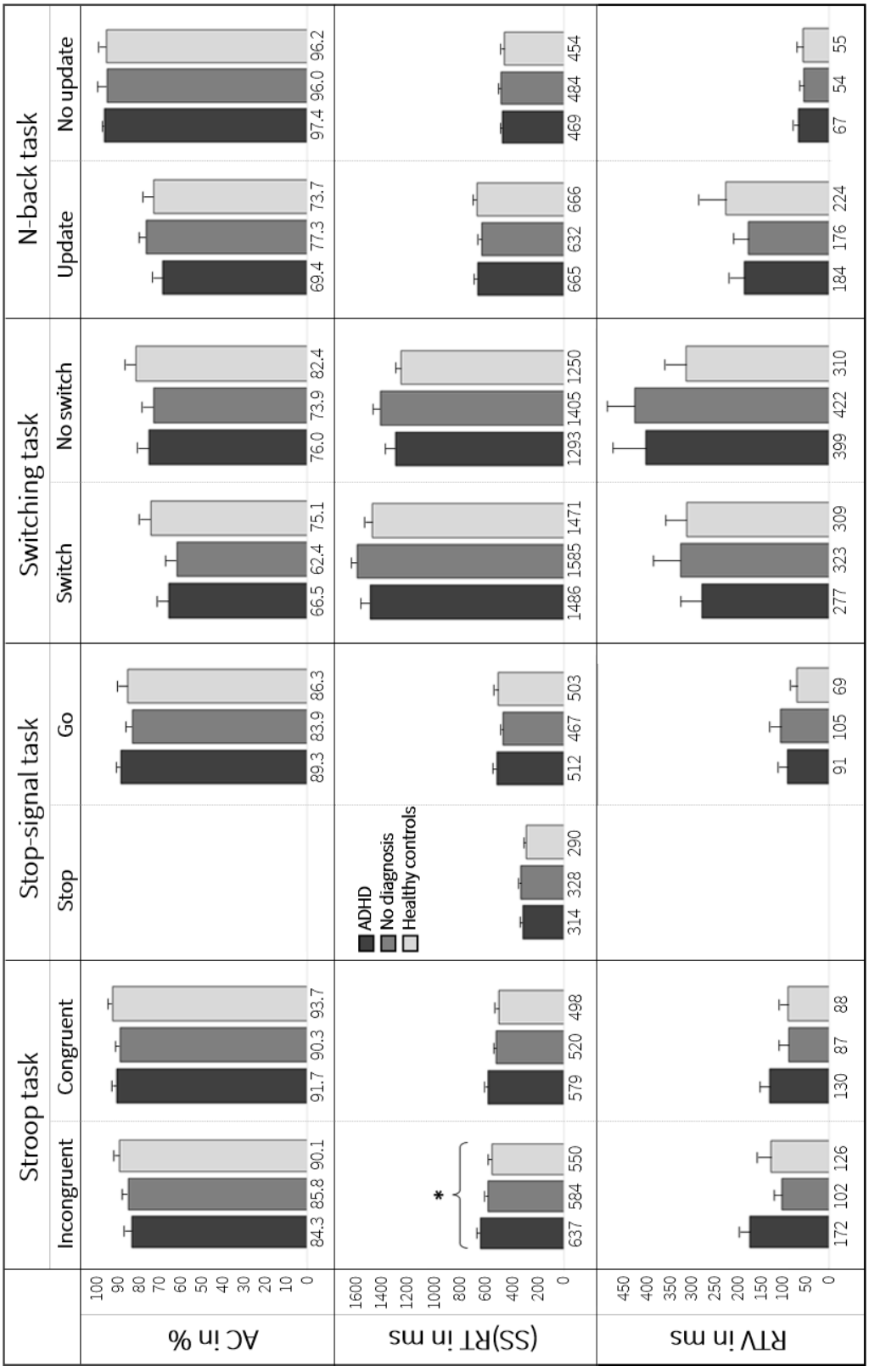

Figure 1. Mean accuracy (AC), reaction time (RT), and RT variability (RTV) of the correct responses on all conditions of the Stroop, Stop-signal, Switching, and N-back task for the ADHD group, No diagnosis group, and controls. Note: Error bars represent the standard error of the mean. * Significant difference ($p \leq .05$).

3.3. Theta power

Figure 2 shows the mean power per time window and ROI of the correct responses for the conditions of Stroop, Stop-signal, Switching, and N-back task. In the following, the results of the RM ANOVAs for each task per ROI are described. For a full overview of the RM ANOVAs results and plots of the event-related potentials, ERSPs, and topographies see Supplementary material Table 2 and Figures 1-4.

For the Incongruent condition of the Stroop task, the RM ANOVAs showed significant large main effects of TIME for all four ROIs: FM (F(2.661,178.264) = 86.487, p < .001, η_p^2 = .563), FLr (F(2.765,185,277) = 99.274, p < .001, η_p^2 = .597), FLl (F(3.024,202.629) = 53.484, p < .001, η_p^2 = .444), and parietal region (F(2.158,144.594) = 158.936, p < .001, η_p^2 = .703). Furthermore, there was as expected a significant interaction effect of TIME × GROUP for FM (F(5.321,178.264) = 2.769, p = .017, η_p^2 = .076) and FLr (F(5.531,185.277) = 3.060, p = .009, η_p^2 = .084), indicating that in these ROIs power change over time differed between the groups. Post-Hoc one-way ANOVAs for FM and FLr, comparing power at Time window 4 across groups, revealed a medium significant group difference for FLr (F(2,67) = 3.460, p = .037, η^2 = .094), but not for FM (F(2,67) = 2.645, p = .078). Tukey's HSD test for FLr showed a significantly lower power in Time window 4 for the ADHD group (M = 3.734, SD = .851) in comparison to controls (M = 4.527, SD = 1.444; p = .042, 95% confidence interval −1.565, −.023). In the ADHD group the results for power in the FLr of participants using stimulant medication (n = 16, M = 3.812, SD = .961) was similar to non-users (n = 11, M = 3.620, SD = .688). There were no significant power differences in this time window between the other groups. Lastly, there were no significant main effects of GROUP.

Similar large main effects of TIME in all ROIs were found for the three other task conditions: Stop condition of the Stop-signal task (FM: F(2.659,146.269) = 95.530, p < .001, η_p^2 = .635, FLr: F(2.688,147.844) = 66.024, p < .001, η_p^2 = .546, FLl: F(2.586,142.234) = 47.998, p < .001, η_p^2 = .466, and parietal region: F(2.290,125.972) = 42.463, p < .001, η_p^2 = .436), Switch condition of the Switching task (FM: F(1.819,101.880) = 9.518, p < .001, η_p^2 = .145, FLr: F(2.288,128.149) = 19.272, p < .001, η_p^2 = .256, FLl: F(1.872,104.858) = 11.844, p < .001, η_p^2 = .175, and parietal region: F(1.717,96.134) = 100.096, p < .001, η_p^2 = .641), and Update condition of the N-back task (FM: F(2.714,165.554) = 43.160, p < .001, η_p^2 = .414, FLr: F(2.817,171.826) = 51.700, p < .001, η_p^2 = .459, FLl: F(2.818,171.891) = 50.768, p < .001, η_p^2 = .454, and parietal region: F(1.965,119.877) = 159.715, p < .001, η_p^2 = .724). However, for the Stop, Switch, and Update condition there were no significant main effects of GROUP or interaction effects TIME × GROUP.

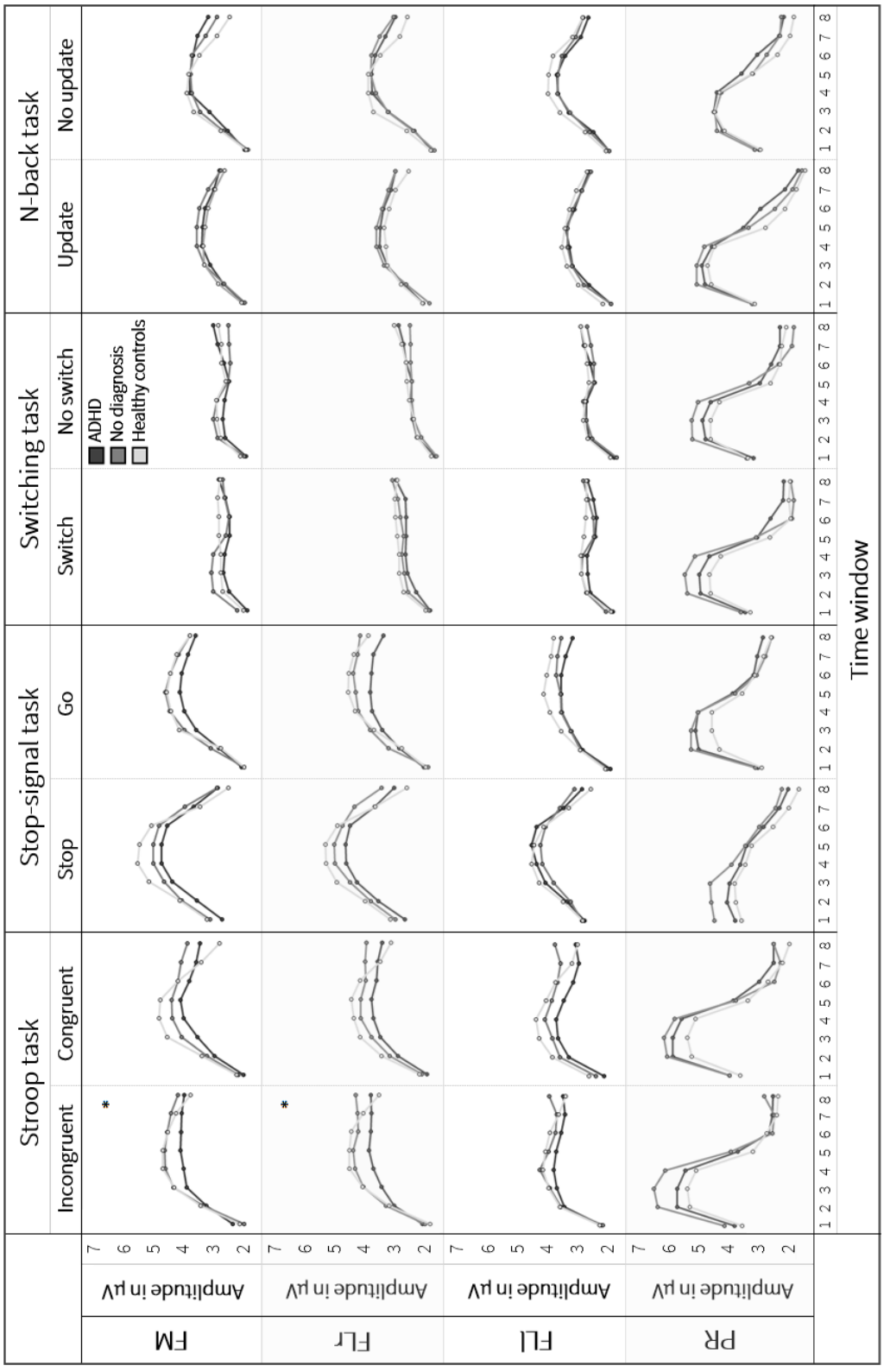

Figure 2. Mean power in the frontal-midline (FM) region, frontolateral right (FLr) and left (FLl) region, and parietal region across eight (overlapping) 200 ms sliding time windows (i.e., −100 to 800 ms after stimulus onset) for the correct responses on the Stroop, Stop-signal, Switching, and N-back task for the ADHD group, No diagnosis group, and controls. Note: * Significant interaction TIME × GROUP ($p \leq .05$).

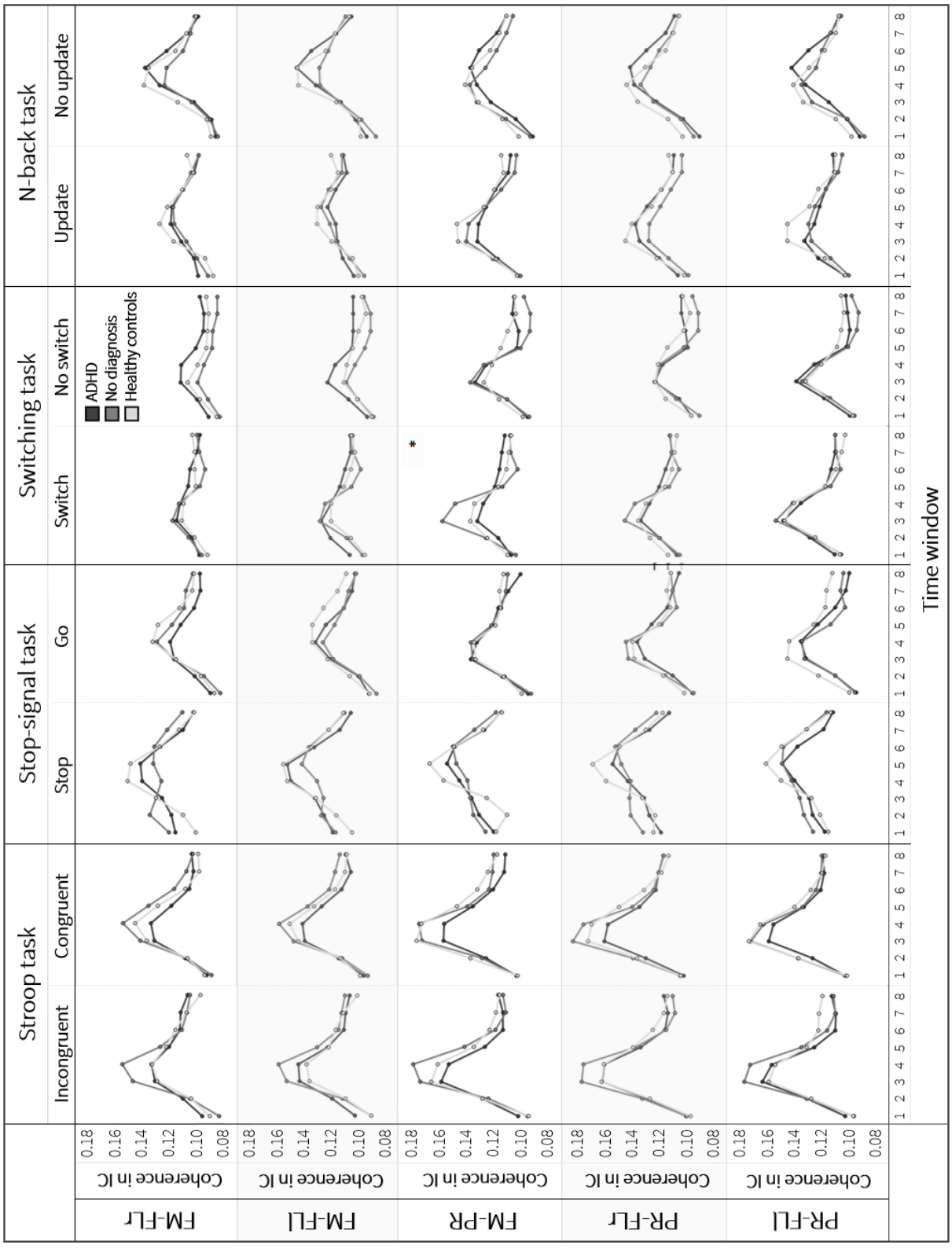

Figure 3. Mean connectivity between midcingulate cortex (FM), frontolateral right (FLr) and left (FLl) region, and parietal region across eight (overlapping) 200 ms sliding time windows (e.g., from −100 to 800 ms after stimulus onset) for the correct responses on the conditions of the Stroop, Stop-signal, Switching, and N-back task for the ADHD group, No diagnosis group, and controls. Note: IC = imaginary coherence. * Significant interaction TIME × GROUP ($p \leq .05$).

Overall, the FM, FLr, and FLl show a relatively similar progression over time for all tasks; power increases gradually until Time window 4 or 5 (i.e., 200-400 or 300-500 ms), and then slowly decreases again, but not to the initial level. Only the Switch condition shows a different pattern in these three ROI, with a relatively small power increase in the first two time windows (i.e., −100-100 and 0-200 ms) and a stable level thereafter. In contrast, the parietal region shows a sharp increase from Time window 1 to 2 for most tasks, remains relatively stable until Time window 4 (i.e., 200-400 ms), and then drops to an even lower level than initial. The exception is the Stop condition, which did not show this steep increase in the first time windows, but did reach a lower level of power at the end as compared to the start.

3.4. Functional theta connectivity

Figure 3 shows the mean connectivity per time window and ROI pair of the correct responses for the conditions of Stroop, Stop-signal, Switching, and N-back task. In the following, the results of the RM ANOVAs for each task per ROI pair are described, for a full overview see Supplementary material Table 3.

For the Incongruent condition of the Stroop task, the RM ANOVAs demonstrated significant large main effects of TIME for all five connectivity pairs: FM-FLr (F(2.397,160.592) = 35.244, p < .001, η_p^2 = .345), FM-FLl (F(2.761,184.979) = 39.995, p < .001, η_p^2 = .374), FM-parietal region (F(3.070,205.676) = 71.888, p < .001, η_p^2 = .518), parietal region-FLr (F(2.774,185.850) = 72.485, p < .001, η_p^2 = .520), and parietal region-FLl (F(2.728,182.752) = 71.901, p < .001, η_p^2 = .518). The same effect of TIME was found for the Stop condition of the Stop-signal task (FM-FLr: F(3.078,169.263) = 13.945, p < .001, η_p^2 = .202, FM-FLl: F(3.142,172.808) = 19.097, p < .001, η_p^2 = .258, FM-parietal region: F(2.899,159.431) = 14.142, p < .001, η_p^2 = .205, parietal region-FLr: F(3.142,172.818) = 15.192, p < .001, η_p^2 = .216, and parietal region-FLl: F(2.975,163.601) = 15.814, p < .001, η_p^2 = .223). For both the Incongruent and Stop condition, there were no significant main effects of GROUP or interaction effects TIME × GROUP.

For the Switch condition of the Switching task there were again significant main effects of TIME for all ROI pairs: FM-FLr (F(3.628,203.142) = 8.527, p < .001, η_p^2 = .132), FM-FLl (F(3.490,195.434) = 16.705, p < .001, η_p^2 = .230), FM-parietal region (F(3.156,176.731) = 24.287, p < .001, η_p^2 = .303), parietal region-FLr (F(3.435,192.367) = 20.835, p < .001, η_p^2 = .271), and parietal region-FLl (F(3.257,182.416) = 49.877, p < .001, η_p^2 = .471). Additionally, there was as expected a significant medium interaction effect of TIME × GROUP for FM-parietal region (F(6.312,176.731) = 2.324, p = .032, η_p^2 = .077). However, a post-hoc one-way ANOVA did not show a significant group

difference in connectivity between FM and parietal region for Time window 4 ($F(2,56) = 1.720$, $p = .188$). Lastly, there were no significant main effects for GROUP.

Finally, for the Update condition of the N-back task there were also significant large main effects of TIME for all ROI pairs: FM-FLr ($F(3.041,185.500) = 13.862$, $p < .001$, $\eta_p^2 = .185$), FM-FLl ($F(3.486,212.665) = 12.087$, $p < .001$, $\eta_p^2 = .165$), FM-parietal region ($F(2.684,163.706) = 21.573$, $p < .001$, $\eta_p^2 = .261$), parietal region-FLr ($F(2.900,176.874) = 18.813$, $p < .001$, $\eta_p^2 = .236$), and parietal region-FLl ($F(2.721,165.983) = 20.227$, $p < .001$, $\eta_p^2 = .249$). There were no significant main effects for GROUP or interaction effects TIME × GROUP.

Overall, all ROI pairs showed a similar course of connectivity over time for all tasks. For the Incongruent, Switch, and Update condition, connectivity increased from the start and peaked around Time window 3 or 4 (i.e., 100-300 or 200-400 ms), before decreasing again. Only in the Stop condition, the peak of connectivity was slightly later at Time window 5 (i.e., 300-500). The Incongruent and Stop condition had relatively higher connectivity peaks as compared to the Switch and Update condition.

3.5. Neurocognitive associations between neurophysiological markers and behavior

For the Incongruent condition of the Stroop task, we found significant medium correlations between the power in the FLr at Time window 4 and both RT ($r(70) = -.459$, $p < .001$) and scores on the Task monitor subscale of the BRIEF-A ($r(70) = -.309$, $p = .009$). This suggests that greater power in this ROI at this time point is related to faster RT and fewer complaints on the Task Monitor subscale. Additionally, significant correlations were found between RT and power in the FM and FLl at Time window 4 ($r(70) = -.450$, $p < .001$) and $r(70) = -.390$, $p = .001$), respectively). The Stop condition of the Stop-signal task did not show any significant correlations. For the Switch condition of the Switching task, there was a significant medium correlation between power in the FLr at Time window 4 and AC ($r(59) = .418$, $p = .001$), indicating that greater power at this ROI and time is associated with a higher AC. However, no other significant correlations between power and connectivity in the other ROIs/ROI pairs and behavioral outcomes were found. Finally, the Update condition of the N-back task showed significant medium correlations between five neurophysiological markers and RT. Specifically, power at Time window 4 in the FM ($r(64) = -.415$, $p = .001$), FLr ($r(64) = -.357$, $p = .004$), and FLl ($r(64) = -.433$, $p < .001$), and connectivity between FM-FLr ($r(64) = -.370$, $p = .003$) and FM-FLl ($r(64) = -.372$, $p = .002$), were all positively correlated with RT. In other words, higher power or connectivity was associated with faster RT. For an overview of all correlations, see Supplementary material Table 4.

4. DISCUSSION

The current study examined theta power and functional theta connectivity in the sensor space of the superordinate network as neurophysiological markers of the core EFs: conflict monitoring, response inhibition, set-shifting, and working memory updating. Additionally, behavioral performance on these four EFs was assessed. Three groups were formed: participants with EF complaints & ADHD diagnosis, participants with EF complaints without a diagnosis, and controls without EF complaints. This grouping allows the assessment of the sole effect of having subjective EF complaints, as well as the additional effect of an ADHD diagnosis next to experiencing EF complaints.

As expected, all four EF tasks show a dynamical increase in theta power over time in the FM, FLl, FLr, and parietal region, as well as in functional theta connectivity between these regions. This indicates that across groups, the four EFs tasks elicit power and connectivity changes in and between these regions. Strong group differences are found especially for conflict monitoring, with neural differences in power in the FM and FLr. Interestingly, these neural markers are also associated with actual behavioral performance and complaints in daily life. For set-shifting, group differences are less pronounced, and for response inhibition and working memory updating, no group differences are found at all. Below, we discuss the results for each EF in more detail.

4.1. Conflict monitoring

In conflict monitoring, as expected, the results show group differences in the theta power dynamics over time in the FLr and FM and in the behavioral outcome RT, as well as neurocognitive associations between them and with complaints in daily life. Although in the critical time window for EFs (i.e., 200-400 ms), only the power in the FLr is significantly lower for the participants with EF complaints & ADHD compared to controls. In general, conflict monitoring describes a situation with competing or conflicting actions that requires additional cognitive resources to be resolved. The MCC monitors and detects these situations and the DLPFC resolves potential conflict by focusing attention to important aspects of a task or inhibiting inappropriate actions via the rIFC (Egner & Hirsh, 2005; Forstmann et al., 2008; Van den Wildenberg et al., 2010). The current findings suggest that adults with EF complaints & ADHD, have less involvement of right lateral frontal brain regions, such as the DLPFC, which reduces attention to task-relevant aspects. Detection of conflict by brain areas in the FM, such as the MCC, appears to function normally in the group with ADHD, while impairments in the FM

have been found in other studies (Vogt, 2019; Bush et al., 1999). In contrast to group differences in power, connectivity was similar between groups, indicating that information exchange in the network is not impaired in individuals with EF complaints with or without ADHD diagnosis.

Interestingly, greater power in the FLr at the time window critical for EFs (i.e., 200-400 ms) is associated with a faster RT, and most importantly, with fewer complaints in this EF domain in daily life (e.g., less problems with impulsiveness, being distracted, or rushing things). Additionally, greater power in the FM and FLl at this same time window are also associated with a faster RT. These neurocognitive associations fit with the observed group differences in RT; participants with EF complaints & ADHD are slower than the controls. Our results fit with other studies, showing slower responses on the Stroop task in individuals with ADHD (e.g., Snyder et al., 2015; Lampe et al., 2007; Woods et al., 2002). Generally, slower responding is assumed to reflect less efficient or disengaged processing, as RT reflects the time needed for perceptual and motor-planning computations required to prepare and execute a response (Brenner & Smeets, 2018).

In summary, individuals with EF complaints & ADHD are less able to upregulate theta power in the FLr (i.e., hypoactivation) during conflict monitoring, which is associated with less efficient conflict monitoring, and may reflect less directing of attention to relevant aspects of the task. Since our ADHD sample mainly comprises the inattentive subtype, it may be a salient feature especially in this group. The subjective experience of EF complaints alone did not influence task performance as differences between the participants with EF complaints without a diagnosis and the controls were not significant. Notably, the current results are observed despite stimulant use by 2/3 of the participants with ADHD. In general, this drug class is considered to increase activation in regions such as the FM (Bush, 2009) and rIFC (Rubia et al., 2014), and can at least in children with ADHD improve conflict monitoring (Langleben et al., 2006; Nakanishi et al., 2017). However, stimulant use does not seem to have an effect here, as power in the FLr and RT was similar for ADHD participants who used stimulants and non-users.

4.2. Response inhibition

There were no group differences in response inhibition in terms of neural measures and behavioral performance. Participants with EF complaints & ADHD thus exhibit relatively normal performance and unaffected neural functioning. Additionally, there were no associations between the neural measures and behavior. In children, impaired response inhibition is usually found as a central feature of ADHD (Alderson et al., 2007), but in adults the results are mixed

(e.g., Congdon et al., 2014). On the one hand, this finding could indicate that inhibitory control develops to a normal level in adulthood. On the other hand, the lack of significant differences in the current study could be related to other factors. First, our ADHD sample mainly included participants with the inattentive subtype, who generally seem to show better response inhibition than individuals with the combined ADHD subtype (Bluschke et al., 2016). Second, individuals with ADHD may have developed compensatory mechanisms that could mask their cognitive impairments (Planton et al., 2021). Third, stimulant use by the majority of the ADHD participants could have improved response inhibition (Aron et al., 2003; Overtoom et al., 2009). However, findings on the effects of stimulants on response inhibition are mixed (Congdon et al., 2014), which can reflect differences in the sampling and inclusion of ADHD and its subtypes in different studies. Fourth, it could be that ADHD more strongly affects the strength of pre-trial (proactive) theta band activity instead of theta during response inhibition trials (Adelhöfer et al., 2021).

One limitation to the analyses of connectivity and power in this task is the lack of statistical power. The group with controls only includes sixteen participants, although eighteen participants are required to demonstrate a medium effect. For the behavioral outcome SSRT, there are no statistical power issues.

4.3. Set-shifting

For set-shifting, the groups show very similar patterns of both power, connectivity, and behavior. Only for connectivity between the FM and parietal regions there are significant group differences in the dynamics over time, but without group differences in the time window critical for EFs (i.e., 200-400 ms). In general, connectivity between the FM and parietal region seems to reflect signaling of a detected condition that requires cognitive control (Liston et al., 2006; Niendam et al., 2012). In this study, connectivity between the FM and parietal region was not associated with any of the behavioral outcomes of set-shifting or complaints in daily life in this EF domain. In contrast, greater power in the FLr at the time window critical for EFs (i.e., 200-400 ms) was associated with a higher AC. There were, however, no behavioral differences between groups regarding set-shifting. Given the absence of both behavioral differences and associations between connectivity and set-shifting performance, it is challenging to provide context for any group differences in connectivity between the FM and the parietal region. Therefore, this isolated finding should be interpreted with caution, as it may be a false positive result.

The lack of differences in neural underpinnings and behavior in the group with EF complaints & ADHD compared to controls contrasts earlier studies. These show adults with ADHD with specific difficulties in set-shifting (e.g., Luna-Rodriguez et al., 2018), which has been linked to functional abnormalities in regions such as the prefrontal cortex, parietal lobe, and anterior cingulate cortex (Bálint et al., 2015). The use of stimulant medication by the majority of the participants with ADHD could be an explanation for the non-deviating performance, as some studies found that they can improve set-shifting in ADHD (e.g., Ni et al., 2013). Fitting with this thought is a recent fMRI analysis demonstrating similar activation of brain areas during set-shifting in controls and ADHD patients treated with stimulant medication, as opposed to ADHD patients not treated with medication (Berberat et al., 2021). Nevertheless, the results on the effects of stimulants on cognition, including set-shifting, are mixed (Advokat, 2010). It should also be noted that studies on the effects of stimulants often assess 'set-shifting' using the Wisconsin Card Sorting Test or its equivalent, which is not a pure measure of set-shifting, as it requires both multiple EFs and non-EF abilities. The specific effects of stimulants on set-shifting and its neural basis are, therefore, still unclear in ADHD, and further research is needed in this area. Finally, compensatory mechanisms may play a role in ADHD or other neuronal aspects involved in set-shifting may be more strongly affected, for instance oscillatory synchronization in the delta band (López et al., 2019).

4.4. Working memory updating

For working memory updating, there were no group differences in neural measures and behavioral performance. Interestingly, a faster reaction time in working memory updating was associated with greater power in the FM, FLr, and FLl and with greater connectivity between FM and both FLr and FLl. This result suggests that theta activity in the fronto-medial and lateral brain regions is closely associated with the efficiency of working memory updating. Notably, this association is not affected by the presence of EF complaints or ADHD diagnosis.

In general, individuals with ADHD seem to perform poorly on working memory tasks, although, there is no scientific consensus on exactly which process (e.g., span, recall) or mechanisms are affected (Ortega et al., 2020) and contrary results have also been shown (e.g., Zhao et al., 2020). It is possible that there are simply no differences between the groups because the subjective experience of EF complaints has no influence on the updating of working memory. The unaffected performance of the group with EF complaints and ADHD could also be due to the cognitive effects of taking stimulants, as the majority of participants with ADHD take medication (Tamminga et al., 2021). Another reason might be the use of compensatory

mechanisms, such as prolonged maintenance of theta synchronization after the occurrence of a stimulus (Missonnier et al., 2013).

4.5. Subjective executive function complaints in daily life without diagnosis

There are several explanations for possible subjective EF complaints in daily life without a clinical diagnosis. First, there could be an underlying disorder or condition that affects EFs and is not (yet) diagnosed, for example, undiagnosed ADHD is particularly common in women (Quinn, 2005). The use of compensatory strategies by individuals with ADHD can also mask their symptoms and delay a diagnosis (e.g., Canela et al., 2017). This explanation in particular is likely for some participants in the current study, as the group without a diagnosis had a similar number of attention symptoms as the ADHD group and seven participants suspected a diagnosis of ADHD. Second, individuals who do not meet the full criteria for a clinical diagnosis of, for example ADHD, may have attention and behavioral difficulties that are not at the extreme end of the continuum (McLennan, 2016). The value of a continuum of trait distributions in the population rather than using discrete categorical diagnoses is also emphasized, for example, in the Research Domain Criteria framework (Cuthbert, 2014). Third, psychological factors, including personality factors, depressive symptoms and perceived stress, may contribute to the experience of EF complaints (Smit et al., 2021). However, whether or not there is an underlying disorder, subjective cognitive difficulties can interfere with daily functioning in healthy people (e.g., Stenfors et al., 2013) and should be considered in research and treatment.

4.6. Final remarks

The main strength of the current study is the use of an integral approach; assessing multiple neurophysiological markers in the sensor space of different regions of the superordinate network for the four core EFs in participants with subjective EF complaints in daily life and controls. It is, however, important to note that presenting the results of multiple neurophysiological markers and EF tasks in the same paper does increase the risk of false positives (i.e., type I errors) due to multiple comparisons. We have taken this into account in the interpretation of the findings. Furthermore, our results apply only to scalp measures of theta (4-8 Hz) and are evaluated in a specific time window (i.e., −100 to 800 ms after stimulus onset) and ROIs (pairs), so they do not apply to other neuronal features, such as frequency coupling and further neural oscillations. Moreover, medication use was not an exclusion criterion, which has the advantage that a representative group was included and statements can be generalized, and the disadvantage that stimulant use is a confounding factor in the

ADHD group. Understanding the neural basis of EFs, such as neural oscillations, has the potential to contribute to the understanding of EF deficits and offers solutions for developing new interventions that target specific neural dysfunctions.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethic Committee of the Faculty for Social Sciences, University of Groningen, Netherlands. The participants provided their written informed consent to participate in this study.

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Declaration of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at:
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Chapter 3

Long-term improvements in executive functions after frontal-midline theta neuro-feedback in a (sub)clinical group

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ABSTRACT

Impairments in executive functions (EFs) are common across disorders and can greatly affect daily functioning. Frontal-midline (FM) theta neurofeedback (NF) has been shown effective in enhancing EFs in healthy adults, prompting interest in exploring its potential as an alternative treatment for EFs in (sub)clinical samples. This study aims to determine the effects of FM theta NF on EFs in a sample of 58 adults (aged 20-60 years) with pronounced subjective EF complaints in daily life. Using a pre/post/follow-up design with a sham NF group, the present study assessed upregulation of FM theta in an eight-session individualized FM theta NF training and its immediate and long-term transfer effects on objective and subjective measures of EFs. These included behavioral performance on EF tasks assessing working memory updating (N-back task), set-shifting (Switching task), conflict monitoring (Stroop task), and response inhibition (Stop-signal task), as well as FM theta power during these tasks, and subjective EFs in daily life (BRIEF-A). The results indicate that there are only differences in FM theta self-upregulation between the NF group and sham group when non-responders are excluded from the analysis. Regarding behavioral transfer effects, NF-specific improvements are found in working memory updating reaction time (RT) and conflict monitoring RT variability at 6-month follow-up, but not immediately after the NF training. The effects on FM theta power during the EF tasks and subjective changes in EFs in daily life were not specific to the NF training. As a next step, research should identify the best predictors to stratify NF training, as well as explore ways to improve NF responsiveness, for instance by increasing neuroplasticity.

1. INTRODUCTION

Impairments in executive functions (EFs) can be regarded as a transdiagnostic feature in many psychiatric disorders (Snyder et al., 2015; Abramovitch et al., 2021), and are associated with a range of health problems such as reduced daily functioning, poorer quality of life, and depressive symptoms (Vaughan & Giovanello, 2010; Letkiewicz et al., 2014; Zhang et al., 2021). EFs refer to a set of separate but interrelated higher cognitive (control) processes (Friedman & Miyake, 2017), including working memory updating, set-shifting, conflict monitoring, and response inhibition (Miyake et al., 2000b; Enriquez-Geppert et al., 2010). Given the crucial role of EFs in enabling independent, flexible, and goal-oriented behavior in everyday life (Diamond, 2013), and their frequent impairment in various disorders, there is a need for effective treatment approaches to improve them. Neurofeedback (NF) has shown promise in effectively boosting EFs in healthy adults (Viviani & Vallesi, 2021), leading to the question of whether these effects can be replicated in (sub)clinical populations.

Neuroscientific treatment approaches such as NF, transcranial alternating current stimulation, and transcranial direct current stimulation aim to directly target underlying brain mechanisms of cognition or clinical symptoms. NF is particularly promising as it is an active self-neuromodulation approach that includes learning mechanisms (Enriquez-Geppert et al., 2017; Sitaram et al., 2017) and neuroplastic effects (Ros et al., 2014), and thus potentially leads to more sustainable long-term effects (e.g., Van Doren et al., 2019). NF is a non-invasive technique that employs a brain-computer-interface to record brain activity, analyze it, and feeds selected brain features back to the participant in real-time (Marzbani et al., 2016). This real-time feedback serves as a guiding mechanism for the participant to modulate and regulate those brain features in the desired direction with the end goal of influencing cognition or clinical symptoms (e.g., Enriquez-Geppert et al., 2013a).

A systematic review by Viviani and Vallesi (2021) demonstrated that NF studies applying a frontal-midline (FM) theta protocol were most successful in targeting EFs. Theta oscillations (4-8 Hz) recorded at the FM region are considered crucial for EFs. During events requiring the engagement of EFs, theta oscillations are increased with a main generator in midcingulate cortex (MCC; Cavanagh & Frank, 2014; Eisma et al., 2021). The MCC is an important hub within the superordinate fronto-cingulo-parietal network (Niendam et al., 2012). Increased theta oscillatory power has been found to be linked to stronger neuronal spike-field coupling in the theta band (Helfrich & Knight, 2016). Furthermore, this increase is associated with better

performance on tasks requiring EFs (e.g., Nigbur et al., 2011; Itthipuripat et al., 2013; Cooper et al., 2017; Eschmann et al., 2018). Based on these findings, four studies have assessed a NF protocol specifically targeting FM theta oscillatory power to enhance EFs in healthy young and older adults (Wang & Hsieh, 2013; Enriquez-Geppert et al., 2014a; Brandmeyer & Delorme, 2020; Eschmann & Mecklinger, 2022). These studies showed a significantly larger increase in FM theta power for the NF group as compared to an active control group after the NF training, and most importantly behavioral transfer effects on proactive processes of EFs (for the distinction between proactive and reactive processes the article by Braver, 2012).

In the search for an effective treatment approach for executive dysfunctions, the current study investigates the effects of a FM theta NF training in individuals with pronounced self-reported EF complaints in daily life, independent of whether or not they have a psychiatric diagnosis. The focus on this (sub)clinical group is considered a next step in evaluating the efficacy of FM theta NF as a treatment option for individuals with subjectively experienced impairments of EFs beyond its known effects in healthy participants. This study will assess the self-regulatory ability of FM theta through NF, as well as its immediate and long-term effects on objective measures of EFs and self-reported EFs. These results will contribute to the ultimate goal of developing a transdiagnostic NF training that can be used as a standalone treatment in a clinical context, but also in combination with other therapies.

2. METHODS

2.1. Recruitment and inclusion criteria

Participants were recruited via advertisements on social media and completed the Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A; Roth et al., 2005) to assess their eligibility. EF complaints were operationalized as a score in 90th percentile or higher (i.e., high to very high/impaired range) on the BRIEF-A total score (≥ 128) or on at least one of the subscales: Working memory (≥ 15), Shift (≥ 12), Task monitor (≥ 12), or Inhibit (≥ 15). These subscales are thought to represent the four EFs: working memory updating, set-shifting, conflict monitoring, and response inhibition, respectively (Roth et al., 2005). For this study, individuals with a severe neurological disorder (such as a brain tumor) or psychiatric disorder (such as schizophrenia) significantly affecting daily functioning were excluded. The study allowed the use of medication to not withhold medication from participants for an extended period of time and to be able to generalize results.

2.2. Participants

A convenience sample of 58 Dutch speaking adults with pronounced self-reported EF complaints in daily life participated in this study. Participants were pseudo-randomly assigned to either the NF group (n = 29) or the sham group (n = 29) to dissociate NF-specific effects from other non-specific effects. The groups were matched as closely as possible in terms of age, gender, education level, and psychiatric disorders. Education level was rated on an eight-level scale and classified into low (i.e., primary education [1] or preparatory secondary vocational education [2]), intermediate (i.e., secondary vocational education [3], senior general secondary education [4], or pre university education [5]), or high (i.e., higher vocational education [6], university bachelor [7], or university master [8]). The CONSORT flow diagram of the study is presented in Figure 1. Prior to the start, information about voluntary participation in the study was provided and all participants gave written consent. The study was single-blinded; participants were only informed of assignment to one of two different NF training protocols. The majority of research assistants performing the NF sessions were aware of the group assignments due to its visibility in the used NF software. Instructions and interactions with participants were kept as similar as possible between both groups. The study protocol was approved by the Ethical Committee of the Behavioral and Social Science Faculty of the University of Groningen, Netherlands, and conducted in accordance with the Declaration of Helsinki.

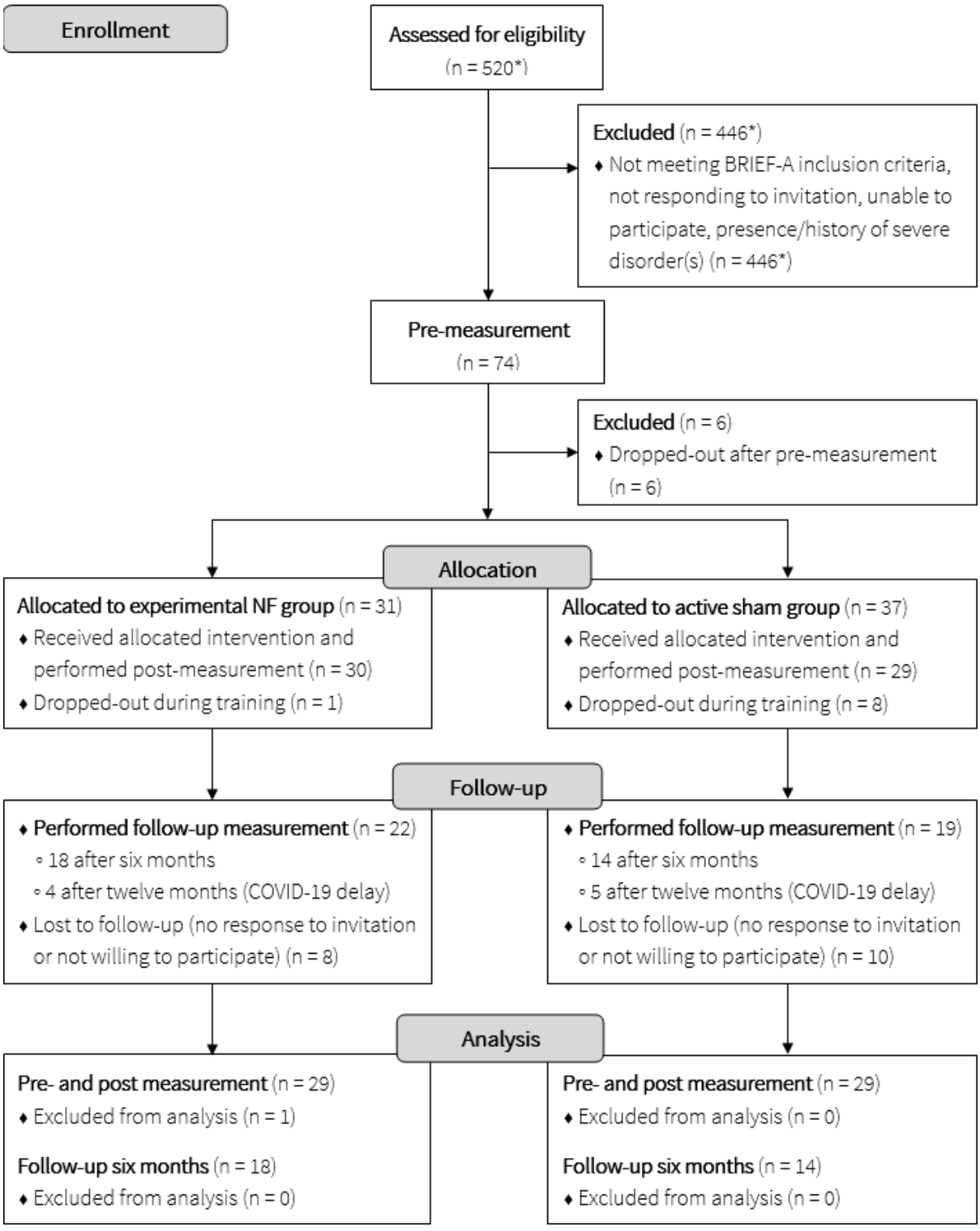

Figure 1. CONSORT flow diagram of measurements performed in the lab. Note: *Estimation.

2.3. Procedure and materials

Data collection took place in a sound-attenuated EEG lab at the Heymans institute at the University of Groningen, Netherlands. Participants in both the NF and sham group followed the

same training schedule, which consisted of a pre-measurement, eight NF training sessions, and a post-measurement, all completed within approximately three consecutive weeks (*M* = 19 days, *SD* = 5.0). Six months after the NF training, participants were invited for a follow-up measurement. Due to COVID-19 restrictions, 30% of the sample did not complete this 6-month follow-up measurement. Participants who were unable to come to the lab for the follow-up measurement were asked to complete the BRIEF-A questionnaire online from home. Nine participants had their follow-up measurement twelve months post-training. After completing the follow-up measurement, participants were asked to guess which group they belonged to and were then debriefed about their group assignment.

2.3.1. Pre-, post-, and follow-up measurements

The measurements (pre-, post-, and follow-up) had a consistent structure and included questionnaire(s), a resting state EEG recording, and four computerized EF tasks. Each measurement session took approximately 120 to 150 min to complete. On average, the 6-month follow-up measurement was performed 203 days (*SD* = 30.6, n = 32) after the post-measurement, and the 12-month follow-up measurement 342 days (*SD* = 20.1, n = 9) after the post-measurement.

2.3.1.1. Questionnaires

In the pre-, post-, and follow-up measurements, participants completed the BRIEF-A questionnaire while the EEG cap was set. The BRIEF-A assesses the frequency of certain EF problems in daily life on a 3-point scale over the past month (Roth et al., 2005). In this study, the total score (i.e., combination of nine subscales) and the subscales Working Memory, Shift, Task Monitor, and Inhibit were used.

At post-measurement, two additional questionnaires were administered to assess the presence of depressive symptoms and ADHD symptoms during the NF training. The Beck Depression Inventory II (BDI-II) was used to assess depressive symptoms over the past two weeks (Beck et al., 1996). For 21 items, referring to specific symptoms, participants had to choose one of four statements that best applied to them. A score of < 13 is considered minimal, 14-19 mild, 20-28 moderate, and > 29 severe. The Self-report Questionnaire on Attention problems and Hyperactivity for adulthood and childhood (Dutch: Zelf-rapportage Vragenlijst over Aandachtsproblemen en Hyperactiviteit voor volwassenheid en kindertijd [ZVAH]) was used to assess ADHD symptoms (Kooij et al., 2005). Participants were asked to rate on a 4-point scale how often they displayed certain behaviors in the past six months and during childhood. The adulthood version was used, which assesses nine criteria for attentional symptoms and

nine for hyperactivity. A score of four or more out of nine criteria was used as a cut-off (Kooij et al., 2005).

2.3.1.2. Executive function tasks

After completing the questionnaires, participants completed an eight min EEG resting state measurement (eyes open and closed, not used in this study), followed by four computerized EFs tasks while their EEG was being measured: the N-back, Switching, Stroop, and Stop-signal task (Figure 2).

The N-back task was used to assess working memory updating and includes a No update (0-back) and an Update condition (3-back). In the No update condition, participants had to press a button when a letter matched a target letter presented at the beginning of a letter sequence. In the Update condition, participants were instructed to press a button when a letter matched the letter presented three positions earlier in the sequence. There were ten Update sequences and nine No update sequences with 24 trials (i.e., letters) per sequence and eight target letters. Each trial lasted 2000 ms and included a fixation cross and the letter presentation.

A Switching task was utilized to assess set-shifting. In this task, participants were presented with number-letter pairs on a colored background and had to classify either the number or letter. In the first two unmix blocks, participants had to categorize only the number (i.e., even or odd) or letter (i.e., vowel or consonant) to get familiar with the task. In the third mixed block, classification of either the number or letter was based on the background color. A Switch condition required a switch between number and letter classification and in a No switch condition the classification category remained the same as in the previous trial. The mixed block included a total of 234 trials of which 70 were switch trials. Each trial lasted 3000 ms and included a fixation cross and the presentation of the letter-number pair, followed by a filler period.

The Stroop task was used to assess conflict monitoring. Participants were presented with color words in either the same or different color as the word (i.e., the Congruent and Incongruent condition, respectively) and had to indicate the color. For both conditions there were 72 trials, each lasting an average of 2700 ms. Trials included a fixation cross, color word presentation, and an inter-trial interval. Feedback on performance was automatically given after every sixteen trials to encourage fast and accurate responses.

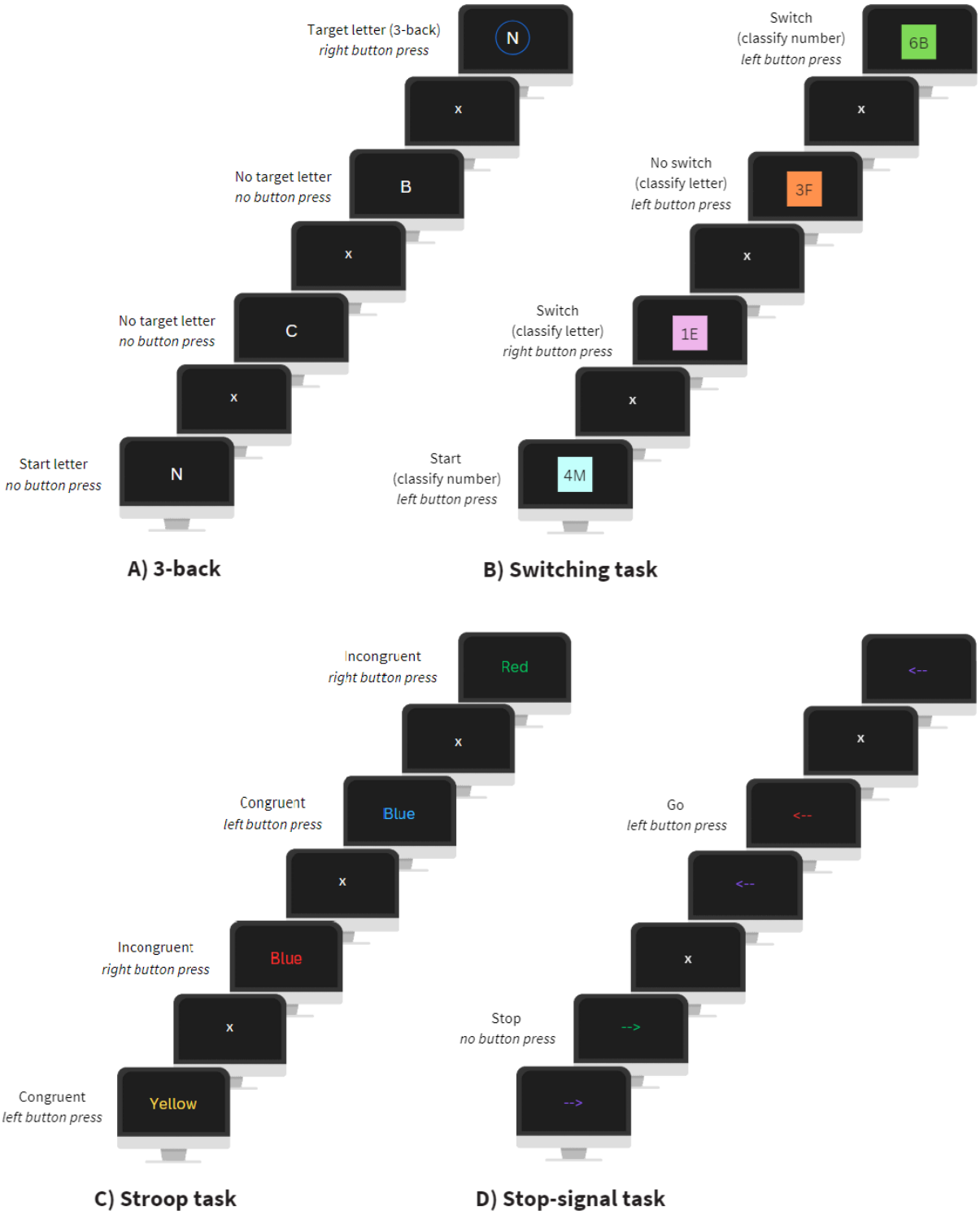

Figure 2. Visual illustration of the 3-back (update) condition of the N-back task (A), Switching task (B), Stroop task (C), and Stop-signal task (D).

The Stop-signal task was used to assess response inhibition. In this task, participants were presented with arrows pointing left or right that changed color during their presentation and had to press the corresponding button (i.e., Go condition). A change to a specific color

indicated to inhibit their motor response (i.e., Stop condition). For this, the timing of the color change was adjusted dynamically, adding 50 ms after every second correct or subtracting 50 ms after an incorrect stop trial, to ensure that participants would stop their response in 50% of the trials. There were 300 trials, including 100 Stop condition trials. Each trial lasted 2000 ms and included a fixation cross, an arrow presentation (adjusted by a stop signal delay), and again a fixation cross. For more details on the four tasks see Chapter 2.

There were two lists, with a different order of the tasks and stimulus-response assignment. Prior to each task, written instructions and a short practice were provided to familiarize participants with the task. Participants were required to respond to stimuli using a button box with two answering options. During the completion of the tasks, participants were instructed to maintain still and reduce blinking to a minimum. Breaks were given between tasks upon request. Each task included a condition that required EFs (i.e., Update, Switch, Incongruent, Stop) and a control condition (i.e., No update, No switch, Congruent, Go), and lasted between eight and nine min. The EF tasks were administered in a sound-attenuated room using Presentation software (Neurobehavioral Systems version 14.8).

2.3.1.3. EEG recordings and pre-processing

All EEG measurements were carried out by trained researchers and assistants with a background in (neuro)psychology. EEG was recorded using a 64 Ag/AgCl electrodes Waveguard connect cap, an average reference Twente Medical Systems International BV (TMSi) REFA amplifier, and Openvibe recording software (Renard et al., 2010). Electrodes were placed according to the extended version of the international 10-20 system, with additional vertical and horizontal electrodes on the dominant eye for recording the electro-oculogram (EOG). Electrode impedances were regularly checked to ensure they were below 10 kΩ. The amplifier provided 24-bit resolution EEG data at a sampling rate of 256 Hz.

All offline preprocessing was performed in MATLAB version R2019B using the EEGLAB toolbox (Brunner et al., 2013). First, the data was filtered using a low-pass filter (40 Hz) and a high-pass filter (0.1 Hz), down-sampled to 250 Hz, and re-referenced to two mastoid electrodes. Next, independent component analysis using the *runica* algorithm was applied for removal of eye blinks and horizontal eye movements. The continuous EEG data was then epoched from −1250 to 1250 ms relative to stimulus onset (e.g., presentation of color word in the Stroop task or target letter in the N-back task). Rest-artifact correction was performed in a semi-automated procedure in which trials exceeding a threshold of 60 μV were flagged and visually inspected.

Electrodes with excessive noise-related fluctuations (e.g., due to impedance increase) were interpolated. For each task, a maximum difference of ten epochs between the two conditions and measurements was achieved by randomly removing correct trials for each participant. The minimum number of epochs for a condition was 27. Table 1 shows the final sample sizes included in the EEG analyses.

Table 1. Sample sizes per measurement, group, and task included in the EEG analyses. Note: *Due to COVID-19 regulations, not all participants could perform the 6-month follow-up measurement. Therefore, nine participants did a 12-month follow-up measurement instead.

	Pre-measurement		Post-measurement		6-month follow-up*		12-month follow-up	
Task	NF group (n = 29)	Sham group (n = 29)	NF group (n = 29)	Sham group (n = 29)	NF group (n = 18)	Sham group (n = 14)	NF group (n = 4)	Sham group (n = 5)
N-back	27	27	27	28	17	14	4	5
Switching	24	23	28	26	18	13	4	5
Stroop	28	28	29	29	18	14	4	5
Stop-signal	25	23	26	26	13	13	3	3

Next, event-related spectral perturbations (ERSPs) were calculated using the *newtimef* function, which transforms the data to represent log-transformed changes in power in dB relative to the baseline (Delorme & Makeig, 2004). For the time-frequency decomposition a Morlet wavelet transform was used with an increasing number of cycles with increasing frequencies (range: 2-30 Hz, starting with one cycle at two Hz and increasing by 0.5 cycles per one Hz increment, ending with fifteen cycles at 30 Hz). To visualize changes in power relative to activity before stimulus onset, the mean power across trials was divided by frequency-specific baseline values for each frequency. The mean ERSP values were calculated for the FM region using electrodes Fz, FC1, FCz, FC2, and Cz.

2.3.2. Individualized eight session neurofeedback training

The FM theta NF training was personalized for each participant based on the individual theta peak (ITP), which can vary significantly between individuals but has high intra-individual stability (Näpflin et al., 2008). The ITP was based on the EEG data collected during the four EF tasks in the pre-measurement. For each task condition requiring EFs, the ITP was identified in the ERSPs for the FM region, and the mean peak across the four tasks was calculated. The mean peak ± 1 Hz was used for the NF training. The feedback signal was based on the EEG data recorded at five electrodes at the FM: Fz, FC1, FCz, FC2 and Cz. Recordings were online

referenced to the nose, and Fp1 and Fp2 were used for the EOG. EEG signals were read out in real-time and processed by the Matlab-based software NeuroSuite 2.0. The sampling rate was 500 Hz.

The eight NF sessions consisted of an EOG calibration, start baseline, six NF blocks, transfer block, and end baseline, with self-paced breaks in between (see Figure 3). EOG calibration (three min) was used to identify artifacts (e.g., eye blinks). A manual threshold was first set, and 2-second epochs centered around the artifact peaks were extracted. The mean and SD of all epoch values exceeding 0.75 times the threshold were then calculated, and the final threshold was determined as the mean minus the SD. During online processing in subsequent blocks, incoming data underwent detrending and rectification, and an epoch was flagged as an artifact if it exceeded the final threshold. During the start baseline (five min), resting state activity was measured and participants were instructed to rest without engaging in any cognitive process or forcing a state of relaxation. During the NF blocks (five min each), participants were instructed to actively increase FM theta power relative to the start baseline by using mental strategies. All participants in both groups were presented with a list of mental strategies, including mental acts (e.g., mental arithmetic, mental rotations of objects), relaxation (e.g., focus on breathing), imagining emotions (positive or negative), retrieving memories (e.g., about family, holidays), auditory strategies (e.g., imagining music), cheering for a red square, imagining movement or activities (e.g., foot movement or practicing sport), and remembering or imagining nature (e.g., rain, sunset), or daily activities (e.g., cooking, shopping). Additionally, they were encouraged to test their own strategies and use the most effective ones. A colored square on the computer screen provided real-time feedback on the effectiveness of the strategy, with the color ranging from highly saturated blue (i.e., below 2.5% of the amplitude range) to gray in the middle as an anchor to highly saturated red (i.e., above 97.5% of the amplitude range) in 21 color steps. The feedback signal was updated every 250 ms based on a two second sliding window that captured the incoming data. Fast-Fourier Transform was used to calculate the amplitude of the individually determined theta band. The participants' goal was to color the square as red as possible, indicating an increase in FM theta power relative to the baseline, while blue represented a decrease. A gray square indicated no difference in FM theta amplitude or the detection of an artifact. The color of the feedback signal was scaled such that a maximal saturation corresponded to theta amplitudes ± 2 SD from the mean of the baseline.

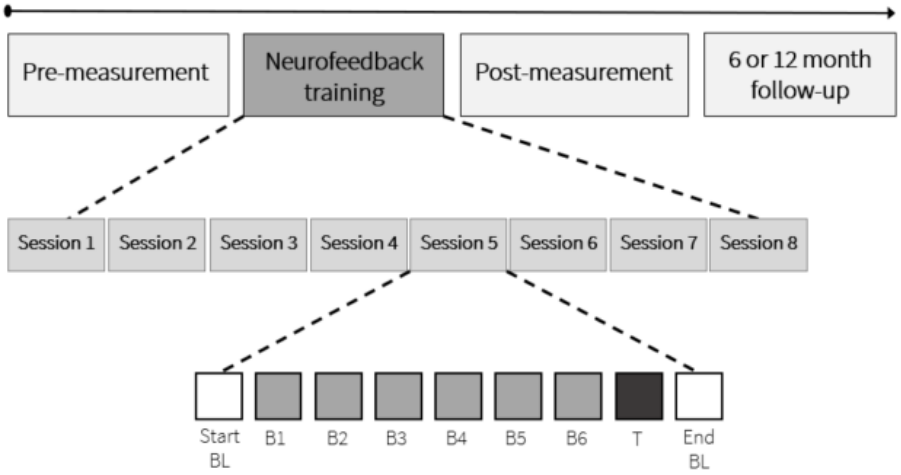

Figure 3. Neurofeedback training schedule. The neurofeedback training consisted of eight sessions with each 35 min of FM theta upregulation time; five min per block (i.e., neurofeedback block (B) 1 to 6 and transfer block [T]). The start and end baseline (BL) also took five min each and assessed resting state EEG.

Participants in the sham group received a replay of feedback from a matched participant in the NF group for the same session and block, in order to provide both groups with similar visual feedback. To enhance the credibility of the feedback in the sham group, participants received real feedback on their own (eye) artifacts (i.e., gray square). After the six NF blocks, a transfer block (five min) was conducted in which participants were again asked to apply mental strategies to increase FM theta power, but without visual feedback (i.e., the square remained gray). After each NF block and transfer block participants were asked to write down the mental strategies they used and to evaluate their effectiveness on a 7-point Likert scale. The sessions concluded with a resting-state end baseline measurement (five min) in which no strategies were required and the instructions were the same as for the start baseline. During both the start and end baseline measurements, the square changed colors with a random gradient to provide visual stimulation similar to the NF blocks. Finally, in each session, participants were asked to self-evaluate their motivation for participating in the study, their level of commitment to the study, and their perception of difficulty, using a 7-point Likert scale. Each NF session took approximately 75 min to complete.

2.4. Statistical analyses

2.4.1. Neurofeedback training effects

As a first step, the amplitudes in all blocks were normalized to the overall power (1-30 Hz) in four individualized frequency bands: theta (ITP ± 1 Hz), delta (ITP – 3.5-1.5 Hz), alpha (ITP + 3-5

Hz), and beta (ITP + 7-24 Hz). Subsequently, two learning indexes were used to evaluate the effects of the individualized FM theta NF training on the upregulation of theta. Next, a within-session baseline correction was applied, in which the increase in FM theta was calculated as the difference in mean amplitude between a specific block and the baseline of that respective session (e.g., mean amplitude NF Block 1 in Session 1 − mean amplitude Start baseline in Session 1). This approach minimizes the effects of inter-individual differences in FM theta amplitude and measurement variability across sessions.

For the first learning index (Learning Index 1), the changes in FM theta amplitude from session to session were assessed. For each session, the mean relative theta amplitude across the six NF blocks was calculated. Training effects were analyzed using repeated measures (RM) ANOVA with SESSION (1-8) as the within-subject factor and GROUP (NF vs. sham) as the between-subjects factor. With the second learning index (Learning Index 2), the dynamical changes within sessions were assessed (Enriquez-Geppert et al., 2014b). For each block, the mean relative theta amplitude across all sessions was calculated. Effects were analyzed using RM ANOVA with within-subject factor BLOCK (start baseline, NF blocks 1-6, transfer block, and end baseline) and between-subjects factor GROUP (NF vs. sham). To determine the specificity of the FM theta NF training, the same analyses were performed for delta, alpha, and beta.

2.4.2. Classification of responders and non-responders

Previous research on NF has demonstrated that a portion of participants seems unable to regulate their own brain activity (Alkoby et al., 2018; Haugg et al., 2021). Therefore, we conducted an additional analysis to assess FM theta NF learning in the responders. This distinction is crucial in the context of clinical applications, as it has the potential to inform about a personalized treatment approach where only individuals who demonstrate a positive response to NF would receive it. Such a stratification could significantly enhance the overall effectiveness of the treatment, as well as improve patient outcomes. Participants were classified as responders or non-responders to NF based on the regression slope (i.e., negative slope (≤ 0) = non-responders and positive slope (> 0) = responders) across seven values: the mean relative amplitude for the start baseline (i.e., zero) and the six separate NF blocks averaged across all sessions (i.e., Learning Index 2). This approach takes into account potential changes in theta in the start baseline over the sessions. For theta, RM ANOVAs were conducted for the two learning indices, using GROUP as the between-subjects factor (NF responders vs. sham). In addition, descriptive statistics were compiled for both responders and non-responders to gain insight into the reasons for any differences in theta upregulation.

2.4.3. Testing the credibility of the sham group

To assess the credibility of the sham NF and ensure that the participants were unaware of their group assignment, a chi-square test of independence was conducted. Additionally, RM ANOVA was performed on the dependent variables motivation, commitment, and perceived difficulty with SESSION (1-8) as the within-subject factor and GROUP (NF vs. sham) as the between-subjects factor. Missing data (i.e., eight items were not filled in) was imputed using the mean of the session before and after for the same participant. Finally, descriptive statistics were compiled to qualitatively determine if there were differences between participants who completed the follow-up measurement and those who dropped out after the post-measurement.

2.4.4. Behavioral transfer effects

To evaluate the transfer effects of the NF training on behavioral EF performance, the mean accuracy (AC), reaction time (RT), and RT variability (RTV) were calculated for the correct trials of the EF tasks at the pre-, post-, and follow-up measurement. For the Stop-signal task, the stop-signal reaction time (SSRT) was estimated (Logan & Cowan, 1984). Analyses were only performed on conditions requiring EFs (i.e., Update, Switch, Incongruent, and Stop) to test our hypotheses and reduce the number of statistical tests. To assess the immediate transfer effect of the NF training, RM ANOVA was performed for AC, RT, and RTV with TIME (pre vs. post) as the within-subject factor and GROUP (NF vs. sham) as the between-subjects factor. To assess the long-term effects after six months, RM ANOVAs were repeated with TIME (pre vs. follow-up) as the within-subject factor and GROUP (NF vs. sham) as the between-subjects factor. Descriptive data was provided for participants who completed the 12-month follow-up (n = 9).

2.4.5. Correlations between self-regulation of frontal-midline theta and behavioral changes in executive functions

To explore the association between upregulation success in the NF training and change in behavior (i.e., AC, RT, and RTV) immediately after the NF training and in the long-term, Pearson correlation coefficients were calculated. Upregulation success was quantified as the average of all NF blocks across the eight sessions relative to their baseline and changes in behavior by the differences between the scores at the pre-measurement and the post- or 6-month follow-up measurement.

2.4.6. Transfer effects to frontal-midline theta during executive function tasks

To evaluate the transfer effects of the NF training on FM theta power during the four EF tasks, mean ERSP values were calculated for the theta frequency range (4-8 Hz) from 100 to 500 ms

after stimulus onset in electrodes Fz, FC1, FCz, FC2, and Cz. This time range was chosen because of the known engagement of EFs recruitment during this period. Individual time and frequency picking was conducted within the specified range. Subsequently, we computed the average FM theta power by considering a time interval of ± 50 ms and a frequency range of ± 1 Hz around the identified peak. The data was averaged for each participant, task, and condition. To examine the immediate transfer effect of the NF training on FM theta power, a RM ANOVA was conducted for each task condition requiring EFs (i.e., Update, Switch, Incongruent, and Stop) with TIME (pre vs. post) as the within-subject factor and GROUP (NF vs. sham) as the between-subjects factor. To assess the long-term effect after six months, RM ANOVAs were conducted again for the four task conditions with TIME (pre vs. follow-up) as the within-subject factor and GROUP (NF vs. sham) as the between-subjects factor. Descriptive data is provided for participants who completed the 12-month follow-up (n = 9).

2.4.7. Transfer effects to executive functions in daily life

The effects of NF training on subjective EFs in daily life were evaluated using RM ANOVA. The outcome variables were the BRIEF-A total score and the subscales Working memory, Shift, Task Monitor, and Inhibit. To examine the immediate transfer effect, the within-subject factor was TIME (pre vs. post) and the between-subjects factor was GROUP (NF vs. sham). To assess the long-term effect after six months, RM ANOVA was conducted again for the five BRIEF-A outcomes with TIME (pre vs. follow-up) as the within-subject factor and GROUP (NF vs. sham) as the between-subjects factor. Descriptive data is provided for participants who completed the 12-month follow-up measurement (n = 10).

2.4.8. Data preparation and interpretation

A winsorizing approach was applied to all data, in which outlying values (i.e., > three SD from the mean) for each group were replaced with a less extreme value (i.e., mean ± three times the *SD*) to minimize their influence (Sullivan et al., 2021). For the NF data, a total of fifteen missing blocks and four blocks with clearly erroneous values were replaced for individual participants (i.e., end baseline replaced with start baseline from the same session, NF block replaced with previous NF block from the same session, and transfer block replaced with transfer block from previous session).

For statistical tests, a *p*-value of ≤ .05 was used to determine significant differences. Multiple test correction was not applied for the RM ANOVAs due to the clear a priori hypotheses about the effects based on previous research. However, the interpretation and discussion of the results took into account the increased risk of type I errors that can occur due to multiple

testing (Streiner & Norman, 2011). To correct for multiple comparisons in the exploratory correlational analyses, the Benjamini-Hochberg adjustment with a false discovery rate of .05 was applied (Chen et al., 2017). In case of violations of sphericity in RM ANOVA, the Greenhouse-Geisser correction was applied and corrected degrees of freedom and *p*-values were reported. The effect size for RM ANOVA was indicated by partial eta squared (η_p^2) and interpreted as small (< .06), medium (≥ .06), or large (≥ .14). Pearson correlations were interpreted as small (< .3), medium (≥ .3), or large (≥ .5).

For all analyses of transfer effects, a conservative approach was used (i.e., comparison of NF vs. sham rather than NF responders vs. sham) to determine if the findings from previous research on FM theta NF could be replicated in this subclinical population. Finally, in order to detect a medium effect of η_p^2 = .06 (i.e., smallest effect size of interest) with 95% power in a within-between subjects RM ANOVA design with eight or nine measurements (two groups, α = .05, correlation among repeated measures = .5, non-sphericity correction epsilon = .5), G*Power 3.1.9.4, suggested we needed at least nineteen or seventeen participants per group, respectively. For the same RM ANOVA design with two measurements (two groups, α = .05, β = .95, η_p^2 = .06, correlation among repeated measures = .7, non-sphericity correction epsilon = 1), at least seventeen participants per group are required. Statistical analyses were performed using SPSS 26.

3. RESULTS

3.1. Group characteristics

Table 2 presents an overview of the demographics, ITP, and questionnaire scores for the NF and sham groups. Age ($t(56) = .689$, $p = .494$), education level ($X^2(2, n = 58) = 1.040$, $p = .595$), gender ($X^2(1, n = 58) = .305$, $p = .581$), and ITP ($t(56) = .964$, $p = .339$) did not differ between the NF and sham groups. Similarly, there were no significant differences between the groups in the number of reported depressive symptoms ($t(54) = -.212$, $p = .833$), with both groups scoring on average in the minimal range (≤ 13). Regarding ADHD symptoms, both groups had a similar number of attentional symptoms ($t(54) = .287$, $p = .776$). In the NF group, 69.0% of participants reported four or more attentional symptoms, and in the sham group 62.1%. The NF and sham groups also did not differ regarding the number of hyperactivity symptoms ($t(54) = -1.103$, $p = .275$), 31.0% of participants in the NF group and 48.3% in the sham group reported four or more hyperactivity symptoms.

Table 2. Demographic characteristics and questionnaire scores for the NF and sham groups. Note: ITP = individual theta peak, BDI-II = Beck Depression Inventory II, ZVAH = Self-report questionnaire on attention problems and hyperactivity for adult- and childhood (adult version). * Information is missing for two participants (n = 27).

	NF group (n = 29)	Sham group (n = 29)
Categorical variables	n (%)	n (%)
Education level (low / intermediate / high)	1 (3.4%) / 12 (41.4%) / 16 (55.2%)	0 (0%) / 13 (44.8%) / 16 (55.2%)
Sex (female)	18 (62.1%)	20 (69.0%)
Continuous variables	*M* (*SD*)	*M* (*SD*)
Age (in years)	34.5 (11.8) Range: 20-60	32.5 (9.8) Range: 20-52
ITP	6.1 (.8)	5.9 (.9)
BDI-II total score at T2	9.4 (7.4) *	9.8 (6.2)
ZVAH Attentional symptoms at T2	5.1 (2.6) *	4.9 (3.0)
ZVAH Hyperactivity symptoms at T2	2.8 (2.1) *	3.6 (3.0)

In the NF group, nine participants reported receiving a diagnosis of attention deficit disorder (ADD). Additionally, three participants had been diagnosed with ADHD, four with autism spectrum disorder (with one also reporting bipolar disorder), and one with post-traumatic stress disorder. The sham group included nine participants reporting a diagnosis of ADD, seven with ADHD (one of which additionally reported borderline personality disorder), two with autism spectrum disorder, and one reported a history of depression and anorexia. For most

participants, the diagnosis was confirmed by a mental healthcare organization through their general practitioner, but for three participants, the reported diagnosis was either not confirmed or no permission was obtained from the participant. In the NF group and sham group, there were three and four participants, respectively, who suspected to suffer from AD(H)D, but this was not confirmed by a medical expert (yet).

During the NF training, nine participants in the NF group reported taking medications that could potentially impact their cognition. These medications included seven stimulants, one antidepressant, and one atypical antipsychotic. In the sham group, eleven participants were taking medications, including eight stimulants (one combined with an antidepressant), two antidepressants, and one an antidepressant plus an anticonvulsant. Two participants in the sham group voluntarily ceased taking stimulants until after the post-measurement was conducted.

3.2. Neurofeedback training effects

3.2.1. Neurofeedback training effects in the full groups

Figure 4 gives an overview of the absolute FM theta amplitude (A) and FM theta amplitude relative to the respective baseline (B) for all blocks and sessions for both the NF and sham group, as well as the session-to-session changes in the NF blocks (C) and the dynamical changes within sessions for each block (D). The descriptive Figures 4A, B show that visually the absolute FM theta amplitudes seem higher in the sham group relative to the NF group, however, this observed trend is reversed when FM theta amplitudes are considered relative to the respective baselines. Additionally, Table 3 gives an overview of the depicted estimated marginal means with their 95% confidence interval.

When statistically assessing relative changes in amplitude from session-to-session (i.e., Learning Index 1), a RM ANOVA for FM theta revealed no significant interaction effect SESSION × GROUP (F(4.038,226.119) = .364, p = .836), and no main effect of GROUP (F(1,56) = 1.815, p = .183), which both is contrary to expectations. Additionally, no main effect was found for SESSION (F(4.038,226.119) = .692, p = .559), and also not for delta, alpha, and beta amplitudes.

Regarding the dynamical changes in amplitude within sessions (i.e., Learning Index 2), a RM ANOVA for FM theta again showed no significant interaction effect BLOCK × GROUP (F(3.069,171.880) = 1.124, p = .342) or main effect for GROUP (F(1,56) = 1.512, p = .224). There

was, however, a main effect for BLOCK (F(3.069,171.880) = 2.818, p = .039, η_p^2 = .048), see Figure 4D. For delta, alpha, and beta, there were also significant main effects for BLOCK (delta: F(3.433,192.230) = 21.575, p < .001, η_p^2 = .278; alpha: F(2.431,136.127) = 12.299, p < .001, η_p^2 = .180; and beta: F(2.366,132.476) = 6.500, p = .001, η_p^2 = .104). In both groups, delta decreased in amplitude across blocks within sessions, while alpha and beta showed an increase. A full overview of all RM ANOVA results can be found in Supplementary material Tables 1 and 2.

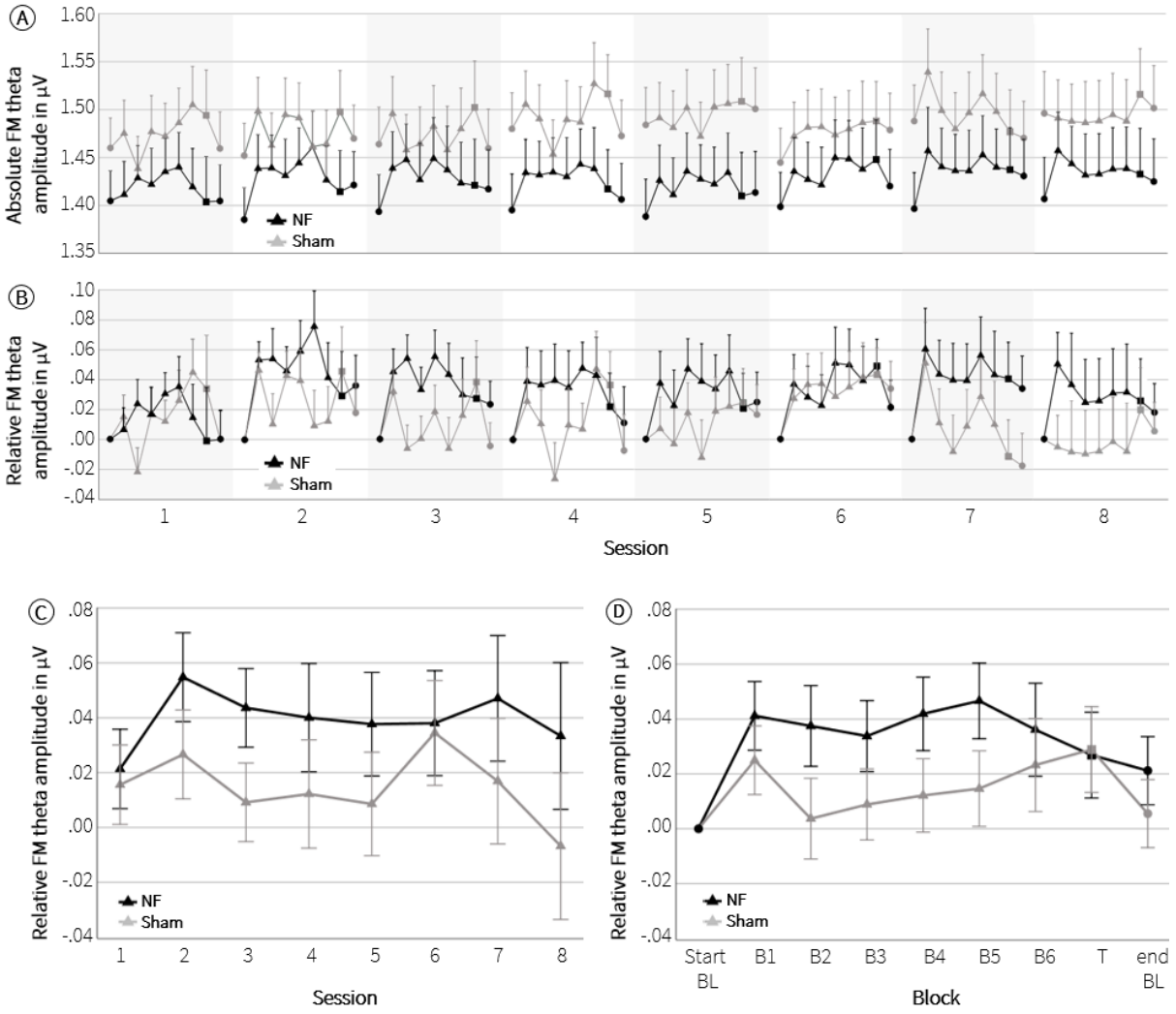

Figure 4. Neurofeedback (NF) results for the NF group and sham group; (A) mean absolute FM theta amplitude for each block per session, (B) mean FM theta amplitude relative to the respective start baseline for each block per session, (C) learning Index 1: Mean FM theta amplitude relative to the respective start baseline per session across the six NF blocks (i.e., session-to-session changes), and (D) learning Index 2: Mean FM theta amplitude relative to the respective start baseline per block across sessions (i.e., dynamical changes within sessions). Note: Error bars indicate the standard error of the mean. • = baseline (BL) start or end, ▲ = NF block(s), and ■ = transfer (T) block.

Table 3. Estimated marginal means for the neurofeedback (NF) sessions in Learning Index 1 and the blocks in Learning Index 2 for the NF group and sham group. Note: The start baseline is not included because this is zero. SEM = standard error of the mean, CI = confidence interval, B1 = neurofeedback block 1, etc. T = transfer block, End BL = end baseline (resting state EEG).

		NF group (n = 29)				**Sham group** (n = 29)			
	Session/			95% CI				95% CI	
	Block	*M*	*SEM*	Left	Right	*M*	*SEM*	Left	Right
Learning	1	.021	.014	−.008	.050	.016	.014	−.013	.045
Index 1	2	.055	.016	.022	.087	.027	.016	−.006	.059
	3	.044	.014	.015	.072	.009	.014	−.020	.038
	4	.040	.020	.000	.080	.012	.020	−.027	.052
	5	.038	.019	−.000	.075	.009	.019	−.029	.046
	6	.038	.019	−.000	.076	.034	.019	−.004	.073
	7	.047	.023	.001	.093	.017	.023	−.029	.063
	8	.033	.027	−.020	.087	−.007	.027	−.060	.047
Learning	B1	.041	.013	.016	.066	.025	.013	−.000	.050
Index 2	B2	.037	.015	.008	.067	.004	.015	−.026	.033
	B3	.034	.013	.008	.060	.009	.013	−.017	.035
	B4	.042	.013	.015	.069	.012	.013	−.015	.039
	B5	.047	.014	.019	.074	.015	.014	−.013	.042
	B6	.036	.017	.002	.070	.023	.017	−.011	.057
	T	.027	.016	−.004	.058	.029	.016	−.002	.060
	End BL	.021	.012	−.004	.046	.006	.012	−.019	.030

3.2.2. Neurofeedback training effects responders in the NF group vs. sham group

In the NF group, 62.1% of the participants were classified as responders (n = 18) and 37.9% as non-responders (n = 11). In the sham group 51.7% (n = 15) were also classified as responders and 48.3% (n = 14) as non-responder. Figure 5 shows the session-to-session changes in FM theta amplitude in the NF blocks and the dynamical changes within sessions for each block for the responders in the NF group and the sham group. The RM ANOVA for session-to-session changes (i.e., Learning Index 1) revealed a significant main effect of GROUP ($F(1,45) = 4.269$, $p = .045$, $\eta_p^2 = .087$). Responders in the NF group exhibited significantly higher FM theta amplitudes throughout the eight NF sessions, starting from the first NF session, in comparison to the sham group. However, the study revealed a lack of significant interaction effect between SESSION × GROUP ($F(3.874,174.319) = .432$, $p = .779$). Both results together suggest that there was a consistent difference in FM theta upregulation starting from the first session, without a further significant increase throughout the NF session among the NF responders compared to the sham group. Furthermore, there was no significant main effect for SESSION ($F(3.874,174.319) = .467$, $p = .754$).

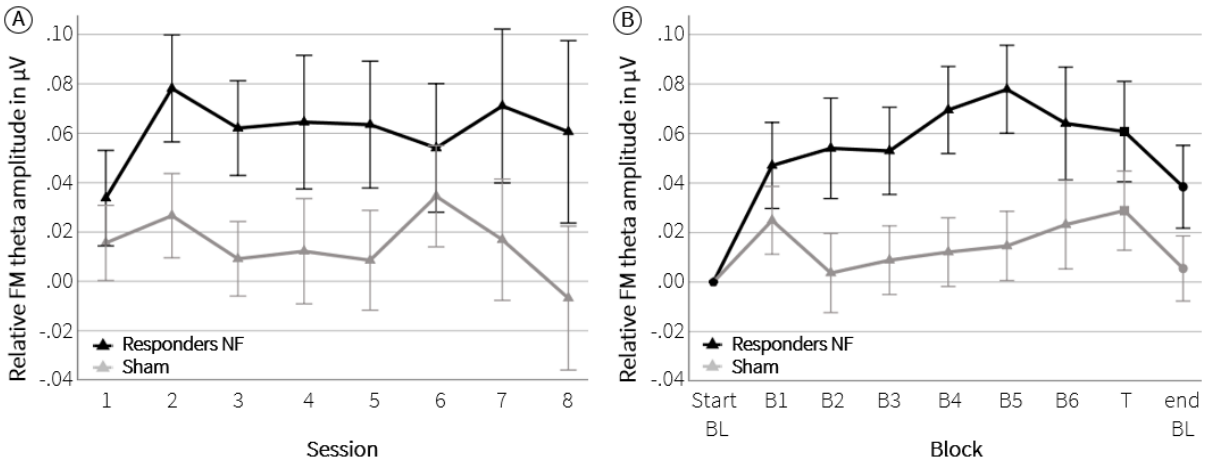

Figure 5. Neurofeedback (NF) learning indices for the responders in the NF group and the sham group. (A) Learning Index 1: Mean FM theta amplitude relative to the respective start baseline per session across the six NF blocks (i.e., session-to-session changes) and (B) Learning Index 2: Mean FM theta amplitude relative to the respective start baseline per block across sessions (i.e., dynamical changes within sessions). Note: Error bars indicate the standard error of the mean. • = baseline (BL) start or end, ▲ = NF block(s), and ■ = transfer (T) block.

Repeated measures ANOVA for dynamical changes in FM theta amplitude within sessions (i.e., Learning Index 2) revealed similar results. Again, there was a significant main effect of GROUP (F(1,45) = 4.692, p = .036, η_p^2 = .094); across the blocks, responders in the NF group showed a higher FM theta amplitude compared to the sham group, including the end baseline block, in which participants were not asked to upregulate their FM theta. There was no other significant interaction effect of BLOCK × GROUP (F(2.907,130.834) = 1.612, p = .191), suggesting that the difference between the responders in the NF group and the sham group on FM theta was consistently higher across blocks. Finally, a significant main effect of BLOCK was found (F(2.907,130.834) = 3.755, p = .013, η_p^2 = .077).

3.2.3. Characteristics responders vs. non-responders

Table 4 provides an overview of demographic characteristics, questionnaire scores, and NF outcomes for the responders and non-responders in the NF group. Overall, the two groups were very similar, but the responders included relatively more participants without a psychiatric disorder (X^2(2, n = 29) = 7.735, p = .021).

Table 4. Demographic characteristics and questionnaire scores, and NF outcomes of the responders and non-responders in the NF group. Note: BRIEF-A = Behavior Rating Inventory of Executive Function - Adult Version, BDI-II = Beck Depression Inventory II, ZVAH = Self-report questionnaire on attention problems and hyperactivity for adult and childhood (adult version), ADD = attention deficit disorder, ADHD = attention deficit hyperactivity disorder, ASD = autism spectrum disorder, PTSD = post-traumatic stress disorder, T1 = pre-measurement, and T2 = post-measurement. * In both groups, information is missing for one participant. Self-reported motivation, commitment, and difficulty were rated on a 7-point Likert scale and averaged across eight sessions.

	Responders (n = 18)	Non-responders (n = 11)
Continuous variables	*M* (*SD*)	*M* (*SD*)
Mean FM theta amplitude during first resting state in NF session 1	1.425 (.140)	1.372 (.115)
Motivation	5.7 (1.0)	5.6 (1.0)
Commitment	5.2 (1.2)	5.7 (1.1)
Difficulty	4.5 (.7)	4.8 (.7)
Age	34.1 (11.1)	35.0 (13.5)
BRIEF-A total score (T1)	155.1 (18.7)	154.9 (18.8)
BRIEF-A Working memory (T1)	18.6 (2.6)	19.7 (3.0)
BRIEF-A Shift (T1)	13.1 (3.3)	13.6 (3.0)
BRIEF-A Task monitor (T1)	14.9 (2.2)	14.0 (2.6)
BRIEF-A Inhibit (T1)	16.0 (3.3)	15.5 (3.6)
BDI-II total score (T1)	9.3 (8.2) *	9.6 (6.0) *
ZVAH Attentional symptoms (T2)	4.8 (2.5) *	5.7 (2.7) *
ZVAH Hyperactivity symptoms (T2)	2.8 (2.1) *	2.7 (2.3) *
Categorical variables	n (%)	n (%)
Educational level	Low: 0 (0.0%), Intermediate: 6 (33.3%), High: 12 (66.7%)	Low: 1 (9.1%), Intermediate: 6 (54.5%), High: 4 (36.4.3%)
Sex (female)	11 (61.1%)	7 (63.6%)
Presence of disorder	No diagnosis: 7 (38.9%), ADD : 7 (38.9%), ADHD: 1 (5.6%), ASD: 2 (11.0%), PTSD: 1 (5.6%)	No diagnosis: 2 (18.2%), Suspect AD(H)D: 3(27.2%), ADD: 2 (18.2%), ADHD: 2 (18.2%), ASD: 1 (9.1%), ASD + bipolar disorder: 1 (9.1%)
Medication use	No medication: 13 (72.2%), Stimulants: 4 (22.2%), Atypical antipsychotic: 1 (5.6%)	No medication: 7 (63.6%), Stimulants: 3 (27.3%), Antidepressant: 1 (9.1%)

3.3. Credibility sham group

A chi-square test of independence showed that there was no significant association between actual and guessed group membership ($X^2(1, n = 41) = 1.90$, $p = .168$). Additionally, there were no significant differences between groups in motivation, commitment, and perceived difficulty

during the training. However, for motivation there was a significant main effect of SESSION (F(5.567,311.769) = 8.313, p < .001, η_p^2 = .129); both groups showed a decrease in motivation over the course of the sessions. The levels of commitment and perceived difficulty were stable throughout the training. A full overview of the results can be found in Supplementary material Table 3.

Finally, Table 5 provides an overview of demographic characteristics, questionnaire scores, and NF success for participants who completed the follow-up measurement (n = 41) and those who dropped out (n = 17). Overall, the two groups are very similar, but the group that completed the follow-up appears to have relatively more participants with a disorder.

3.4. Transfer effects on behavior

3.4.1. Immediate behavioral transfer effects

Figure 6 provides an overview of behavioral performance on the four EF tasks (i.e., N-back, Switching, Stroop, and Stop-signal task) at pre-, post-, and follow-up measurements. For the Update condition of the N-back task, RM ANOVAs demonstrated, contrary to our expectations, no significant interaction effects of TIME × GROUP. There was a significant main effect of TIME for AC (F(1,56) = 22.148, p < .001, η_p^2 = .283) and RT (F(1,56) = 7.627, p = .008, η_p^2 = .120); both groups improved their AC and reduced RT immediately after the NF training. There were no significant main effects of GROUP.

For the Switch condition of the Switching task, again contrary to expectations, there were no significant interaction effects TIME × GROUP. For RTV, there was a significant main effect of GROUP (F(1,56) = 4.524, p = .038, η_p^2 = .075); the NF group scored significantly higher than the sham group across both measurements. Additionally, there were significant main effects of TIME for AC (F(1,56) = 41.460, p < .001, η_p^2 = .425) and RT (F(1,56) = 36.683, p < .001, η_p^2 = .396), both groups improved their AC and reduced RT immediately after the NF training.

For the Incongruent condition of the Stroop task, no significant interaction effects TIME × GROUP or main effects of GROUP were found. There was a significant main effect of time for AC (F(1,56) = 7.113, p = .010, η_p^2 = .113), RT (F(1,56) = 28.787, p < .001, η_p^2 = .340), and RTV (F(1,56) = 4.976, p = .030, η_p^2 = .082); both groups improved AC and reduced RT and RTV immediately after the NF training.

Table 5. Demographic characteristics and questionnaire scores, and NF outcomes of participants who completed the follow-up measurement (either after six or twelve months) and those who dropped out after the post-measurement. Note: BRIEF-A = Behavior Rating Inventory of Executive Function - Adult Version, BDI-II = Beck Depression Inventory II, ZVAH = Self-report questionnaire on attention problems and hyperactivity for adult and childhood (adult version), ADD = attention deficit disorder, ADHD = attention deficit hyperactivity disorder, BPD = borderline personality disorder, ASD = autism spectrum disorder, PTSD = post-traumatic stress disorder, T1 = pre-measurement, and T2 = post-measurement. Motivation, commitment, and difficulty were self-rated on a 7-point Likert scale and averaged across eight sessions. * Information is missing for two participants (n = 15).

	Completed follow-up (n = 41)	**Drop-outs** (n = 17)
Continuous variables	*M* (*SD*)	*M* (*SD*)
Motivation	5.7 (.9)	5.4 (1.0)
Commitment	5.7 (1.0)	5.1 (1.3)
Difficulty	4.6 (.8)	4.7 (.9)
Age	33.4 (10.7)	33.6 (11.5)
BRIEF-A total score (T1)	156.4 (18.4)	154.1 (17.9)
BRIEF-A Working memory (T1)	19.8 (2.6)	18.9 (2.7)
BRIEF-A Shift (T1)	13.3 (2.6)	13.0 (2.6)
BRIEF-A Task monitor (T1)	14.9 (2.3)	14.5 (2.0)
BRIEF-A Inhibit (T1)	16.0 (3.4)	16.3 (3.3)
BDI-II total score (T2)	9.5 (7.2)	9.9 (5.7) *
ZVAH Attentional symptoms (T2)	5.0 (3.0)	5.0 (2.2) *
ZVAH Hyperactivity symptoms (T2)	3.1 (2.7)	3.5 (2.4) *
Categorical variables	n (%)	n (%)
NF success (responder)	33 (80.5%)	14 (82.4%)
Educational level	Low: 0 (0.0%), Intermediate: 16 (39.0%), High: 25 (61.0%)	Low: 1 (5.9%), Intermediate: 7 (41.2%), High: 9 (52.9%)
Sex (female)	26 (63.4%)	12 (70.6%)
Presence of disorder	No diagnosis: 8 (19.5%), Suspect AD(H)D: 5 (12.2%), ADD: 13 (31.8%), ADHD: 6 (14.7%), ADHD + BPD: 1 (2.4%), ASD: 5 (12.2%), ASD + bipolar disorder: 1 (2.4%), PTSD: 1 (2.4%), History of depression + anorexia: 1 (2.4%)	No diagnosis: 7 (41.2%), Suspect AD(H)D: 2 (11.8%), ADD: 5 (29.4%), ADHD: 3 (17.6%)
Medication use during NF training	No medication 26 (63.4%), Stimulants: 10 (24.4%), Antidepressant: 2 (4.9%), Stimulant + anticonvulsant: 1 (2.4%), Stimulant + antidepressant 1: (2.4%), Atypical antipsychotic: 1 (2.4%)	No medication: 12 (70.6%), Stimulants: 4 (23.5%), Antidepressant: 1 (5.9%)

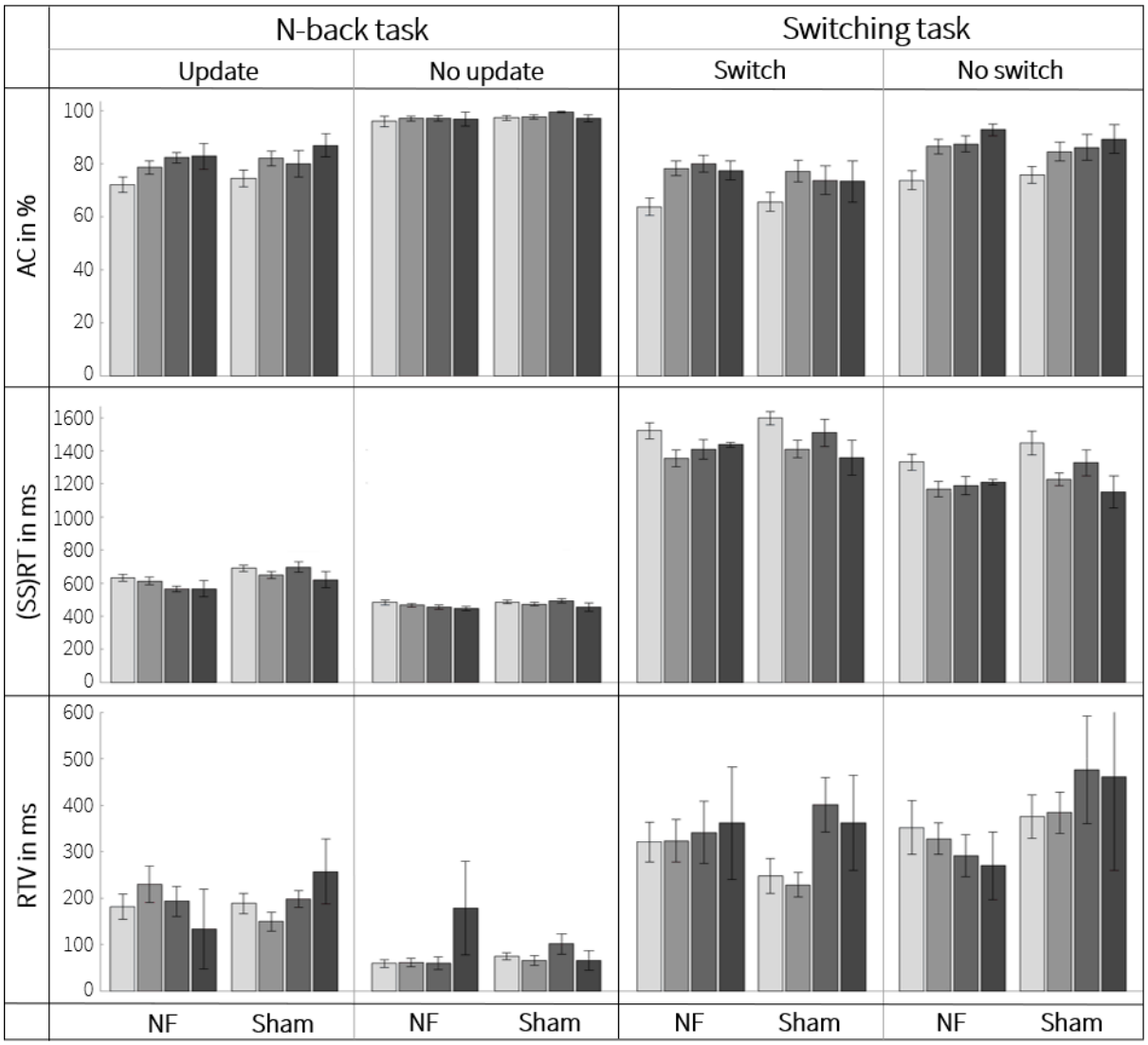

Figure 6. Mean accuracy (AC), reaction time (RT), and RT variability (RTV) for all conditions of the N-back, Switching, Stroop, and Stop-signal task at pre-measurement, post-measurement, 6-month follow-up*, and 12-month follow-up* for the NF group and sham group. Note: Error bars indicate the standard error of the mean. *Due to COVID-19 regulations, not all participants could perform the 6-month follow-up measurement. Therefore, nine participants did a 12-month follow-up measurement instead.

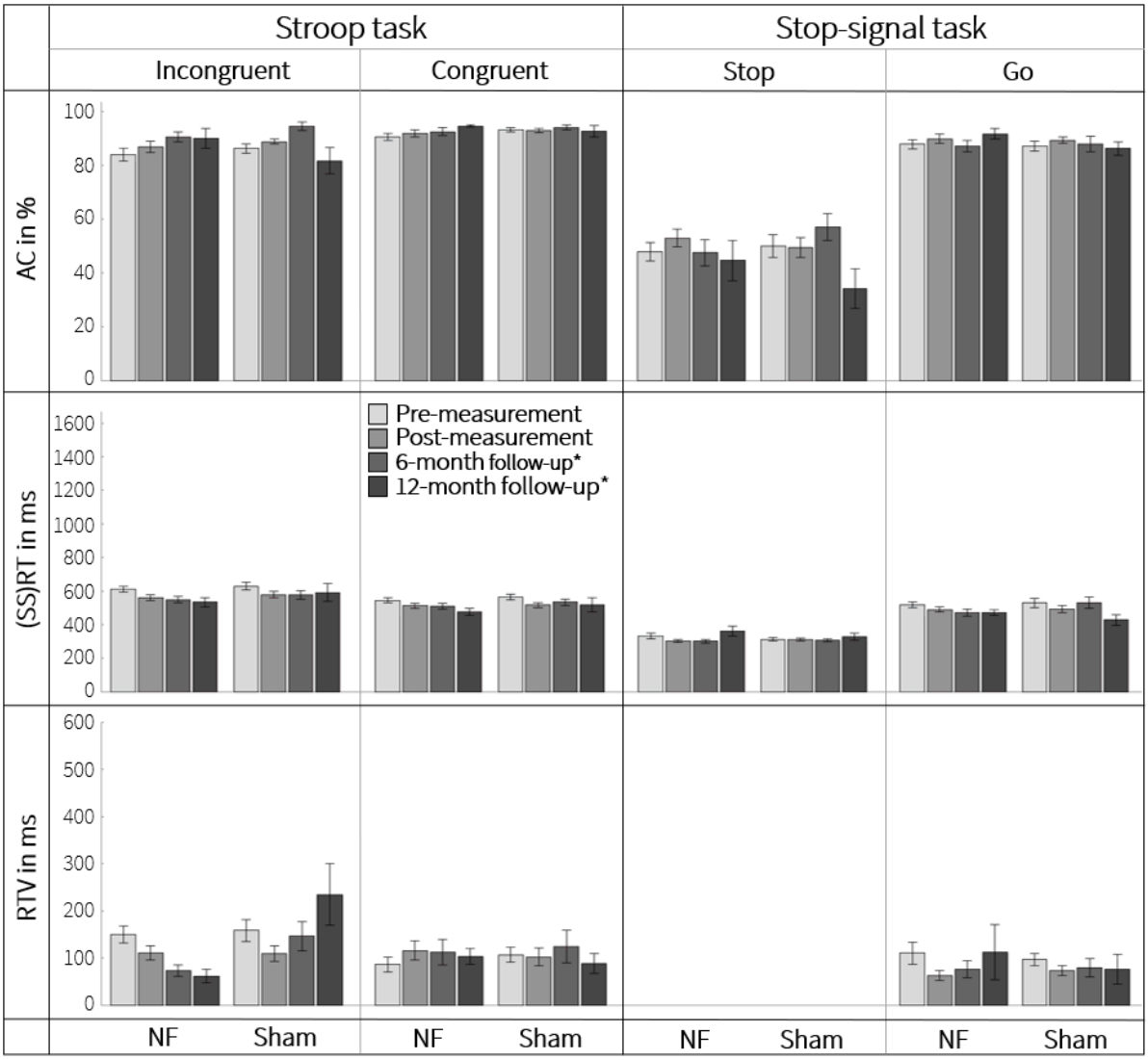

Figure 6. Continued.

Finally, for the Stop condition of the Stop-signal task, there was no significant interaction between TIME × GROUP, and again only a significant main effect of TIME for the SSRT (F(1,56) = 3.996, p = .050, η_p^2 = .067); both groups improved their SSRT. A full overview of all RM ANOVA results can be found in Supplementary material Table 4.

3.4.2. Long-term behavioral transfer effects

The assessment of NF training effects after six months (i.e., pre- vs. 6-month follow-up measurement) revealed significant results for the Update condition of the N-back task. For RT, the RM ANOVA showed as expected a significant interaction effect TIME × GROUP (F(1,30) = 4.410, p = .044, η_p^2 = .128) and a main effect of GROUP (F(1,30) = 6.991, p = .013, η_p^2 = .189). The results showed that both prior to the NF training and six months later, the NF group had faster RTs compared to the sham group. However, the difference between groups was even larger at the 6-month follow-up measurement, suggesting specific FM theta NF effects on RT. Additionally, there was a significant main effect of TIME for AC (F(1,30) = 6.808, p = .014, η_p^2 = .185); both groups showed higher AC six months after the NF training compared to before the training.

For the Switch condition of the Switching task, there was no significant interaction TIME × GROUP. Only a significant main effect of TIME was found for AC (F(1,30) = 25.136, p < .001, η_p^2 = .456), with both groups showing a higher AC at the 6-month follow-up measurement than before the training.

Regarding the Incongruent condition of the Stroop task, RM ANOVA revealed a significant interaction effect TIME × GROUP (F(1,30) = 4.446, p = .043, η_p^2 = .129), as well as a main effect of TIME (F(1,30) = 7.308, p = .011, η_p^2 = .196) for RTV. These results indicate that both groups showed a reduction in reaction time variability (RTV) six months after the training, however, the reduction in RTV was greater for the NF group compared to the sham group, suggesting specific FM theta NF effects on RTV. Additionally, significant main effects of TIME were observed for AC (F(1,30) = 11.835, p = .002, η_p^2 = .283) and RT (F(1,30) = 15.931, p < .001, η_p^2 = .347); both groups improved AC and reduced RT six months after the NF training.

Finally, considering the Stop condition of the Stop-signal task, no significant interaction effects or main effects were found. A full overview of all RM ANOVA results can be found in Supplementary material Table 5.

3.5. Correlations between self-regulation of frontal-midline theta and behavioral changes in executive functions

Table 6 shows an overview of the Pearson correlations between upregulation success in the NF training and change in behavior (i.e., AC, RT, and RTV) immediately after the NF training (i.e., pre- vs. post-measurement) and in the long-term (i.e., pre- vs. follow-up measurement). The results show that there were no significant associations (i.e., p > Benjamini-Hochberg critical value) when considering the whole sample.

Table 6. Pearson correlations between FM theta upregulation success and the behavioral outcomes accuracy (AC), reaction time (RT) or stop-signal reaction time (SSRT), and RT variability (RTV) immediately after neurofeedback training and after six months

		Pre- versus post-measurement (n = 58)		Pre- versus 6-month follow-up measurement (n = 32)	
Task condition	Change in	*r*	*p*	*r*	*p*
Update	AC	−.067	.617	−.171	.349
	RT	−.152	.256	−.207	.257
	RTV	−.024	.860	.032	.860
Switch	AC	−.177	.185	−.337	.059
	RT	−.148	.268	.069	.709
	RTV	−.170	.203	−.161	.379
Incongruent	AC	−.041	.758	−.168	.357
	RT	.247	.061	.148	.420
	RTV	.221	.095	.297	.099
Stop	SSRT	.085	.523	.109	.553

3.6. Transfer effects to frontal-midline theta

3.6.1. Immediate transfer effects to frontal-midline theta during executive function tasks

Figure 7 gives an overview of the mean FM theta power across the pre-, post-, and follow-up measurements. RM ANOVAs of the immediate effects of the NF training on theta power 100 to 500 ms after stimulus onset (i.e., pre- vs. post-measurement), revealed no significant interaction effect TIME × GROUP or main effects for TIME or GROUP for the four task conditions. A full overview of all RM ANOVA results can be found in Supplementary material Table 6.

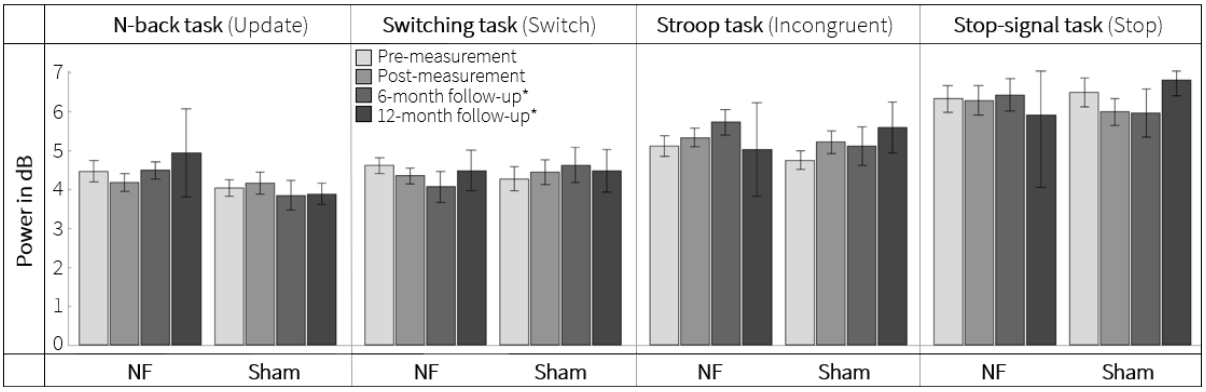

Figure 7. Mean frontal-midline (FM) theta power (± 1 Hz and ± 50 ms around the highest peak in FM theta power identified within 100 to 500 ms after stimulus onset between 4 and 8 Hz) for the task conditions requiring EFs (i.e., Update condition of the N-back task, Switch condition of the Switching task, Incongruent condition of the Stroop task, and Stop condition of the Stop-signal task) at pre-measurement, post-measurement, 6-month follow-up*, and 12-month follow-up* for the NF group and sham group. Note: Error bars indicate the standard error of the mean. *Due to COVID-19 regulations, not all participants could perform the 6-month follow-up measurement. Therefore, nine participants did a 12-month follow-up measurement instead.

3.6.2. Long-term transfer effects to frontal-midline theta during executive function tasks

For the effects after six months (i.e., pre- vs. 6-month follow-up measurement), RM ANOVA showed no significant interaction effect TIME × GROUP or main effect for GROUP. There was, however, a significant main effect of TIME for the Incongruent condition of the Stroop task (F(1,28) = 7.003, p = .013, η_p^2 = .200); theta power was significantly higher in both groups six months after the NF training compared to before the training. A full overview of all RM ANOVA results can be found in Supplementary material Table 7.

3.7. Transfer effects to daily life

3.7.1. Immediate transfer effects to executive functions in daily life

Figure 8 provides an overview of scores on the BRIEF-A outcomes at pre-, post-, and follow-up measurements. Regarding the immediate effects after the NF training (i.e., pre- vs. post-measurement), RM ANOVA showed a significant interaction effect TIME × GROUP (F(1,56) = 5.865, p = .019, η_p^2 = .095) and main effect of TIME (F(1,56) = 7.863, p = .007, η_p^2 = .123) for the Working memory subscale. Contrary to expectation, the sham group showed a larger decrease in complaints than the NF group. Additionally, there were significant main effect of TIME for the BRIEF-A total score (F(1,56) = 19.497, p < .001, η_p^2 = .258) and subscales Shift (F(1,56) = 10.915, p = .002, η_p^2 = .163) and Task monitor (F(1,56) = 7.287, p = .009, η_p^2 = .115). Both groups showed a decrease in the number of complaints on these BRIEF-A outcomes immediately after the NF

training. For the Inhibit subscale, no significant interaction or main effects were found. A full overview of all RM ANOVA results can be found in Supplementary material Table 8.

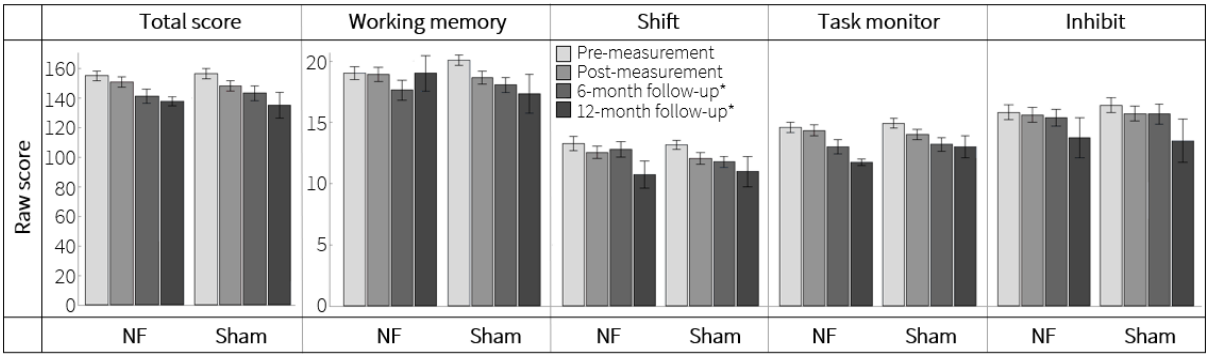

Figure 8. Mean scores on the BRIEF-A total score and subscales Working memory, Shift, Task monitor, and Inhibit at pre-measurement, post-measurement, 6-month follow-up*, and 12-month follow-up* for the NF group and sham group. Note: Error bars indicate the standard error of the mean. *Due to COVID-19 regulations, not all participants could complete the BRIEF-A at 6-month follow-up. Therefore, ten participants completed it at 12-month follow-up.

3.7.2. Long-term transfer effects to executive functions in daily life

In total, 39 participants completed the BRIEF-A six months after the NF training, and ten participants completed it after twelve months. Regarding the effects after six months (i.e., pre- vs. 6-month follow-up measurement), no significant interaction effect TIME × GROUP or main effect for GROUP were found. However, there were significant main effects of TIME for all BRIEF-A outcomes: total score ($F(1,37) = 48.168$, $p < .001$, $\eta_p^2 = .566$) and subscales Working memory ($F(1,37) = 23.317$, $p < .001$, $\eta_p^2 = .387$), Shift ($F(1,37) = 12.483$, $p = .001$, $\eta_p^2 = .252$), Task monitor ($F(1,37) = 43.887$, $p < .001$, $\eta_p^2 = .543$), and Inhibit ($F(1,37) = 10.081$, $p = .003$, $\eta_p^2 = .214$). In both groups, the number of complaints measured by these outcomes was significantly lower six months after training than before training. A full overview of all RM ANOVA results can be found in Supplementary material Table 9.

4. DISCUSSION

This study examined for the first time the effects of FM theta NF on EFs in a (sub)clinical population characterized by notable self-reported EF complaints in daily life. Using a pre/post/follow-up design with a sham NF group, the immediate and long-term effects of an 8-session individualized FM theta NF training were assessed in 58 adults aged 20-60 years. First, it was examined whether the NF training resulted in improved upregulation of FM theta using two NF learning indices. Second, the immediate and long-term transfer effects of the NF training were assessed. This included behavioral performance on proactive and reactive EF tasks (assessing working memory updating, set-shifting, conflict monitoring, and response inhibition), FM theta power during these tasks, and subjective EFs in daily life.

The findings indicate that there is only a significant difference in the upregulation of FM theta between the NF group and sham group when participants who did not respond to the NF are excluded from the analysis. Additionally, the study demonstrates that the NF group displays stronger improvement in behavioral performance for working memory updating and conflict monitoring at the 6-month follow-up. However, there are no NF-specific effects identified immediately after the NF training. Furthermore, no immediate or long-term effects specific to the NF training are observed for FM theta power during the EF tasks and EFs in daily life. These results regarding FM theta upregulation and transfer effects, as well as predictors of NF learning and NF training relative to other interventions for EFs, are discussed in more detail below.

4.1. Effects of non-responders on training efficacy

Our findings indicate that FM theta amplitudes are not significantly different between the NF and sham groups, when both indices of NF learning are examined and all participants are considered. This result cannot be explained by initial group differences or participants' awareness of group assignment. Yet, the proportion of participants non-response in the NF group (i.e., 37.9%) could play a role, which is a rate consistent with the findings of previous NF studies (e.g., Alkoby et al., 2018). Excluding these non-responders, the analysis reveals that the responders in the NF group exhibit the anticipated outcome of higher FM theta amplitudes compared to the sham group. However, an increasing number of NF sessions for the responders in the NF group greater upregulation of FM theta, instead remaining constant when compared to the sham group. These findings differ from previous studies in healthy young and older adults, which demonstrated a greater increase in FM theta in the NF group also across sessions without accounting for non-responders (Wang & Hsieh, 2013; Enriquez-Geppert et al.,

2014a; Brandmeyer & Delorme, 2020; Eschmann & Mecklinger, 2022). Inherent to their EF complaints, it is possible that the participants in this study had more difficulty retaining instructions, sitting still, focusing on the feedback, and maintaining the use of strategies and adapting them as needed (e.g., Roth et al., 2005), which might have reduced their ability to learn from the feedback and self-regulate FM theta. Moreover, it may be that our participants had lower baseline levels of FM theta compared to healthy individuals, which is disadvantageous for upregulation success (Weber et al., 2020). Finally, the current study included a highly heterogeneous group of participants in terms of age, educational level, presence of psychiatric disorder, and medication use. This may have resulted in weaker learning compared to previous FM theta NF studies that included mostly healthy, young, highly educated students (e.g., Hooghe et al., 2010). It may be necessary to conduct a greater number of sessions in individuals with (sub)clinical conditions to attain the same level of upregulation observed in a healthy sample. For example, NF for ADHD in clinical settings typically consists of 30-40 sessions (Arns et al., 2020).

It is worth noting that the learning curve for session-to-session changes (reflected in Learning Index 1) in the NF group shows a pattern similar in the first part of the training to that observed in other studies on FM theta NF. Nonetheless, in the second part of the NF training, FM theta upregulation appears weaker in our (sub)clinical group, although participants receive the same number of sessions with similar training intensity. A recommended next step is to conduct a mega-analysis to accurately evaluate the overall learning curve of FM theta NF training. By pooling raw data from all FM theta NF studies, a mega-analysis retains a higher level of detail compared to a meta-analysis which is based on summary statistics (Eisenhauer, 2021).

Another difference from prior studies is that effects are not specific to theta activity (Enriquez-Geppert et al., 2014a; Eschmann & Mecklinger, 2022), but are also found in adjacent frequency bands. Both groups showed a significant decrease in delta activity and an increase in alpha and beta activity within sessions. However, one would expect an opposite pattern of an increase in delta and a decrease in alpha and beta due to a gradually increasing level of drowsiness and mind wandering and reduced effort in applying mental strategies over the course of a session (MacLean et al., 2012; Kam et al., 2022). Our contrary findings may indicate an attempt by the brain to maintain attention and focus on applying mental strategies by increasing mental effort (e.g., Klimesch, 2012; Pershin et al., 2023).

Interestingly, 51.7% of participants in the sham group were also classified as a responder. This suggests that, despite receiving sham feedback, the sham group demonstrated a certain degree of FM theta upregulation compared to the start baseline (see Figure 4D) which is rather in contrast to previous studies with healthy participants (e.g., Enriquez-Geppert et al., 2014b; Eschmann & Mecklinger, 2022). The current findings imply that the utilization of suggested mental strategies alone might have contributed to the enhancement of FM theta. However, it is important to note that the effectiveness of these strategies is further augmented by receiving accurate feedback regarding actual brain activity. Two implications follow: First, future studies should explore the association between specific strategies and the increase of FM theta, providing further insights into the underlying mechanisms. Second, these findings also raise the question of identifying an optimal sham group and stimulating discussions regarding the use of real self-regulation of random neural frequencies as an active control group (e.g., in Eschmann & Mecklinger, 2022). Instead of merely replaying feedback from a matched participant in the experimental groups, the alternative approach could contribute to a more accurate interpretation of the results.

4.2. Predictors of neurofeedback learning ability

The responders and non-responders in the NF group exhibited similarities regarding demographics, questionnaire scores, and NF training-related factors. However, it is worth noting that among the non-responders there is a higher proportion of participants that report having or suspecting a psychological diagnosis. The presence of specific disorders and disorder-related features may impact the ability to self-regulate specific brain features. For example, fMRI-based NF training targeting anterior cingulate cortex (ACC) activity in schizophrenia patients resulted in activation of the dorsal ACC (better known as MCC; Vogt, 2016), whereas healthy controls activated the rostral ACC (Cordes et al., 2015). Patients with schizophrenia may have activated the dorsal subregion as a compensatory mechanism to regulate the ACC signal, given that they commonly experience impairments in the rostral ACC (e.g., Habel et al., 2010). Additionally, comorbid conditions, such as anxiety or sleeping difficulties, might further impact the ability to learn and benefit from NF (e.g., Rasch & Born, 2013; Koush et al., 2017).

An important question in the field of interventions is whether healthy individuals or patients get the most benefit from training. This question has important implications for the design and implementation of interventions, because it has the potential to inform how to optimize the impact of NF. One hypothesis assumes that individuals with more pronounced (sub)clinical

impairments have theoretically greater capacity for improvement, whereas the Matthew principle states that those who begin with an advantage will accumulate more advantage over time (Rigney, 2010). NF is an active treatment, as opposed to passive treatments such as medication, and may require some self-regulation skills initially (Weber et al., 2020). For instance, a systematic review by Weber and colleagues (2020) found that higher baseline levels of the trained neural parameter was the strongest predictor for upregulation success. This finding proposes that participants with higher baseline activity have an advantage in improving their self-regulation ability and would therefore benefit more from an NF intervention. However, in the current study, no differences were found between responders and non-responders in terms of baseline levels of FM theta in the first session. In addition to possible neural activity, other psychological or neurophysiological factors may also play a role in NF learning, for instance strategies that participants use to self-regulate brain activity (Autenrieth et al., 2020) or anatomical differences (e.g., regarding the MCC as an FM theta generator; Enriquez-Geppert et al., 2013b). Overall, more research is needed to better understand the underlying mechanisms of non-response to NF, identify predictors of NF learning ability, and explore ways to improve NF responsiveness, for instance by increasing neuroplasticity.

4.3. Neurofeedback-specific transfer to long-term executive function behavioral performance

The main result of this study is the behavioral transfer effect from FM theta NF observed at the 6-months follow-up: the NF group demonstrates greater reductions in RT during working memory updating and in RTV during conflict monitoring compared to the sham group. Faster responding after NF training might indicate increased efficiency or engaged processing, while higher consistency in response speed suggests fewer instances of attention lapses (Tamm et al., 2012; Brenner & Smeets, 2018) through self-regulation of FM theta. In contrast, immediately after the NF training, only repetition or other non-specific effects are present, as evidenced by improved behavioral performance in both groups on all EFs. The lack of immediate effects does not meet our expectations and are inconsistent with findings from FM theta NF studies in healthy participants (Wang & Hsieh, 2013; Enriquez-Geppert et al., 2014a; Brandmeyer & Delorme, 2020; Eschmann & Mecklinger, 2022).

Given the later onset of NF effects, the existing literature on NF studies in clinical groups suggests that transfer effects may be more pronounced when studied after a period of time following the intervention, rather than immediately after NF training (e.g., Garcia Pimenta et al., 2021). The time delay in the appearance of transfer effects after NF can be attributed to the

time required for neuroplastic changes to manifest fully (Ros et al., 2014). Visual inspection of data from participants who completed the 12-month follow-up measurement supports this idea of increased NF effects with time (see Figure 6). The lack of NF-specific effects immediately after the NF training could also be due to the relatively lower FM theta upregulation in our NF group compared to previous studies on healthy individuals. Immediate behavioral effects might be present if we had excluded non-responders and compared only the responders in the NF group with the sham group. However, we adopted a conservative approach and only tested our a priori hypotheses to replicate the previous FM theta NF studies in this (sub)clinical sample.

Regarding the specific transfer profile in this study, long-term behavioral effects of NF are found as expected for proactive aspects, but only for working memory updating and not for set-shifting. Furthermore, the study demonstrates novel findings regarding the impact of FM theta NF on RTV in conflict monitoring, which is a newly included behavioral outcome. Interestingly, this effect was observed in a reactive task rather than a proactive one. It may be that RTV may capture not only the RT variability driven by the reactive conflict processes, but also the variability in RT driven by sustained attention, thus encompassing both reactive and proactive aspects.

Regarding the analysis of long-term effects after six months, it is important to note that there was insufficient power to detect medium effects in RM ANOVA. COVID-19 restrictions prevented 30% of the sample from completing the 6-month follow-up measurement, resulting in a sample size of fourteen participants in the sham group instead of the seventeen required based on power calculations. Furthermore, participants who completed the follow-up were relatively more likely to report a psychiatric diagnosis than those who did not participate. It may be that individuals who dropped out experienced fewer EF complaints in their daily lives after six or twelve months and therefore did not see a need to participate in the follow-up measurement. This factor is a commonly possible variable in studies that involve multiple measurements. Finally, alterations in medication use during the follow-up period may have confounded the effects.

4.4. No neurofeedback-specific transfer to frontal-midline theta during executive function tasks

The results of this study show that there is no immediate impact of NF training on FM theta power during EF task performance. This is consistent with the findings of Brandmeyer and

Delorme (2020) and Eschmann and Mecklinger (2022), but contradicts the results from Enriquez-Geppert and colleagues (2014a). In addition, this study was the first to investigate the long-term effects of FM theta NF on FM theta power during EF tasks, but again no significant effects were found.

The finding of unaffected FM theta power during EFs may be surprising in the context of the long-term behavioral improvements specific to FM theta NF. However, an explanation may be that the NF training in this (sub)clinical group had an impact on neural parameters related to EFs other than FM theta power, such as improved theta connectivity in the higher-order network or frequency coupling (Enriquez-Geppert et al., 2014a). It could be that the need for cognitive control, reflected by an increase in FM theta power (Cavanagh & Frank, 2014), decreases after FM theta NF due to more efficient execution of cognitive control processes over these other neural parameters underlying EFs. Overall, knowledge of the neural mechanisms underlying NF and specifically FM theta NF is still quite limited and further research with brain imaging techniques is needed.

4.5. No neurofeedback-specific transfer to executive functions in daily life

The observed improvement in EFs in daily life, immediately and six months after NF training and visually also twelve months afterward, observed in both the NF group and sham group, suggests that the effects are not specific to the NF training but rather related to other factors. These may include non-specific factors related to the context of NF training (e.g., learning to sit still and avoiding muscular artifacts), but also more general non-specific factors such as the benefits of cognitive training, psychosocial influences expectation effects, support and praise from a trainer, repetition-related improvements and natural fluctuations such as spontaneous remission (Micoulaud-Franchi & Fovet, 2018; Ros et al., 2020; Garcia Pimenta et al., 2021).

One explanation for the lack of NF-specific improvement in EFs in daily life, despite improved long-term objective performance, may stem from differences in what is assessed by subjective and objective EF measures. Subjective measures assess an individual's typical performance in a specific time period, usually involving the integration of multiple cognitive functions, which can be influenced by factors such as perceived stress, depressive symptoms, personality, and self-efficacy beliefs (Facal et al., 2020; Smit et al., 2021). For EFs specifically, the subjective assessment is challenging because EFs are abstract and difficult for people to grasp, unlike more concrete cognitive functions like memory, which are easier to understand. Objective tests, on the other hand, provide a snapshot of a specific EF and require optimal performance

and motivation, but may lack ecological validity and sensitivity/specificity to subtle impairments due to successful compensation by the participant (Chaytor et al., 2006). Subjective and objective measures are therefore often only weakly related to each other (e.g., Fuermaier et al., 2015). However, the inclusion of subjective measures is important since the ultimate goal of interventions is to achieve clinically relevant improvements.

4.6. No correlations between self-regulation of frontal-midline theta and behavioral changes in executive functions

Our results show no significant association between FM theta increases and EFs tasks immediately and six months after NF training, raising several questions. First, beyond the experimental paradigms, what are the key components of real-world behavior that contribute to FM theta upregulation? In addition, this prompts us to investigate how these aspects can be more effectively measured and ultimately correlated with NF learning indices. Cohen (2014a) suggests that FM theta is a preferred frequency band of the brain for EFs because many natural behaviors that are monitored and regulated by the brain, such as typing on a keyboard and speaking, involve temporally sequential micro-actions within the theta frequency range. A recent study addressed the issue of measuring FM theta of real-world behaviors by employing a fully immersive virtual-reality navigation task leading to FM theta modulations, which is a translational model of single-unit electrophysiological recordings from freely moving rodents to a task mimicking real-life goal directed behavior (Lin et al., 2022). This study provides an example for future studies of an effective measure to study the relation between FM theta increases during NF and FM theta during more real-world activities.

4.7. Neurofeedback training relative to other interventions for executive functions

Currently, there are no widely accepted standardized protocols or guidelines for the treatment of EF impairments. One of the rehabilitation treatments available is Goal Management Training, where patients learn to become aware of their deficits and improve their ability to perform everyday tasks through psychoeducation, narrative examples, mindfulness exercises, and other tasks (Levine et al., 2000). It typically involves 20 hours of training and has been shown to produce small to moderate positive outcomes in terms of both (everyday) EF task performance and in patients' subjective EF ratings, which can be maintained at follow-up assessments (Stamenova & Levine, 2018). Computer-based cognitive training is another form of training that involves the repetitive performance of tasks involving affected functions, for instance working memory training (Melby-Lervåg & Hulme, 2013). There is, however, limited evidence for the specific effectiveness of this treatment type for EF impairments (Van de Ven et

al., 2016). In general, most interventions, programs, and approaches for improving EFs produce immediate specific effects that do not transfer to other domains or daily life (Diamond & Ling, 2016).

FM theta NF has the potential to broaden the clinical options for treating EF impairments by utilizing a neuroscientific approach, presenting a new avenue for improvement. In general, it is proposed that an intervention will result in transfer if the intervention and the transfer task involve overlapping processing mechanisms and recruit similar brain regions (e.g., Dahlin et al., 2008). Moreover, the intervention must specifically target and modify the shared underlying processing mechanisms to lead to task transfer (Lövdén et al., 2010), which may explain why most of the EF interventions mentioned above do not have transfer effects. In contrast, FM theta NF has the ability to directly increase the upregulation of FM theta, thus modifying the shared underlying processing mechanisms of EFs (e.g., Enriquez-Geppert et al., 2014a). However, our results suggest, in a (sub)clinical sample this applies only to responders and not to the entire NF group. Furthermore, it should be noted that NF is not the only way to target FM theta. For example, Anguera and colleagues (2013) found that video game training was also able to increase FM theta power in older adults (60-85 years old) compared to both an active and passive control group. Training led also to improvements in multitasking, sustained attention, and working memory, with some effects lasting for up to six months.

Ideally, a treatment protocol for EF impairments, whether it is a single treatment or a combination of treatments, should be tailored to the individual subject to achieve maximum benefit and should be customized based on factors such as severity of EF impairments, presence of other cognitive impairments, general functioning, and personal preferences of the subject. In addition, for NF, personalized protocols that are based on the subject's characteristics can be used to optimize NF learning (Alkoby et al., 2018). Future studies should aim to identify predictors of effectiveness of different types of EF interventions and explore strategies for treatment stratification.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethic Committee of the Faculty for Social Sciences, University of Groningen, Netherlands. The participants provided their written informed consent to participate in this study.

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Declaration of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2023.1163380/full#supplementary-material

Chapter 4

Frontal-midline theta neuro-feedback: A mega-analysis

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ABSTRACT

A protocol attracting significant interest in neurofeedback (NF) research is EEG based NF to enhance frontal-midline (FM) theta with the goal of improving cognitive abilities, particularly executive functions (EFs). Over the last decade, FM theta NF studies have included healthy adults and adults with self-reported EF complaints with or without psychiatric disorder. However, understanding the learning curves and predictors of FM theta self-regulation is crucial to understanding NF learning and key to refining FM theta NF protocols. To provide a more reliable and comprehensive assessment of the overall effects of FM theta NF, this study conducted a mega-analysis by pooling raw data from various available studies. In total, four lab-independent international studies were included in which six to eight sessions of individualized FM theta NF were applied to 149 adults. Statistical analyses were conducted to assess: (i) minimal common FM theta NF effect across the common six sessions using two learning indices (i.e., session-to-session and dynamical within-session effect) and (ii) overall maximum effect from the first to the last session of each study. Both types of analyses were conducted for different frequency bands (i.e., individualized and standard theta, delta, alpha, and beta). In addition, we examined (iii) demographic data to identify predictors of FM theta NF upregulation success and characterize both responder and non-responders. The findings showed that (i) across and within six sessions (minimal common effect), the NF group demonstrated a significant increase in upregulation of the standard FM theta band (4-8 Hz) compared to the active control group. In contrast, a significant increase in upregulation of the narrower individualized FM theta band in the NF group was observed only when non-responders were excluded from the analysis. (ii) When comparing the first and last sessions of each study (overall maximum effect), the NF group exhibited higher upregulation exclusively in the individualized FM theta band, and not in the standard FM theta band, compared to the active control group, even after excluding non-responders. Moreover, NF-specific effects on the delta and beta band were observed. Finally, (iii) the presence of self-reported EF complaints in daily life predicted less successful FM theta upregulation, and non-responders were more likely to report having or suspecting a psychiatric disorder. These findings provide valuable insights into the effectiveness of NF for upregulating FM theta, and may guide future research to optimize NF efficacy and its effect on cognition.

1. INTRODUCTION

To date, several studies have investigated the effectiveness of neurofeedback (NF) for the upregulation of frontal-midline (FM) theta in order to enhance cognitive abilities, in particular executive functions (EFs) (Smit et al., 2023; Eschmann & Mecklinger, 2022; Brandmeyer & Delorme, 2020; Enriquez-Geppert et al., 2014a; Wang & Hsieh, 2013). These individual studies lay the foundation for exploring the benefits of NF in upregulating FM theta for cognitive enhancement, but a more robust and conclusive analysis is required as a step towards broader application. A comprehensive mega-analysis of their pooled raw data offers such an analysis and addresses the issue of limited sample sizes in individual studies. This analysis enhances statistical power, allows for the inclusion of a more heterogeneous and representative participant sample, and ultimately provides a more reliable assessment of the overall effectiveness of FM theta NF (Eisenhauer, 2021).

Electroencephalography (EEG) based NF is a non-invasive neuromodulation technique that enables individuals to self-regulate their oscillatory brain activity and thereby directly alter the neural mechanisms underlying cognition and behavior (Sitaram et al., 2017). NF is a form of brain-computer interface in which brain activity is recorded, processed, extracted, and fed back to the participant in real-time. In doing so, online brain features of interest are displayed or presented to the participant in the form of simple colors, tones, or complex game-like representations (Marzbani et al., 2016) that serve as feedback to guide the participant to self-neuromodulate the selected brain features (Enriquez-Geppert et al., 2017). NF is an active approach involving learning mechanisms such as operant conditioning, which can elicit neuroplastic effects (Sitaram et al., 2017; Ros et al., 2014), potentially resulting in more durable long-term outcomes (e.g., Garcia Pimenta et al., 2021). A promising NF application is the targeting of neural oscillations underlying EFs; higher-level cognitive processes essential for flexible and goal-directed behavior in daily life (Burgess & Simons, 2005; Diamond, 2013). NF may serve as a form of cognitive enhancement or peak performance training in healthy individuals (e.g., Gruzelier, 2014) or as a means to address impaired EFs that are common in various psychiatric disorders (Snyder et al., 2015).

For EFs, FM theta oscillations (4-8 Hz) are particularly relevant and are generated in response to events that require increased cognitive control (e.g., Eisma et al., 2021). The midcingulate cortex, a highly interconnected brain structure (Vogt, 2016) within the superordinate network that underlies various EFs (Niendam et al., 2012), is thought to be the main generator of phasic task-related theta (Cavanagh & Frank, 2014). Increases in FM theta power are associated with

stronger coupling between neuronal spikes in the theta frequency and the phase of the population theta cycle (Helfrich & Knight, 2016; Cavanagh & Frank, 2014). During performance of tasks requiring EFs, the upregulation of FM theta power appears to reflect the amount of cognitive control recruitment (e.g., Cooper et al., 2017; Eschmann et al., 2018). Altogether, this evidence indicates that FM theta is a promising target for NF interventions aimed at improving EFs (Viviani & Vallesi, 2021).

Research by Eschmann and colleagues (2020), Brandmeyer and Delorme (2020), Enriquez-Geppert and colleagues (2014a), and Wang and Hsieh (2013) has consistently demonstrated that in primarily young but also in older healthy participants, those who underwent real FM theta NF training showed a significant increase in FM theta over seven to twelve sessions compared to an active control group. Smit and colleagues (2023) explored FM theta NF in individuals who reported EFs complaints in their daily life, regardless of whether they had a psychiatric diagnosis. Their results revealed a significant increase in FM theta power over the course of the NF sessions only when non-responders in the NF group were excluded from the analysis. Non-response is common in NF studies with approximately one-third of participants unable to effectively self-regulate their brain activity (Alkoby et al., 2018; Haugg et al., 2021). This phenomenon presents an ongoing challenge in both research and clinical practice, making the identification and understanding of underlying factors contributing to non-response crucial for progress. Analyzing the learning curve is fundamental to understanding how individuals learn to self-regulate FM theta, which is a cornerstone for further development of this NF protocol.

In our present study, we adopted a cumulative approach and conducted a mega-analysis by pooling raw data from a range of published and unpublished studies that applied FM theta NF. Mega-analyses are considered the golden standard in empirical research because they allow the preservation of more detailed information and improve the treatment of differences in variance, distinguishing them from meta-analyses that rely on summary statistics (Eisenhauer, 2021; Koile & Cristia, 2021). The primary objective of this mega-analysis is to increase the sample size, thereby increasing the power and precision of the effect size estimate. This, in turn, makes the evaluation of the overall learning curve of FM theta NF more reliable. Specifically, we evaluate (i) the minimal common effect using two learning indices as well as the overall maximum effect, (ii) which demographic and clinical variables serve as predictors of FM theta upregulation success, and (iii) the distinction between NF responders and non-responders in terms of their demographic characteristics.

2. METHODS

2.1. Inclusion

For the current mega-analysis, the corresponding authors of all known studies in which multiple sessions of FM theta NF were conducted (retrieved from Viviani & Vallesi, 2021) were contacted to share their raw data. Additionally, we searched for newer studies described in peer-reviewed articles, conference papers, and master's theses. Studies involving only a single NF session (e.g., Eschmann et al., 2022) or modulation of additional frequency bands (e.g., Reis et al., 2016) were excluded. Ultimately, datasets collected by research groups from four universities were included: University of Groningen (58 participants from Smit et al., 2023 and seventeen participants from an unpublished pilot study by the same research group), Saarland University (35 participants from Eschmann et al., 2020), University of Toulouse (25 participants from a study described in Lafont et al., 2021), and University of Oslo (fourteen participants from a study described in Hussain, 2020). In the following, these studies will be referred to as the Groningen, Saarland, Toulouse, and Oslo studies, respectively. Data from Brandmeyer and Delorme (2020), Enriquez-Geppert and colleagues (2014a), and Wang and Hsieh (2013) were not included because the available data did not allow for the extraction of parameters necessary for the normalization across studies.

2.2. Participants and study characteristics

The mega-analysis included 149 participants, consisting of 83 female, 65 male, and one participant reported 'other' as sex. The mean age of the participants was 28.1 years (*SD* = 8.9). All studies included healthy adults, with the exception of the Groningen study, which recruited adults with self-reported EF complaints in daily life based on the Behavior Rating Inventory of Executive Function - Adult Version (Roth et al., 2005) with or without a self-reported psychiatric disorder. The disorders included: 22 participants with attention deficit disorder (ADD), twelve with attention deficit hyperactivity disorder (ADHD) of which one presented with an additional borderline personality disorder, ten with autism spectrum disorder (ASS) of which two presented with additional bipolar disorder, two with post-traumatic stress disorder (PTSD), one with dysthymia, and one with a history of depression and anorexia. For most participants, the diagnosis was confirmed by a mental health care organization through their general practitioner, but for eight participants the reported diagnosis was either not confirmed or no permission for confirmation was obtained from the participant. Additionally, seven participants suspected to suffer from ADD or ADHD, but had no official diagnosis. In the Toulouse study by Lafont and colleagues (2021), the participants were aerospace engineering

students. In all studies, participants' highest completed education was rated as low (i.e., primary education, preparatory secondary vocational education, or equivalent), intermediate (i.e., secondary vocational education, senior general secondary education, pre university education, or equivalent), or high (i.e., higher vocational education, university bachelor (license)/master, doctorate, or equivalent). Participants were either randomly assigned to the experimental group or active control group, or pseudo-randomly matched based on characteristics such as age, sex, education, or psychiatric disorder. Most studies were single-blinded, only the Oslo study was double-blinded. All participants gave written consent to the protocol approved by the ethical committee of the relevant universities.

Individual theta peaks (ITP) for FM theta NF, were estimated in two different ways: In the Toulouse study, the average amplitude of the ITP ± 1 Hz was used for the NF training, which was computed during the first NF training session at rest and with eyes closed. In the three other studies, the ITP ± 1 Hz was estimated based on EEG data measured during cognitive tasks performed before the NF training. In the Groningen and Oslo studies these were the Stroop, Stop-signal, N-back, and Switching tasks, and in the Saarland study the Source memory, Delayed matching to sample, and Stroop tasks.

During the NF sessions, participants had to increase FM theta amplitude by using mental strategies. In all studies, participants were given a list of example strategies and were encouraged to use any strategy, including self-invented ones, to reach the best possible outcome. In the Saarland study, participants were additionally asked to use the same best-working strategy from the fourth session onwards. Table 1 provides a complete overview of the characteristics of the individual studies; for more details, please refer to the original articles.

2.3. Data preparation

2.3.1. Analyzed frequency bands

To assess the results, the amplitudes of the following standard frequency bands were extracted: theta (4-8 Hz), delta (1-3.5 Hz), alpha (8.5-12 Hz), and beta (12.5-30 Hz, Saarland study: 12.5-24 Hz). Additionally, the amplitudes of the individualized theta (ITP ± 1 Hz), delta (ITP − 3-1.5 Hz), alpha (ITP + 3-5 Hz), and beta (ITP + 7-24 Hz, Saarland study: ITP + 7-17 Hz) frequency bands were extracted. The standard and individualized beta frequencies in the Saarland study had a lower range, as the data was normalized to 1-24 Hz to match the

Table 1. Overview of the included studies. Note: ITP = individual theta peak.

Variable	Groningen (n = 75) *Smit et al., 2023*	Saarland (n = 35) *Eschmann et al., 2020*	Toulouse (n = 25) *Lafont et al., 2021*	Oslo (n = 14) *Hussain, 2020*
Sessions & NF blocks	8 sessions, 6 NF blocks (5 min)	7 sessions, 6 NF blocks (5 min)	8 sessions, 6 NF blocks (5 min)	6 sessions, 5 NF blocks (5 min)
Electrode(s) for feedback	Fz, FC1, FC2, FCz, Cz	Fz	Fz, FC1, FC2, FCz, Cz	Fz, FC1, FC2, FCz, Cz
Amplifier & Software	TMSi amplifier, NeuroSuite 2.0. programmed in Matlab	ProComp5 Infinity amplifier, BioGraph Infinity software	LiveAmp amplifier, NeuroSuite 2.0. programmed in Matlab	BrainAmp amplifier, NeuroSuite 2.0. programmed in Matlab
Feedback signal	2 sec epochs updated every 250 ms	1 sec sliding window with a 300 ms butterworth buffer	2 sec epochs updated every 200 ms	2 sec epochs updated every 200 ms
Feedback type	Color of a square, goal: turn the square red	Roller coaster animation, goal: accelerate the roller coaster speed	Color of a square, goal: turn the square green	Color of a square, goal: turn the square blue
(eye) Artifacts	Square turned gray	Roller coaster stopped and a light next to it lit up in red	Square turned gray	Square turned gray
Active control group	Replay of feedback from matched participant in the experimental group	Feedback to one of seven randomly chosen 2 Hz bands (10-12 to 22-24 Hz)	Replay of feedback from matched participant in the experimental group	Replay of feedback from matched participant in the experimental group
Duration	2-3 weeks	10 days	2 weeks	2-4 weeks
Rewards	None	Paid €8 per hour	Paid €10 per session	Gift card of 500 NOK
Size NF group	39 (52.0%)	17 (48.6%)	13 (52.0%)	8 (57.1%)
ITP	*M* = 5.9, *SD* = .9 Range: 4.0-8.0 Hz	*M* = 5.8, *SD* = .7 Range: 5.0-7.0 Hz	*M* = 6.0, *SD* = .7 Range: 4.5-7.5 Hz	*M* = 4.8, *SD* = .4 Range: 4.0-5.5 Hz
Age	*M* = 32.3, *SD* = 10.4 Range: 20-60 years	*M* = 23.0, *SD* = 2.5 Range: 19-30 years	*M* = 23.4, *SD* = 3.5 Range: 20-33 years	*M* = 26.3, *SD* = 5.4 Range: 20-41 years
Sex	51 female (68.0%), 24 male (32.0%)	24 female (68.6%), 11 male (31.4%)	4 female (16.0%), 20 male (80.0%), 1 other (4.0%)	4 female (28.6%), 10 male (71.4%)
Education level	1 low (1.3%), 34 intermediate (45.3%), 40 high (53.3%)	35 intermediate (100.0%)	11 intermediate (44.0%), 14 high (56.0%)	12 intermediate (85.7%), 2 high (14.3%)
Psychiatric disorders	20 no disorder (26.7%), 48 disorder present (64.0%), 7 suspect disorder (9.3%)	35 no disorder (100.0%)	25 no disorder (100.0%)	14 no disorder (100.0%)

randomly chosen frequency bands of the active control group (i.e., 10-24 Hz). In all other studies, data was normalized to 1-30 Hz (i.e., mean amplitude in a specific standard or individualized frequency band / mean amplitude in full frequency band 1-30 Hz).

2.3.2. Missing data

For individual participants, missing blocks or blocks with clearly erroneous values were replaced (i.e., NF block replaced with previous NF block from the same session and end baseline replaced with start baseline from the same session). In the Groningen study, sixteen individual blocks were replaced; thirteen were missing and three had clearly erroneous values. In the Toulouse and Oslo studies, nine and twelve missing blocks were replaced for individual participants, respectively. The Saarland study had no missing data and did not require any replacements. Additionally, in the Toulouse study, seven participants missed NF session 8, which was not replaced. Note that this procedure for the replacement of missing values represents a conservative approach that potentially minimizes the treatment effect.

2.3.3. Z-score standardization

In order to combine the data of the different studies, the data was standardized for each participant by calculating Z-scores relative to the baseline of the respective session (e.g., mean amplitude NF Block 1 Session 1 – mean amplitude Start baseline Session 1 / *SD* amplitude Start baseline Session 1). This within-session baseline correction also reduces the impact of inter-individual differences in FM theta amplitude and measurement variability between sessions.

2.4. Statistical analyses

To assess the effects of FM theta NF, two types of analyses were conducted for the standard and individualized frequency bands. First, two learning indices were assessed in the common six sessions with five NF blocks each from all included studies (i.e., minimal common FM theta NF effect). For this purpose, undirected repeated measures (RM) ANOVAs were used, as the exact temporal pattern across all sessions and blocks is unknown. Second, the overall maximum effect was assessed by comparing upregulation in the NF blocks in the first and last session of each study, regardless of the number of conducted sessions and NF blocks per session. Here, one-sided Independent Samples *t*-tests were used as there were clear a-priori hypotheses about the overall effect; the NF group shows a larger increase in FM theta than the active control group. Both analyses are described in more detail in the following sections as well as how the results are interpreted (Section 2.4.5.).

2.4.1. Two learning indices for the minimal common frontal-midline theta neurofeedback effect

Learning Index 1 reflects changes in FM theta amplitude from session to session. To assess this learning index, the mean Z-score of the common five NF blocks was calculated for each of the six sessions. Effects were analyzed using repeated-measures (RM) ANOVA with the within-subjects factor SESSION (1-6) and between-subjects factor GROUP (NF vs. active control). Additionally, the same RM ANOVA was repeated with only the responders (instead of the full NF group) versus the active control group. Distinguishing responders from non-responders is important for eventual application in clinical settings, where only individuals showing a positive response to NF training would receive this intervention. Section 2.4.4. explains how responsiveness to the NF was determined.

Learning Index 2 reflects the dynamical changes in FM theta amplitude within sessions (Enriquez-Geppert et al., 2014b). Thus, for each block, the mean Z-score was calculated across the six sessions. Effects were analyzed using RM ANOVA with the within-subjects factor BLOCK (start baseline [i.e., zero], NF blocks 1-5, and end baseline) and between-subjects factor GROUP (NF vs. active control). Again, the same RM ANOVA was repeated with only the responders in the NF group versus the active control group.

To determine the specificity of FM theta NF training, the two learning indices described above were assessed for both the standard and individualized theta bands, as well as for standard and individualized delta, alpha, and beta frequency bands.

2.4.2. Overall maximum frontal-midline theta neurofeedback effect

To assess the overall maximum effect of FM theta NF training, the mean Z-score of the NF blocks in the first and last session of each study were calculated. Depending on the specific study, there were five or six NF blocks and the last session was the sixth, seventh, or eighth session. In the Toulouse study, Session 7 was the last session for seven participants because they had not completed the actual last Session 8. The NF group and active control group were compared using a one-sided Independent Samples *t*-test on the differences score between the first and last session (i.e., mean Z-score in the last session − mean Z-score in the first session) for both standard and individualized theta. Additionally, the same *t*-tests were repeated with only the responders in the NF group (instead of the full NF group) versus the active control group. Furthermore, to determine the specificity of FM theta NF training, two-sided Independent Samples *t*-tests were performed for the standard and individualized delta, alpha, and beta frequency bands.

2.4.3. Predictors of frontal-midline theta neurofeedback upregulation success

In order to investigate which factors may predict the success of FM theta upregulation in the NF group, separate linear regression analyses were performed for each predictor (Step 1). The predictors were: age (in years), ITP, baseline level of FM theta in the first session, sex (male/female), education level (low/intermediate/high), presence of self-reported EF complaints (yes/no), and presence of a disorder (yes/no/suspected). In Step 2, a multiple regression analysis was conducted using the enter method with the significant predictors from Step 1. Upregulation success was defined as the average Z-score of the common five NF blocks across the six sessions. This was based on either the standard or individualized theta band, whichever had the largest effect size for the minimal common FM theta NF effect. The baseline level of FM theta in the first session was calculated separately for each of the four included studies using Z-scores (i.e., mean amplitude Start baseline of single participant − mean amplitude Start baseline of whole group from same study / *SD* amplitude Start baseline of whole group from same study).

2.4.4. Neurofeedback responders and non-responders

To determine whether participants were classified as responders or non-responders, their regression slope was examined, where a negative slope (≤ 0) indicated non-responders and a positive slope (> 0) indicated responders. The slope was calculated over six values: the mean Z-scores for the baseline (i.e., zero) and the five separate NF blocks averaged over six sessions (i.e., dynamical change within sessions; Learning Index 2). This approach was used to account for possible changes in theta in the start baseline over the course of the sessions. To assess the NF effects on standard and individualized FM theta for the responders in the NF group, responsiveness was based on the slope of the standard or individualized theta band, respectively. To better understand and clarify any differences in FM theta upregulation, descriptive statistics were calculated for both responders and non-responders in the NF group, based on the FM theta band (i.e., standard or individualized) with the largest effect size in the common NF sessions.

2.4.5. Interpretation of statistical tests

For all statistical tests assessing the theta bands, a *p*-value of ≤ .05 was used to identify significant effects. Due to clear a priori hypotheses for the FM theta NF effects, no correction for multiple testing was applied (Streiner & Norman, 2011). However, for the analyses of the other frequency bands (i.e., controls) and the exploratory regression analyses, the Benjamini-Hochberg adjustment was applied with a false discovery rate of .05 (Chen et al., 2017). To test

for multicollinearity in the multiple regression analysis, the variance inflation factor (VIF) was assessed, with values above ten indicating problematic correlations between predictors (Belsley et al., 2005). In case of violation of sphericity in RM ANOVA, the Greenhouse-Geisser correction was used and corrected degrees of freedom and *p*-values were reported. The effect size for RM ANOVA was indicated by partial eta squared (η_p^2) and interpreted as: ≤ .01 is small, ≥ .06 is medium, or ≥ .14 is large. For Independent Samples *t*-tests the effect size was indicated by Cohen's *d* (≤ .2 is small, ≥ .5 is medium, and ≥ .8 is large). For the simple linear regression, the effect size was indicated by the percentage of explained variance (R^2) and classified as small (≤ .08), medium (.09 to .24), or large (≥ .25) (Cohen, 1988). For the multiple linear regression analysis, the squared semi-partial correlation (sr^2) was used as an effect size, and classified as small (< .01), medium (.01 to .059), or large (> .059) (Fritz et al., 2012). All statistical analyses were carried out using SPSS (IBM Corp., 2019).

3. RESULTS

3.1. Group characteristics

Table 2 summarizes the demographic characteristics of the full NF and active control groups. The two groups did not differ significantly in terms of age ($t(147) = .894$, $p = .373$), ITP ($t(147) = -.385$, $p = .701$), sex ($X^2(2, n = 149) = 1.230$, $p = .541$), education level ($X^2(2, n = 149) = 1.007$, $p = .604$), presence of self-reported EF complaints ($X^2(1, n = 149) = .006$, $p = .937$), or presence of a disorder ($X^2(2, n = 149) = .740$, $p = .691$). Based on the standard FM theta band, 71.4% of the participants in the NF group were classified as responders (n = 55) and 28.6% were classified as non-responders (n = 22). For the individualized FM theta band this was 67.5% (n = 52) and 32.5% (n = 25) for the responders and non-responders, respectively. The overlap between classifications based on the standard or individualized FM theta band was 83.1% (n = 64).

Table 2 also provides an overview of the demographic characteristics of the responders and non-responders in the NF group based on the standard FM theta band, as this FM theta band showed the largest effect size for the minimum common FM theta NF effect (see Section 3.2.2.). The two groups differed significantly in terms of presence of a psychiatric disorder ($X^2(2, n = 77) = 9.160$, $p = .010$). In general, non-responders were more likely to have or suspect a disorder in contrast to those who did respond to FM theta NF. There were no significant differences between groups regarding age ($t(75) = -.228$, $p = .821$), ITP ($t(75) = -.213$, $p = .832$), sex ($X^2(1, n = 77) = 1.027$, $p = .311$), education level ($X^2(2, n = 77) = 5.483$, $p = .064$), or presence of self-reported EF complaints ($X^2(1, n = 77) = .878$, $p = .349$).

3.2. Minimal common frontal-midline theta neurofeedback effect for two learning indices

Figure 1 shows the session-to-session changes in the NF blocks (i.e., Learning Index 1) and the dynamical changes within sessions for each block (i.e., Learning Index 2). Here, the analyses were restricted to the first six sessions with five NF blocks each that were common to all studies. Effects for the full NF group versus active control group as well as responders in the NF group versus active control group were compared. In the following, the RM ANOVA results for the two learning indices are reported for the standard and individualized FM theta bands, as well as for the standard and individualized delta, beta, and alpha frequency bands.

Table 2. Demographic characteristics of the NF group (i.e., full group and responders and non-responders only classified based on the standard FM theta band) and full active control group. Note: ITP = individual theta peak, S1 = Session 1.

	NF group			Active control group
	Full group (n = 77)	Responders only (n = 55)	Non-responders only (n = 22)	Full group (n = 72)
Continuous variables	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Age	28.7 (9.8) Range: 20-60 years	28.5 (10.0) Range: 20-60 years	29.1 (9.2) Range: 20-59 years	27.4 (7.8) Range: 19-52 years
ITP	5.7 (.8)	5.7 (.8)	5.8 (1.0)	5.8 (.8)
Z-score baseline level standard FM theta in S1	−.042 (.940)	−.032 (.951)	−.068 (.932)	.045 (1.045)
Categorical variables	n (%)	n (%)	n (%)	n (%)
Sex	42 female (54.5%), 35 male (45.5%), 0 other (0.0%)	32 female (58.2%), 23 male (41.8%)	10 female (45.5%), 12 male (54.5%)	41 female (56.9%), 30 male (41.7%), 1 other (1.4%)
Education level	1 low (1.3%), 48 intermediate (62.3%), 28 high (36.4%)	0 low (0.0%), 38 intermediate (69.1%), 17 high (30.9%)	1 low (4.5%), 10 intermediate (45.5%), 11 high (50.0%)	0 low (0.0%), 44 intermediate (61.1%), 28 high (38.9%)
Presence of self-reported EF complaints	38 no EF complaints (49.4%), 39 EF complaints present (50.6%)	29 no EF complaints (52.7%), 26 EF complaints present (47.3%)	9 no EF complaints (40.9%), 13 EF complaints present (59.1%)	36 no EF complaints (50.0%), 36 EF complaints present (50.0%)
Presence of psychiatric disorder	51 no disorder (66.2%), 23 disorder present (29.9%), 3 disorder suspected (3.9%)	40 no disorder (72.7%), 15 disorder present (27.3%), 0 disorder suspected (0.0%)	11 no disorder (50.0%), 8 disorder present (36.4%), 3 disorder suspected (13.6%)	43 no disorder (59.7%), 25 disorder present (34.7%), 4 disorder suspected (5.6%)

3.2.1. Learning Index 1

Standard FM theta band: Regarding the session-to-session changes, a RM ANOVA for the standard FM theta band showed, as expected, a significant interaction effect of SESSION × GROUP ($F(4.488,659.746) = 3.036$, $p = .013$, $\eta_p^2 = .020$) with a significant linear contrast ($F(1,147) = 10.487$, $p = .001$, $\eta_p^2 = .067$) and a main effect of GROUP ($F(1,147) = 5.443$, $p = .021$, $\eta_p^2 = .036$). There was no significant main effect of SESSION ($F(4.488,659.746) = 1.893$, $p = .102$). This indicates that the increase in standard FM theta was more pronounced in the NF group than in the active control group, and that the difference between groups increased linearly over

sessions. When repeating the RM ANOVA with only the responders in the NF group instead of the full NF group, even stronger effect sizes were found (SESSION × GROUP: $F(4.504,562.962) = 3.376$, $p = .007$, $\eta_p^2 = .026$; GROUP: $F(1,125) = 13.993$, $p < .001$, $\eta_p^2 = .101$). There was again no significant main effect of SESSION ($F(4.504,562.962) = 2.158$, $p = .064$).

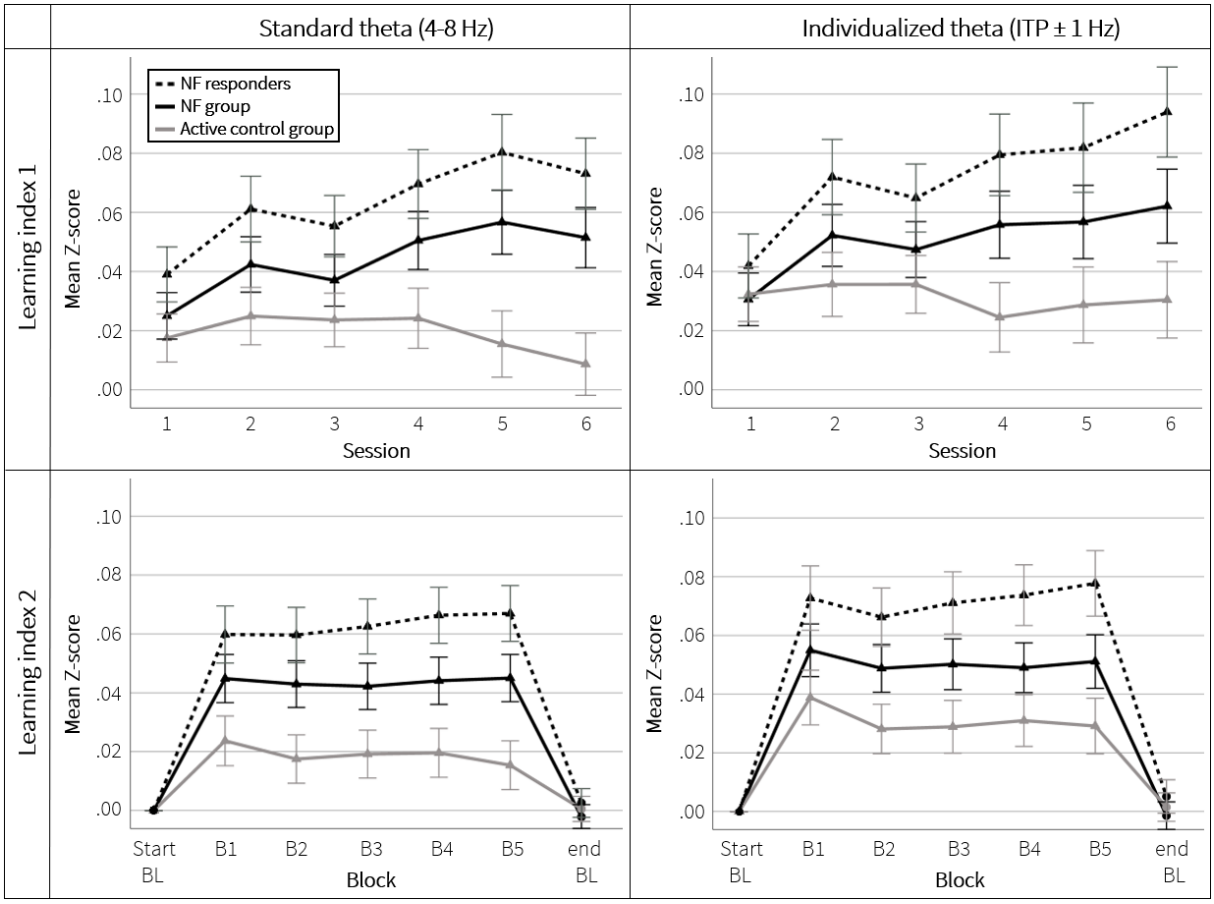

Figure 1. FM theta NF effects for the full NF group, full active control group, and only responders in the NF group; Learning Index 1: mean Z-score per session across the five NF blocks (i.e., session-to-session changes) for the standard FM theta band (4-8 Hz) and individualized FM theta band (ITP ± 1 Hz) and Learning Index 2: mean Z-score per block across the six sessions (i.e., dynamical changes within sessions) for the standard FM theta band (4-8 Hz) and individualized FM theta band (ITP ± 1 Hz). Note: Error bars indicate the standard error of the mean. ITP = individual theta peak. ● = start or end baseline (BL) and ▲ = NF block(s) (B).

Individualized FM theta band: In contrast, the results of the RM ANOVA for the individualized FM theta band showed neither an interaction effect of SESSION × GROUP ($F(4.450,654.124) = 1.573$, $p = .173$) nor main effects of GROUP ($F(1,147) = 3.026$, $p = .084$) or SESSION ($F(4.450,654.124) = .939$, $p = .448$). However, when only the responders in the NF group were included in the RM ANOVA rather than the full NF group, there was a significant interaction

effect SESSION × GROUP (F(4.402,537.035) = 2.597, p = .031, η_p^2 = .021) with a significant linear contrast (F(1,122) = 7.824, p = .006, η_p^2 = .060) and a main effect of GROUP (F(1,122) = 10.187, p = .002, η_p^2 = .077). Responders in the NF group showed a more pronounced upregulation of individualized FM theta than the active control group, and this difference between groups increased linearly across sessions. There was no significant main effect of SESSION (F(4.402,537.035) = 1.778, p = .125).

Other frequency bands: For beta there was a significant interaction effects SESSION × GROUP for the standard band (F(4.073,598.742) = 3.266, p = .011, η_p^2 = .022) as well as main effects of GROUP for both beta band estimates (standard beta: F(1,147) = 10.327, p = .002, η_p^2 = .066; individualized beta: F(1,147) = 10.445, p = .002, η_p^2 = .066). The active control group showed significantly higher standard and individualized beta amplitudes across sessions in comparison to the NF group, and for the standard beta band this group difference increased over the course of the sessions. A full overview of all RM ANOVA results can be found in Supplementary material Table 1.

3.2.2. Learning Index 2

Standard FM theta band: Regarding the dynamical changes within sessions, a RM ANOVA for standard FM theta showed a significant interaction effect of BLOCK × GROUP (F(1.744,256.411) = 5.022, p = .010, η_p^2 = .033) with a significant quadratic contrast (F(1,147) = 6.189, p = .014, η_p^2 = .040), and main effects of GROUP (F(1,147) = 4.841, p = .029, η_p^2 = .032) and BLOCK (F(1.744,256.411) = 28.833, p < .001, η_p^2 = .164). As expected, the NF group showed a higher increase in FM theta compared to the active control group in the NF blocks relative to the start and end baseline. Even stronger effect sizes were found when only the responders in the NF group were included in the RM ANOVA (BLOCK × GROUP: F(1.725,215.584) = 10.859, p < .001, η_p^2 = .080; GROUP: F(1,125) = 13.379, p < .001, η_p^2 = .097; BLOCK: F(1.725,215.584) = 36.503, p < .001, η_p^2 = .226).

Individualized FM theta band: Only a significant main effect of BLOCK was observed (F(1.817,267.035) = 38.569, p < .001, η_p^2 = .208); both the NF and active control groups showed higher upregulation of individualized theta in the five NF blocks than in the start and end baseline. There was no significant interaction effect BLOCK × GROUP (F(1.817,267.035) = 2.614, p = .080) or a main effect of GROUP (F(1,147) = 2.719, p = .101). In contrast, when including only the responders in the NF group in the RM ANOVA instead of the full NF group, both a significant interaction effect BLOCK × GROUP (F(1.772,216.148) = 7.079, p = .002, η_p^2 = .055) with a significant

quadratic contrast (F(1,122) = 9.487, p = .003, η_p^2 = .072), as well as main effects of GROUP (*F*(1,122) = 10.101, *p* = .002, η_p^2 = .076) and BLOCK (*F*(1.772,216.148) = 44.078, *p* < .001, η_p^2 = .265) were found. Responders in the NF group showed higher upregulation of individualized FM theta in comparison to the active control group in the NF blocks relative to the start and end baseline.

Other frequency bands: For delta, the individualized band also showed a significant interaction effect BLOCK × GROUP (*F*(1.679,246.758) = 4.589, *p* = .016, η_p^2 = .030), as well as a main effect of GROUP (*F*(1,147) = 5.040, *p* = .026, η_p^2 = .033) and a main effect of BLOCK (*F*(1.679,246.758) = 38.749, *p* < .001, η_p^2 = .209). The standard delta band showed only a main effect of BLOCK (*F*(1.765,259.405) = 32.760, *p* < .001, η_p^2 = .182). On both the standard and individualized delta bands, the two groups showed greater amplitudes in the five NF blocks compared to the start and end baseline. Moreover, this increase for individualized delta was significantly greater in the NF group than in the active control group. For alpha, significant main effects of BLOCK were found for the standard (*F*(1.680,246.993) = 35.158, *p* < .001, η_p^2 = .193) and individualized bands (*F*(1.687,247.961) = 28.302, *p* < .001, η_p^2 = .161). Compared to the start and end baseline, lower standard and individualized alpha amplitudes were observed during the five NF blocks for both groups. Regarding beta, significant interaction effects BLOCK × GROUP were found for the standard (*F*(2.121,311.766) = 8.900, *p* < .001, η_p^2 = .057) and individualized bands (*F*(2.075,305.002) = 9.202, *p* < .001, η_p^2 = .059). Additionally, for both beta bands, there were significant main effects of GROUP (standard: *F*(1,147) = 8.953, *p* = .003, η_p^2 = .057; individualized: *F*(1,147) = 9.055, *p* = .003, η_p^2 = .058) and main effects of BLOCK (standard: *F*(2.121,311.766) = 12.927, *p* < .001, η_p^2 = .081; individualized: *F*(2.075,305.002) = 14.692, *p* < .001, η_p^2 = .091). The NF group showed lower amplitudes in the five NF blocks for both beta bands as compared to the start and end baseline, while the active control group showed a gradual increase in amplitude across all blocks. A full overview of all RM ANOVA results can be found in Supplementary material Table 2 as well as figures of Learning Index 1 and 2 for standard and individualized delta, alpha, and beta (Supplementary material Figures 1, 2, and 3, respectively).

3.3. Overall maximum frontal-midline theta neurofeedback effect

Figure 2 shows the mean Z-score of the NF blocks in the first and last session of all studies for the full NF and active control groups as well as responders in the NF group for both the standard and individualized FM theta band.

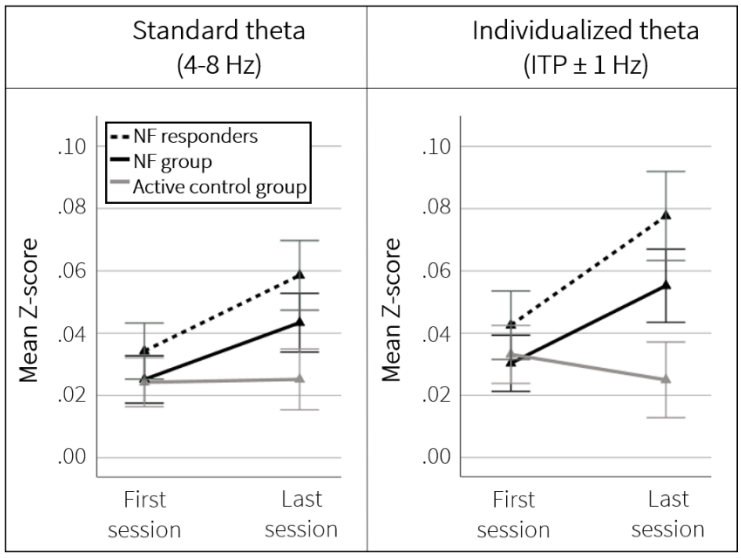

Figure 2. Overall maximum FM theta NF effect for the full NF group, full active control group, and only responders in the NF group: Mean Z-score of the NF blocks in the first and last session for the standard FM theta band (4-8 Hz) and individualized FM theta band (ITP ± 1 Hz). Note: Error bars indicate the standard error of the mean. ITP = individual theta peak. ▲ = NF blocks.

Standard FM theta band: An Independent Samples *t*-test showed no significant effect when comparing the difference score between the first and last NF sessions in the NF group and the active control group ($t(147) = 1.383$, $p = .084$). The same non-significant results were found when only the responders in the NF group (instead of the full NF group) were compared with the active control group ($t(125) = -1.610$, $p = .055$).

Individualized FM theta band: An Independent Samples *t*-test showed a significant difference between the NF group and active control group in the difference score between the first and last sessions ($t(147) = 2.075$, $p = .020$, $d = .340$). As expected, the NF group showed a larger increase in upregulation of the individualized FM theta band than the active control group. When only comparing the difference score in the responders in the NF group with the active control group, the effect size was even larger ($t(122) = 2.321$, $p = .011$, $d = .422$).

Other frequency bands: For the standard and individualized delta, alpha, and beta bands no significant differences were found between the NF group and active control group. A full overview of all Independent Samples *t*-test results can be found in Supplementary material Table 3 as well as figures for change in standard and individualized delta, alpha, and beta (Supplementary material Figures 4, 5, and 6, respectively).

3.4. Predictors of frontal-midline theta neurofeedback upregulation success

To assess the predictors of FM theta upregulation success in the NF group, the standard theta band was used, as this FM theta band showed the largest effect size for the minimum common FM theta NF effect. The results of the simple linear regression analyses in Step 1 showed that the presence of self-reported EF complaints and the presence of a disorder significantly predict FM theta upregulation success with a medium effect size (see Table 3). However, in the multiple linear regression analysis (Step 2), only the presence of self-reported EF complaints remained a significant negative predictor and uniquely explained 7.3% of variance (i.e., large effect). The higher the number of EF complaints, the lower FM theta upregulation success. The VIF value was lower than ten, indicating no multicollinearity problems.

Table 3. Results of the simple linear regression analyses for each predictor separately (Step 1) and multiple linear regression analysis including the significant predictors (Step 2) for FM theta upregulation success in the NF group. Note: * significant if $p <$ Benjamini-Hochberg (BH) critical value. VIF = variance inflation factor, ITP = Individualized theta peak, S1 = Session 1.

Predictors Step 1 *Simple linear regressions*	*B*	*t*	*p*	*BH value*	R^2	VIF
Age	−.002	−2.436	.017	.017	.073	-
ITP	−.002	−.175	.861	.044	< .001	-
Z-score baseline level standard FM theta in S1	−.005	−.507	.613	.039	.003	-
Sex (female)	.029	1.752	.084	.022	.039	-
Education level:					.109	
- Intermediate	.043	.603	.548	.033		-
- High	−.007	−.098	.922	.050		-
Presence of self-reported EF complaints	−.060	−3.913	< .001*	.006	.170	-
Presence of disorder:					.098	
- Disorder suspected	−.056	−1.329	.188	.028		-
- Disorder present	−.047	−2.649	.010*	.011		-
Predictors Step 2 *Multiple linear regression*	*B*	*t*	*p*	*BH value*	sr^2	VIF
Presence of self-reported EF complaints	−.056	−2.543	.013*	.017	.073	1.987
Presence of disorder:						
- Disorder suspected	−.014	−.327	.744	.033	.001	1.183
- Disorder present	−.005	−.233	.817	.050	.001	1.942

4. DISCUSSION

The present study pooled raw data from four lab-independent international FM theta NF studies in order to conduct a mega-analysis for the assessment of FM theta NF efficacy (Smit et al., 2023; Eschmann et al., 2020; Lafont et al., 2021; Hussain, 2020). This approach enhanced the statistical power and precision of effect size estimates while simultaneously reducing noise. Each individual study included a minimum of six sessions with five NF blocks (i.e., equivalent to 25 minutes of self-regulation per session) and aimed at upregulating individualized FM theta amplitudes. Consequently, this mega-analysis offers a more accurate and reliable assessment of the overall impact of NF on the upregulation of FM theta.

The results showed that participants in the NF group were able to upregulate standard FM theta across and within the common sessions and blocks relative to those in the active control group. For individualized FM theta, the NF group only showed higher upregulation relative to the active control group when non-responders were excluded from the analysis. In contrast, a significant increase in overall upregulation between the first and last session in the NF group was only present in the individualized FM theta band and not in the standard FM theta band, even when non-responders were excluded. Furthermore, the results of the study revealed that the presence of self-reported EF complaints in daily life predicted less successful FM theta upregulation. Additionally, the analysis displayed that there were significant distinctions in the incidence of psychiatric disorders between responders and non-responders, with non-responders being more inclined to report having or suspecting a psychiatric disorder. In the following, we elaborate on the results regarding the effects of FM theta NF training, predictors of FM theta upregulation success, differences between responders and non-responders, and their implications.

4.1. Frontal-midline theta neurofeedback training effects: Minimal common vs overall maximum frontal-midline theta neurofeedback effect

Our findings indicate that for the minimal common effect, as anticipated, the NF group exhibited greater upregulation increase in the standard FM theta band both within and across sessions, compared to the active control group, during the six common sessions and five NF blocks across studies. However, when comparing the first and last session of each study (i.e., overall maximum effect), which typically comprised seven or eight sessions, no specific effects of NF are observed in the upregulation of standard FM theta. Interestingly, for the individualized FM theta band, the NF group showed a greater increase in upregulation between

the first and last session than the active control group, but no NF-specific effects on individualized FM theta were observed in the common sessions and blocks.

When assessing only the responders in the NF group (instead of the full NF group), there were significant NF-specific effects on both theta bands in the common sessions and blocks. The NF responders showed across and within sessions higher upregulation than the active control group on both theta bands. Excluding non-responders from the analysis had no effect on the overall maximum FM theta NF effect; the NF responders showed in comparison to the active control group again only a NF-specific increase in individualized FM theta between the first and last session, but not in standard FM theta.

Since all NF studies included in the current mega-analysis focused on training an individualized FM theta band, the above findings possibly suggest a two-stage process. In the first six common NF sessions, upregulation of the standard band appeared to be more pronounced than that of the individualized theta band. This may be because it is relatively easier to increase activity in the broader standard FM theta band, which arises from multiple generators in the frontal cortex (Cavanagh & Frank, 2014), with each distinct FM theta peaks and underlying neural microcircuits (Cohen, 2014a). However, it seems that by the last NF session the NF effect becomes more pronounced in the individualized FM theta band, potentially because learning has progressed and participants developed effective mental strategies to specifically upregulate the narrower individualized FM theta band. Further research is needed to replicate and comprehensively assess these differential effects of FM theta NF on the standard and individualized FM theta bands.

It should be noted that in the current mega-analysis, the effect sizes for the NF-specific effects on FM theta upregulation are relatively small in comparison to the larger effect sizes observed in individual studies (e.g., Eschmann et al., 2020). This disparity can be attributed to the fact that smaller samples typically contain more noise, leading to greater variability and overestimation of effect sizes (Loken & Gelman, 2017). Larger samples, as in this mega-analysis, possess greater statistical power, thereby resulting in more precise (and often smaller) effect size estimates (Algermissen & Mehler, 2018).

Regarding the specificity of the FM theta NF training, similar outcomes were found for the delta band as for the theta band regarding the dynamic changes within sessions. This is the first time the effects of FM theta NF on delta were assessed, and the results indicate that the NF group shows higher individualized delta amplitudes within the common sessions compared to the

active control group. Possible explanations for this finding are the partial overlap in frequencies, particularly between standard theta (4-8 Hz) and individualized delta (on average 2.7-4.2 Hz based on the mean ITP) in this study, but also, in general, a strong overlap between theta and delta activity is found (e.g., Harper et al., 2014). Another possibility is that FM theta NF not only affects the theta band but also the delta band, given that functional imaging studies suggest that delta oscillations during wakefulness originate from similar medial frontal cortical regions as FM theta (Harmony, 2013). For alpha, no NF specific effects are found in the standard and individualized bands, and for beta, differential effects are found for the NF and active control groups, with the active control group showing higher beta amplitudes across and within sessions.

4.2. Self-reported executive function complaints predict lower frontal-midline theta upregulation

To better understand the heterogeneity of NF learning and ultimately optimize NF efficacy and transfer to EFs, it is crucial to investigate the predictors of FM theta upregulation success. Our results showed that the presence of self-reported EF complaints may be predictive of lower upregulation of standard FM theta across sessions. Smit and colleagues (2023) speculated that the ability to upregulate FM theta is weaker in adults with self-reported EF complaints (with or without a disorder) compared to healthy adults, as their (sub)clinical sample showed relatively lower levels of FM theta upregulation. They suggest that the experienced EF complaints, such as difficulty with retaining instructions, maintaining focus on feedback, applying and adapting mental strategies, controlling impulsive urges, ignoring environmental distractions, sitting still, etc., may have impeded the ability to successfully upregulate FM theta. Interestingly, the presence of a psychiatric disorder loses its predictive value when it is combined with the presence of self-reported EF complaints in a regression model. It is noteworthy that the two predictors exhibit significant overlap, as all participants with a psychiatric disorder also self-reported EF complaints in their daily life. Furthermore, baseline level of FM theta in the first session is not a predictor of FM theta upregulation success, contrary to earlier findings by Weber and colleagues (2020).

Regarding responsiveness to the feedback in the NF group, the results show that the proportion of non-responders (i.e., 28.6%) is consistent with findings from other NF studies (e.g., Alkoby et al., 2018). Overall, the assessed demographic variables of responders and non-responders were similar, however, non-responders were more likely to have or suspect a psychiatric disorder as compared to responders. The most commonly reported or suspected

disorder was ADD or ADHD. This psychiatric disorder is characterized by deficits in attention, leading to distraction from the task (Brown, 2009). One possible explanation for the higher level of non-responsiveness in individuals with a psychiatric disorder is that they differ in sensitivity to reward. For instance, in disorders like ADHD, reward-based learning is known to be impaired (e.g., Furukawa et al., 2022; Garcia Pimenta et al., 2021), which could contribute to difficulty to self-regulate FM theta. Another explanation is that individuals with a psychiatric disorder may have morphological differences in relevant underlying brain structures. For instance, individuals with ADHD have thinner cortical patterns of the midcingulate cortex and connections to other prefrontal regions (Makris et al., 2007; Rommelse et al., 2017), both key regions in the EF network and main generators of FM theta (Cavanagh & Frank, 2014). A larger volume of the midcingulate cortex is a known predictor of general responsiveness to FM theta NF and seems to facilitate the ability to modulate FM theta (Enriquez-Geppert et al., 2013b). Conversely, a smaller volume of the midcingulate cortex may increase the likelihood of lower FM theta upregulation, as the joint synchronized firing of fewer (connected) neurons can result in weaker activity. Other factors related to specific psychiatric disorders may include changes in neuroplasticity (e.g., Kasparek et al., 2015), higher levels of (cognitive) fatigue (Rogers et al., 2017), reduced self-efficacy and lower self-esteem (Newark et al., 2016), increased stress or anxiety (Koush et al., 2017), and sleep disturbances (Rasch & Born, 2013). Together, such disorder-related factors could make individuals more likely to be unresponsive to NF.

4.3. Implications for clinical groups and peak-performance training

Fundamental questions in NF research are how to convert non-responders into responders and how to improve overall self-regulation success. Ideally, NF training would only be administered to individuals who are able to self-regulate their brain activity (i.e., NF responders) in order to maximize the transfer effects on behavior and cognition. To identify such individuals, an option would be to predict responsiveness based on their characteristics prior to training, going into the direction of personalized medicine.

Furthermore, there are research efforts in personalizing and improving NF procedures to convert non-responders into responders and enhance upregulation success among responders. For instance, Alkoby and colleagues (2018) propose tailoring different NF training features to the individual. The first feature they mention is the brain parameter that is trained. The authors suggest that adapting the training protocol to the unique brain features of the participant can increase self-regulation success. A discussion of NF based on the standard versus individualized FM theta band is provided in Section 4.5. The second feature is the

feedback. By adapting the type of feedback to the individual's preference, intrinsic motivation and effort can be enhanced (e.g., Patall et al., 2008), leading to greater success in FM theta upregulation. Most studies in this mega-analysis used the color of a square as feedback, but Eschmann and colleagues (2020) used a roller coaster animation, which is intuitively more engaging for participants. This may be particularly relevant for individuals with psychiatric disorders such as ADD/ADHD, who are more easily distracted (Brown, 2009). The third feature is mental strategies. Adapting the mental strategy to the specific brain feature that is trained may improve upregulation success (Alkoby et al., 2018). In all FM theta NF studies included in this mega-analysis, participants were given a list of examples of strategies to use and were asked to come up with strategies themselves. However, none of the studies investigated their effect on upregulation. Although there are some studies on the effect of strategies in NF training with different protocols (e.g., Nan et al., 2012; Kober et al., 2013), future systematic research is needed to investigate if effective strategies for upregulating FM theta can be identified. Additional NF factors that could be personalized are the number and distribution of sessions and minutes of self-regulation per session (e.g., Enriquez-Geppert et al., 2017). For instance, (sub)clinical groups may require a larger number of sessions to achieve a similar upregulation level as healthy individuals (Smit et al., 2023).

Moreover, the effectiveness of FM theta NF could be improved by applying technological advances that improve the precision of measuring FM theta and implementing more advanced techniques for feature generation and extraction. For example, the use of machine learning algorithms to generate individual features and adapt them during the training (Enriquez-Geppert et al., 2017).

4.4. Neurofeedback based on the standard versus individualized frontal-midline theta band

FM theta NF studies vary in terms of which theta band is trained and assessed, with some using standard FM theta (e.g., Wang & Hsieh, 2013) and others individualized FM theta (e.g., Eschmann et al., 2020). Brandmeyer and Delorme (2020) justify the use of the standard theta band by arguing that there are several generators of theta in the frontal cortex, each with distinct FM theta peaks, that can all contribute to FM theta power (Cavanagh & Frank, 2014). They assume that if feedback is based on the individualized FM theta band, participants may struggle to find a mental strategy to effectively enhance overall FM theta power. In contrast, a rationale for using the individualized FM theta band is that the FM theta frequency peak shows inter-individual differences, but high intra-individual stability (Näpflin et al., 2008; Mitchell et al., 2008). It is assumed that tailoring the FM theta band to this individual theta peak could

make NF more effective (e.g., Enriquez-Geppert et al., 2017). Enriquez-Geppert and colleagues (2014a) were the first to train the individualized FM theta band, although they studied the effect on the standard FM theta band. In subsequent studies the individualized theta band was both trained and assessed (Hussain, 2020; Eschmann et al., 2020; Smit et al., 2023). In most of them, the ITP was derived from EEG data collected during cognitive tasks that were also assessed for the transfer. This means that, in addition to the greater individualisation of FM theta NF, the task-dependent FM theta peak is targeted (Senoussi et al., 2022), leading to greater training transfer from FM theta upregulation to untrained tasks.

So far, it has not been systematically investigated whether FM theta NF training is more effective with individualized or standard FM theta band, making this an interesting avenue for future research. However, studies with both protocols have shown significant results. On the one hand, individualized NF may in general be more effective in targeting specific neural pathways or frequencies that are most relevant to the participants' condition. By identifying an individualized frequency band through initial EEG assessments, NF training can be tailored to the participants' unique brain activity patterns. This could lead to more personalized and efficient training, potentially resulting in better outcomes (e.g., Alkoby et al., 2018). On the other hand, non-individualized NF based on a standard frequency band may generally be more practical and easier to use, especially in clinical settings where resources and time are limited.

Ethics statement

The studies involving human participants were reviewed and approved by the ethical committee of the relevant universities. The patients/participants provided their written informed consent for participation.

Funding

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Declaration of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgements

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Supplementary material

Table 1. Repeated measures ANOVA results for session-to-session changes (Learning Index 1) for the standard and individualized frequency bands for the NF group versus active control group. Note: ITP = individual theta peak. Significant * $p \leq .05$ or ** $p <$ Benjamini-Hochberg (BH) critical value

Standard frequency	Factor	Source	Sum of Squares	*df*	*F*	*p*	BH value	η_p^2
Delta (1-3.5 Hz)	Within-subject	Session	.024	4.209	1.211	.304	.033	.008
		Session × Group	.006	4.209	.309	.881	.044	.002
		Error	2.864	618.656				
	Between-subject	Group	.107	1	3.700	.056	.017	.025
		Error	4.264	147				
Theta (4-8 Hz)	Within-subject	Session	.025	4.488	1.893	.102	-	.013
		Session × Group	.040	4.488	3.036	.013*	-	.020
		Error	1.943	659.746				
	Between-subject	Group	.137	1	5.443	.021*	-	.036
		Error	3.701	147				
Alpha (8.5-12 Hz)	Within-subject	Session	.026	4.431	1.491	.198	.028	.010
		Session × Group	.008	4.431	.492	.761	.039	.003
		Error	2.525	651.323				
	Between-subject	Group	.127	1	2.437	.121	.022	.016
		Error	7.661	47				
Beta (12.5-30 Hz, Saarland study: 12.5-24 Hz)	Within-subject	Session	.003	4.073	.151	.964	.050	.001
		Session × Group	.074	4.073	3.266	.011**	.011	.022
		Error	3.338	598.742				
	Between-subject	Group	.337	1	10.32	.002**	.006	.066
		Error	4.802	147	7			
Individualized frequency	**Factor**	**Source**	**Sum of Squares**	***df***	***F***	***p***	**BH value**	η_p^2
Delta (ITP – 3-1.5 Hz)	Within-subject	Session	.019	4.357	1.106	.354	.033	.007
		Session × Group	.031	4.357	1.799	.121	.022	.012
		Error	2.509	640.517				
	Between-subject	Group	.164	1	5.364	.022	.017	.035
		Error	4.502	147				
Theta (ITP ± 1 Hz)	Within-subject	Session	.020	4.450	.939	.448	-	.006
		Session × Group	.033	4.450	1.573	.173	-	.011
		Error	3.063	654.124				
	Between-subject	Group	.086	1	3.026	.084	-	.020
		Error	4.171	147				
Alpha (ITP + 3-5 Hz)	Within-subject	Session	.009	4.437	.429	.807	.044	.003
		Session × Group	.020	4.437	.926	.455	.039	.006
		Error	3.166	652.182				
	Between-subject	Group	.169	1	2.412	.123	.028	.016
		Error	10.276	147				
Beta (ITP + 7-24 Hz, Saarland study: ITP + 7-17 Hz)	Within-subject	Session	.003	4.063	.144	.967	.050	.001
		Session × Group	.071	4.063	3.137	.014	.011	.021
		Error	3.340	597.234				
	Between-subject	Group	.346	1	10.44	.002**	.006	.066
		Error	4.876	147	5			

Table 2. Repeated measures ANOVA results for dynamic changes within sessions (Learning Index 2) for the standard and individualized frequency bands for the NF group versus active control group. Note: ITP = individual theta peak. Significant * $p \leq .05$ or ** $p <$ Benjamini-Hochberg (BH) critical value.

Standard frequency	Factor	Source	Sum of Squares	*df*	*F*	*p*	BH value	η_p^2
Delta (1-3.5 Hz)	Within-subject	Block	.266	1.765	32.760	< .001**	.011	.182
		Block × Group	.023	1.765	2.839	.067	.039	.019
		Error	1.195	259.405				
	Between-subject	Group	.068	1	3.571	.061	.033	.024
		Error	2.801	147				
Theta (4-8 Hz)	Within-subject	Block	.218	1.744	28.833	< .001*	-	.164
		Block × Group	.038	1.744	5.022	.010*	-	.033
		Error	1.109	256.411				
	Between-subject	Group	.078	1	4.841	.029*	-	.032
		Error	2.370	147				
Alpha (8.5-12 Hz)	Within-subject	Block	.491	1.680	35.158	< .001**	.006	.193
		Block × Group	.025	1.680	1.802	.173	.050	.012
		Error	2.054	246.993				
	Between-subject	Group	.088	1	2.548	.113	.044	.017
		Error	5.059	147				
Beta (12.5-30 Hz, Saarland study: 12.5-24 Hz)	Within-subject	Block	.123	2.121	12.927	< .001**	.017	.081
		Block × Group	.085	2.121	8.900	< .001**	.022	.057
		Error	1.403	311.766				
	Between-subject	Group	.199	1	8.953	.003**	.028	.057
		Error	3.266	147				
Individualized frequency	**Factor**	**Source**	**Sum of Squares**	***df***	***F***	***p***	**BH value**	η_p^2
Delta (ITP – 3-1.5 Hz)	Within-subject	Block	.333	1.679	38.749	< .001**	.006	.209
		Block × Group	.039	1.679	4.589	.016**	.033	.030
		Error	1.262	246.758				
	Between-subject	Group	.100	1	5.040	.026**	.039	.033
		Error	2.906	147				
Theta (ITP ± 1 Hz)	Within-subject	Block	.364	1.817	38.569	< .001*	-	.208
		Block × Group	.025	1.817	2.614	.080	-	.017
		Error	1.386	267.035				
	Between-subject	Group	.048	1	2.719	.101	-	.018
		Error	2.602	147				
Alpha (ITP + 3-5 Hz)	Within-subject	Block	.522	1.687	28.302	< .001**	.011	.161
		Block × Group	.041	1.687	2.196	.122	.044	.015
		Error	2.713	247.961				
	Between-subject	Group	.110	1	2.386	.125	.050	.016
		Error	6.805	147				
Beta (ITP + 7-24 Hz, Saarland study: ITP + 7-17 Hz)	Within-subject	Block	.141	2.075	14.692	< .001*	.017	.091
		Block × Group	.088	2.075	9.202	< .001*	.022	.059
		Error	1.411	305.002				
	Between-subject	Group	.204	1	9.055	.003*	.028	.058
		Error	3.304	147				

Table 3. Independent Samples t-test results for the overall maximum FM theta NF effect for the standard and individualized frequency bands for the NF group versus active control group. Note: ITP = individual theta peak. BH = Benjamini-Hochberg critical value. Significant * $p \leq .05$. For theta the *p*-value is one-sided and for delta, alpha and beta two-sided.

Standard frequency	*df*	*t*	*p*	BH value	*d*
Delta (1-3.5 Hz)	147	.240	.810	.050	.039
Theta (4-8 Hz)	147	1.383	.084	-	.227
Alpha (8.5-12 Hz)	147	.349	.727	.033	.057
Beta (12.5-30 Hz, Saarland study: 12.5-24 Hz)	147	–1.028	.306	.017	–.169
Individualized frequency	***df***	***t***	***p***	**BH value**	***d***
Delta (ITP – 3-1.5 Hz)	147	.896	.372	.033	.147
Theta (ITP ± 1 Hz)	147	2.075	.020*	-	.340
Alpha (ITP + 3-5 Hz)	147	1.060	.291	.017	.174
Beta (ITP + 7-24 Hz, Saarland study: ITP + 7-17 Hz)	147	–.746	.457	.050	–.122

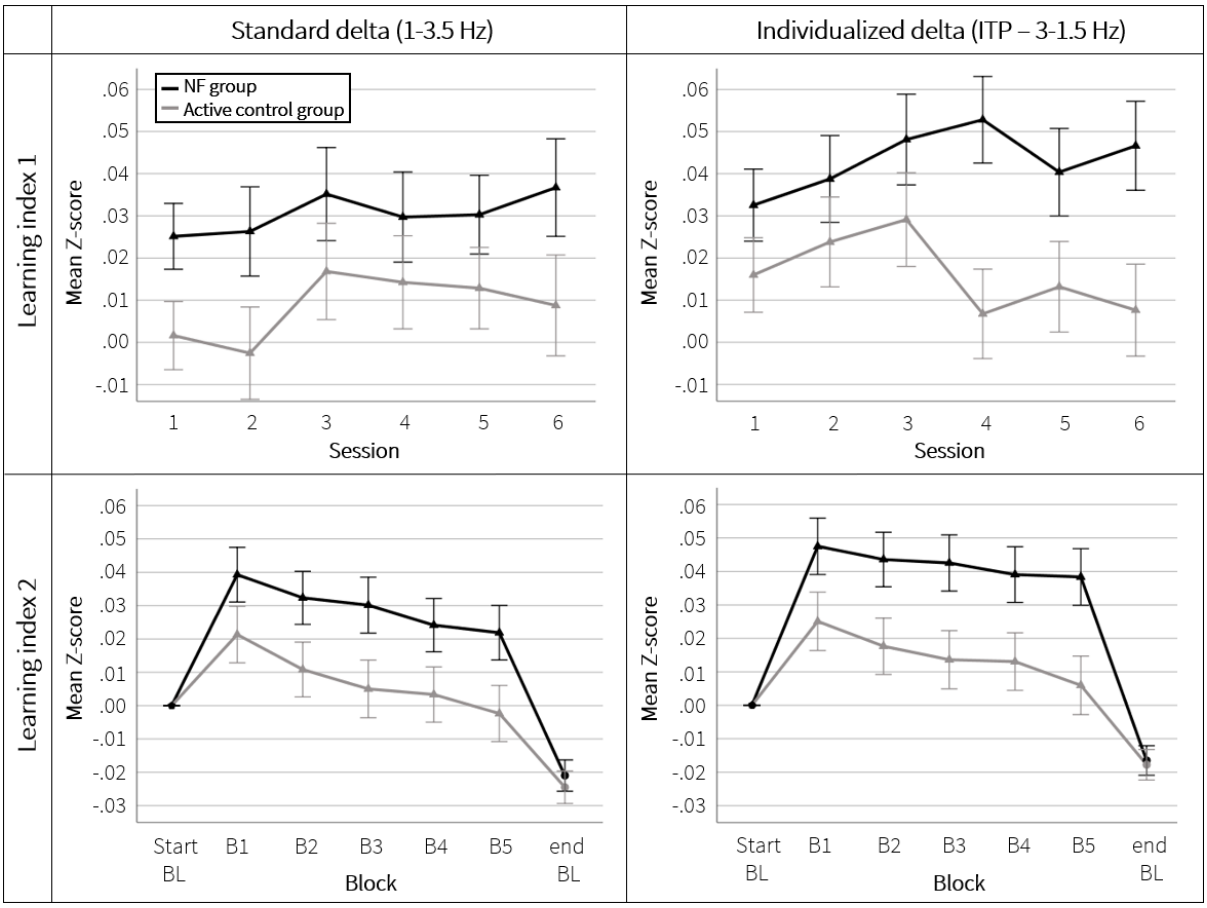

Figure 1. FM theta NF effects on the delta band for the NF group and active control group; Learning Index 1: Mean Z-score per session across the five NF blocks (i.e., session-to-session changes) for the standard delta band (1-3.5 Hz) and individualized delta band (ITP – 3-1.5 Hz) and Learning Index 2: Mean Z-score per block across the six sessions (i.e., dynamical changes within sessions) for the standard delta band (1-3.5 Hz) and individualized delta band (ITP – 3-1.5 Hz). Note: Error bars indicate the standard error of the mean. ● = start or end baseline (BL) and ▲ = NF block(s) (B). ITP = individual theta peak.

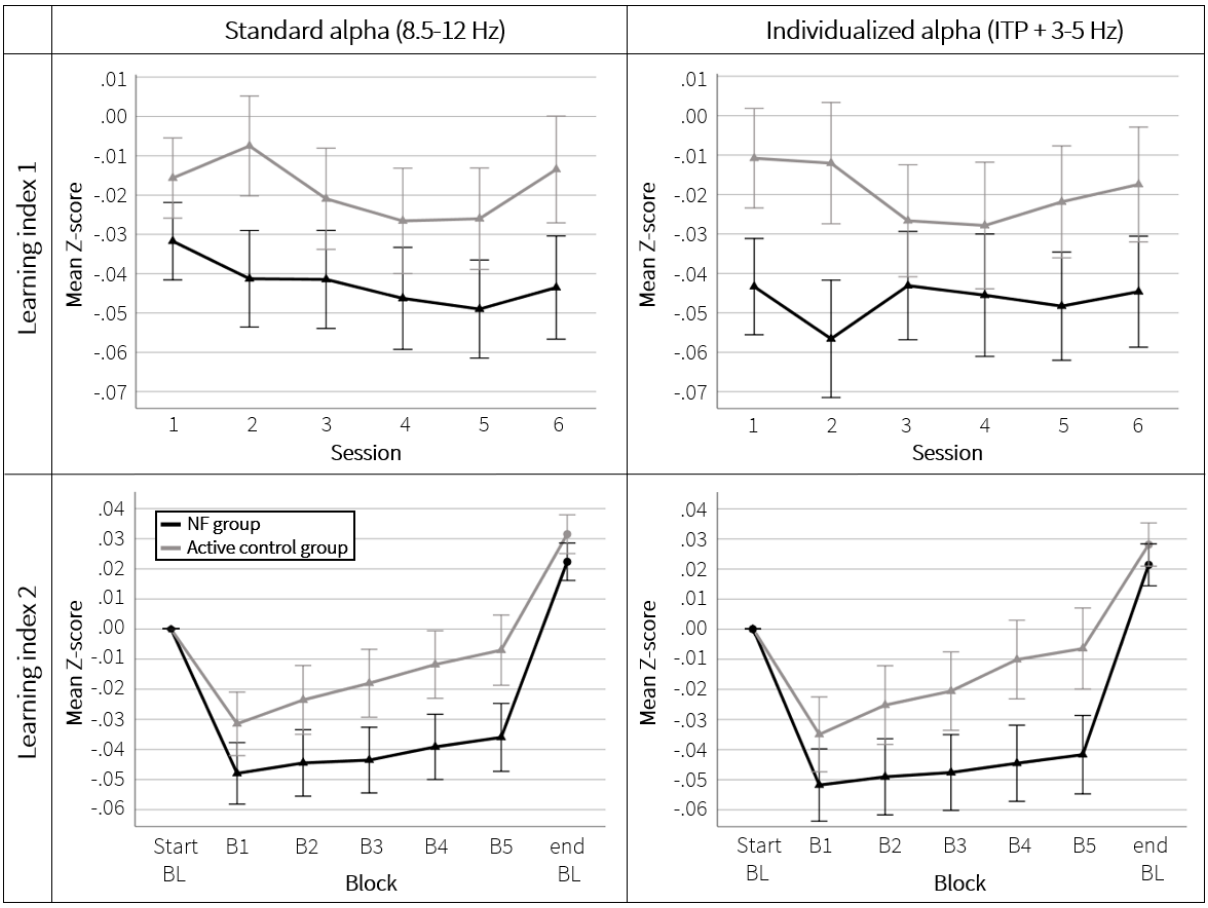

Figure 2. FM theta NF effects on the alpha band for the NF group and active control group; Learning Index 1: Mean Z-score per session across the five NF blocks (i.e., session-to-session changes) for the standard alpha band (8.5-12 Hz) and individualized alpha band (ITP + 3-5 Hz) and Learning Index 2: Mean Z-score per block across the six sessions (i.e., dynamical changes within sessions) for the standard alpha band (8.5-12 Hz) and individualized alpha band (ITP + 3-5 Hz). Note: Error bars indicate the standard error of the mean. ● = start or end baseline (BL) and ▲ = NF block(s) (B). ITP = individual theta peak.

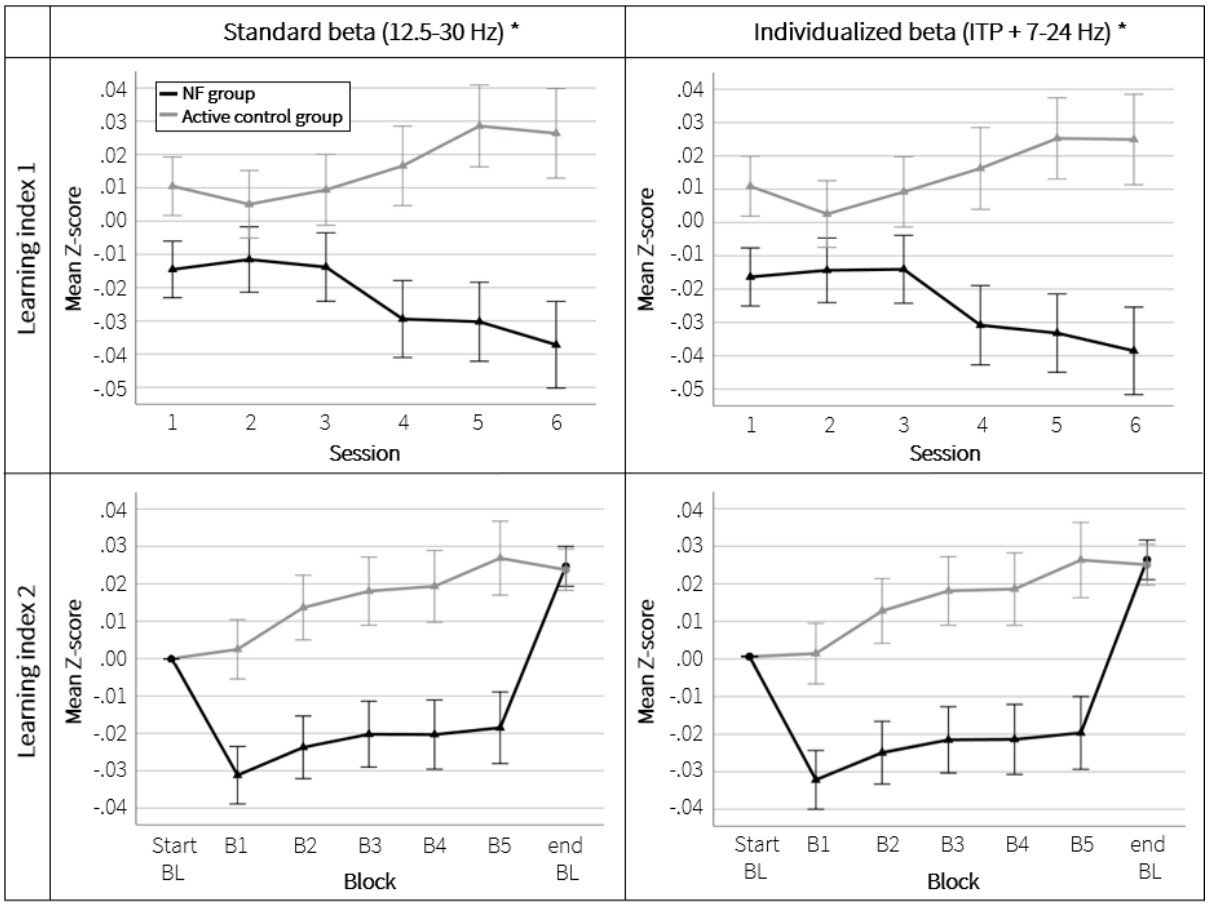

Figure 3. FM theta NF effects on the beta band for the NF group and active control group; Learning Index 1: Mean Z-score per session across the five NF blocks (i.e., session-to-session changes) for the standard beta band (12.5-30 Hz) and individualized beta band (ITP + 7-24 Hz) and Learning Index 2: Mean Z-score per block across the six sessions (i.e., dynamical changes within sessions) for the standard beta band (12.5-30 Hz) and individualized beta band (ITP + 7-24 Hz). Note: Error bars indicate the standard error of the mean. ● = start or end baseline (BL) and ▲ = NF block(s) (B). ITP = individual theta peak. * For the Saarland study, the standard beta band was 13-24 Hz and the individualized beta band ITP + 7-17 Hz).

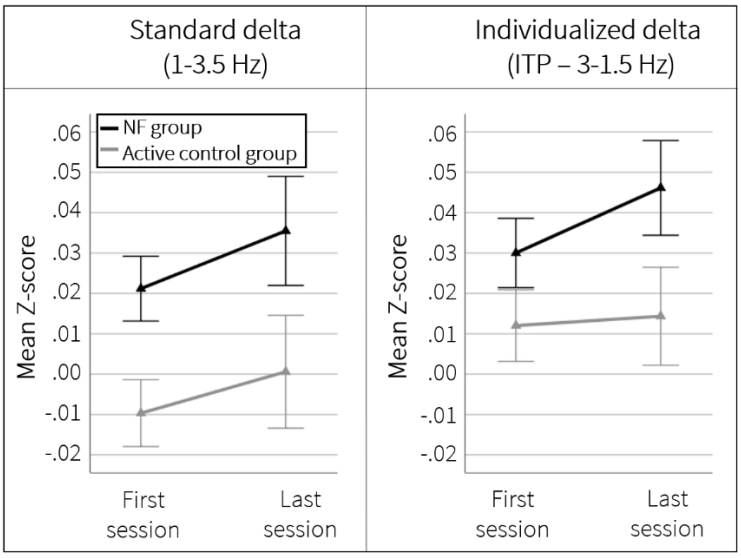

Figure 4. Overall maximum FM theta NF effect on the delta band for the NF group and active control group: Mean Z-score of the NF blocks in the first and last session for the standard delta band (1-3.5 Hz) and individualized delta band (ITP – 3-1.5 Hz). Note: Error bars indicate the standard error of the mean. ▲ = NF blocks. ITP = individual theta peak.

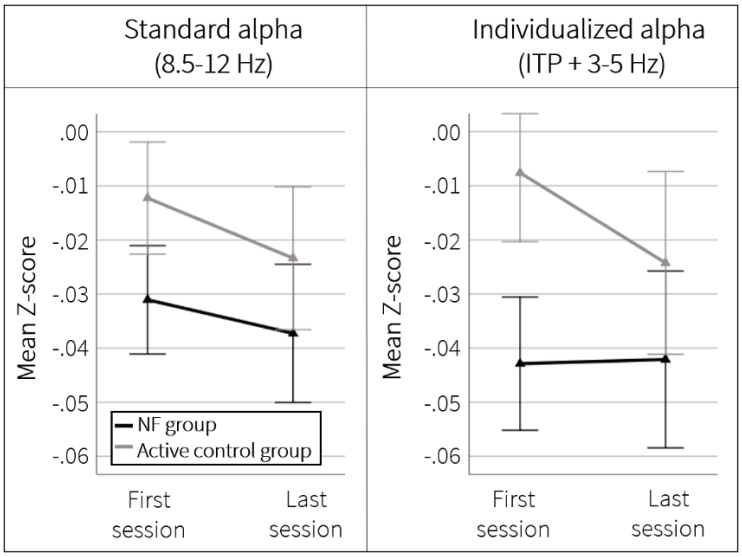

Figure 5. Overall maximum FM theta NF effect on the alpha band for the NF group and active control group: Mean Z-score of the NF blocks in the first and last session for the standard alpha band (8.5-12 Hz) and individualized alpha band (ITP + 3-5 Hz). Note: Error bars indicate the standard error of the mean. ▲ = NF blocks. ITP = individual theta peak.

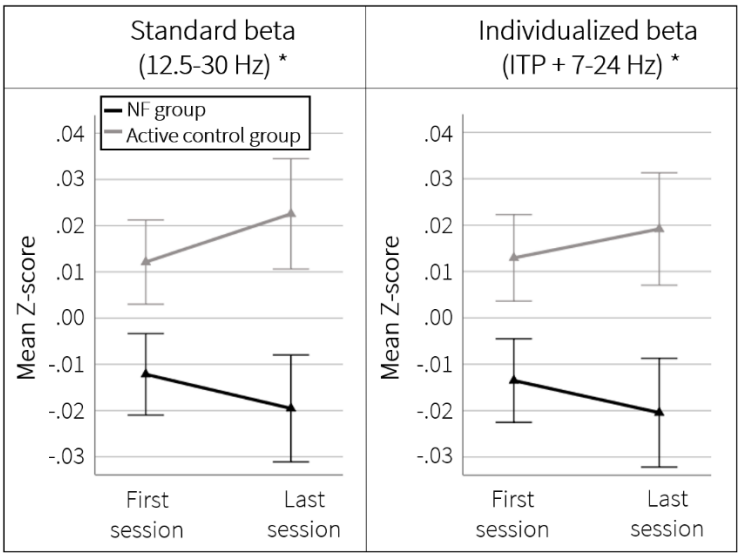

Figure 6. Overall maximum FM theta NF effect on the beta band for the NF group and active control group: Mean Z-score of the NF blocks in the first and last session for the standard beta band (12.5-30 Hz) and individualized beta band (ITP + 7-24 Hz). Note: Error bars indicate the standard error of the mean. ▲ = NF blocks. ITP = individual theta peak. * For the Saarland study, the standard beta band was 13-24 Hz and the individualized beta band ITP + 7-17 Hz).

Chapter 5

Look who is complaining: Psychological factors predicting subjective cognitive complaints in a large community sample of older adults

Smit, D., Koerts, J., Bangma, D. F., Fuermaier, A. B. M., Tucha, L. I., & Tucha, O. M., (2021). Look who is complaining: Psychological factors predicting subjective cognitive complaints in a large community sample of older adults. *Applied Neuropsychology: Adult, 1-15.*
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ABSTRACT

Subjective cognitive complaints (SCCs) are not directly related to objective impairments in cognition. This study examines the role of psychological factors in predicting SCCs in the domains of executive functioning, memory, and attention in older adults. A community sample of 1219 Dutch adults, aged 40 year or older, completed the BRIEF-A, MSEQ, FEDA, NEO-FFI, DASS-21, and a demographic questionnaire. Participants were randomly divided into exploratory (n = 813) and confirmatory samples (n = 406). In the exploratory sample, we analyzed whether personality factors, symptoms of depression and anxiety, perceived stress, and demographics could predict SCCs in the different cognitive domains. For this purpose, a two-step regression approach with bootstrapping was used. To independently validate the results, these analyses were repeated in the confirmatory sample. Concerning executive functioning, complaints regarding the ability to regulate behavior and emotional responses were predicted by lower agreeableness levels and higher levels of neuroticism and perceived stress. Complaints regarding the ability to actively solve problems in different circumstances were predicted by a lower conscientiousness level, higher agreeableness level, and more depressive symptoms. Attentional complaints were predicted by lower levels of conscientiousness and extraversion, together with a higher level of neuroticism. For memory, no significant predictors were consistently found. Psychological factors are of influence on the subjective experience of cognitive complaints. In particular personality factors, perceived stress, and symptoms of depression, seem to predict SCCs in the domains of executive functioning and attention. Clinicians should take these factors into account in older adults who have SCCs.

1. INTRODUCTION

Subjective cognitive complaints (SCCs) refer to an individual's experience of deterioration of capacities in one or more cognitive domains (Jessen et al., 2014). SCCs are frequently reported by older adults, with prevalence rates up to 90% in individuals between the ages of 70 and 90 years (Slavin et al., 2010). The presence of subjective deterioration in cognitive functioning is even a necessary criterion for the diagnosis of mild cognitive impairment (American Psychiatric Association, 2013), which is considered as a prodromal stage of Alzheimer's disease. The latter is supported by findings showing that older adults with SCCs have an increased prevalence of biomarker abnormalities consistent with Alzheimer's disease (Amariglio et al., 2012; Rami et al., 2011) and by longitudinal studies showing that SCCs in older adults represent a risk factor for future cognitive decline and mild cognitive impairment, as well as for Alzheimer's disease (Mitchell et al., 2014).

However, the relationship between SCCs and objective cognitive functioning is not straightforward. Objective cognitive functioning refers to the cognitive ability in any domain (e.g., memory, attention) measured by standardized cognitive tests. Overall, there is only limited support for a link between SCCs and the concurrent level of objective performance on cognitive tests (e.g., Burmester et al., 2016; Fuermaier et al., 2015; Koerts et al., 2012). However, unimpaired performance on a cognitive test does not necessarily mean that cognitive functioning is fully intact. For example, it is possible that subtle cognitive impairments are difficult to detect with standardized cognitive testing due to a lack of sensitivity and specificity. Additionally, unimpaired performance on objective cognitive tests could be the result of successful compensation by the subject or a lack of ecological validity of the test.

Another explanation for the lack of an association between SCCs and objective cognitive functioning is the presence of other (psychological) factors influencing the subjective experience of cognitive complaints. This is supported by studies indicating that the majority of older adults with SCCs do not deteriorate more rapidly than their peers (e.g., Mitchell et al., 2014) and the disappearance of the subjective impression of cognitive impairment occurs frequently (Vestberg et al., 2010).

In the literature, several psychological factors are suggested that may contribute to experiencing SCCs. First, it has been suggested that SCCs are associated with certain personality factors. The most frequently reported personality factor predicting SCCs is a high

level of neuroticism (Kliegel & Zimprich, 2005; Reid & MacLullich, 2006). In addition, conscientiousness and openness are noted to have an inverse relation with SCCs (Slavin et al., 2010). Second, negative affective states seem to play an important role in the subjective experience of cognitive impairment. Several studies indicate that SCCs positively correlate with the number and severity of symptoms of depression, anxiety, and perceived stress (Balash et al., 2013; Rönnlund et al., 2013; Zlatar et al., 2018). Third, an older age, in the context of negative age stereotypes or "dementia worry", could lead to an over-reporting of cognitive complaints (Kessler et al., 2012; Kliegel & Zimprich, 2005). Fourth, some studies found an association between gender and SCCs, reporting a higher rate of SCCs for women in comparison to men (Tomita et al., 2014). However, not all studies reported an effect of gender (e.g., Markova et al., 2017). Finally, various other factors may be related to SCCs, such as sleep (Tsapanou et al., 2018), quality of life (Hill et al., 2017), perceived health status (Montejo et al., 2020), and availability of emotional support (Ha & Pai, 2018).

In sum, the explanations for SCCs in older adults can be multifactorial. The aim of the current study is to investigate which factors best predict SCCs in the cognitive domains of executive functioning, memory, and attention. Based on previous literature, aspects such as personality factors, negative affective states, and demographic information are taken into account. For this study a large community sample of adults aged 40 years or older was used in order to allow generalization of the results.

2. METHODS

2.1. Participants

A community sample of 1219 adults from the general Dutch population participated in this online study. The sample consisted of 567 men (46.5%) and 652 women (53.5%) with a mean age of 60.5 years (SD = 11.3, range 40-97). Educational level was rated on an 8-point scale ranging from primary school to university master. Of all the participants, 16.4% reported to have a lower education level (i.e., primary education or preparatory secondary vocational education), 36.3% an intermediate education level (i.e., secondary vocational education, senior general secondary education, or pre university education), and 46.9% a higher education level (i.e., higher vocational education or university). Four participants did not rate their level of education. Participants were recruited in two ways: (a) via personal contacts or social media of the researchers (these participants received no monetary reward) or (b) via a Dutch online research panel (i.e., https://panelinzicht.nl/; these participants received a small monetary reward). The exclusion criteria and the number of participants that were excluded are presented in Figure 1. Participants were informed about the aim of the study prior to the start of the online survey and gave electronic consent for participation. The study was approved by the Ethical Committee Psychology of the University of Groningen, the Netherlands.

The demographic questions in the survey focused on age (in years), gender (male/female), education level (eight answer alternatives ranging from primary school to university master), marital status (married, living together, partner but not living together, not married, divorced, widow/widower, other), having children (yes/no), having pets (yes/no), profession (open-ended question), net income (6-point scale ranging from < €1,000 to > €5,000 per month), weight (in kilograms), and length (in centimeters). Additionally, questions about sleep (average hours of sleep per night and sleep quality rated by a grade from 0-10), self-rated health ("What do you generally think of your health?" on a 5-point scale ranging from bad to excellent), and quality of life ('How would you rate your quality of life?' rated by a grade from 0 to 10) were included. Finally, participants were asked four questions about their medical history ("Did you ever visit a neurologist, cardiologist, internist, or psychiatrist/psychologist? If yes, for what reason?"). These latter questions were used for the exclusion of participants (Figure 1).

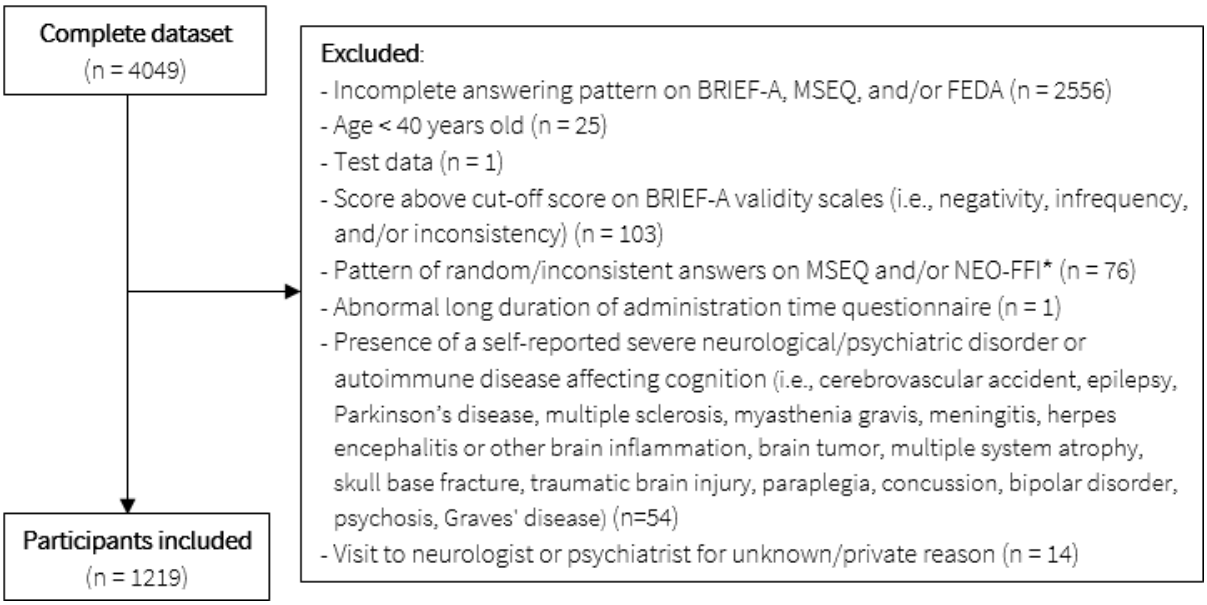

Figure 1. Overview of exclusion criteria. Note. *Random answers were patterns with (almost) always the same answer option, and inconsistent answers on the MSEQ were, for example, a higher estimate of remembering the most difficult level as compared to the easiest difficult level. BRIEF-A = Behavior Rating Inventory Executive Function - Adult version; MSEQ = Memory Self-Efficacy Questionnaire; FEDA = Questionnaire for Experiences of Attention Deficits; NEO-FFI = NEO-Five Factor Inventory.

2.2. Questionnaires

2.2.1. Subjective cognitive complaints

The Behavior Rating Inventory Executive Function - Adult version (BRIEF-A) is a 75-item rating scale aimed at assessing everyday behaviors associated with specific domains of executive functioning (Roth et al., 2005; Scholte & Noens, 2011). Participants have to indicate on a 3-point scale how often they experienced certain executive functioning problems in daily life during the last month. The scale ranges from never [1] to often [3]. An example of an item is: "I have trouble changing from one activity or task to another". The BRIEF-A consists of nine subscales that can be summarized by means of two indexes. The Behavioral Regulation Index (BRI) captures the ability to appropriately regulate behavior and emotional responses, and is composed of four subscales: Inhibit, Shift, Emotional control, and Self-monitor (score range 30-90). The Metacognition Index (MI) captures the ability to actively solve problems in different circumstances, and is composed of five subscales: Initiate, Working memory, Plan/organize, Task monitor, and Organization of materials (score range 40-120). In this study, the BRI and MI were used, as they can be considered separate entities of executive functioning (Scholte & Noens, 2011).

The Dutch version of the Memory Self-Efficacy Questionnaire (MSEQ) is a 20-item rating scale aimed at assessing how participants think about their own memory functioning (Berry et al., 1989). The MSEQ assesses four aspects of memory: (i) where objects were placed, (ii) products on a shopping list, (iii) names of people, and (iv) important points from a story. Each domain is assessed at five levels of difficulty (e.g., for the shopping list, Level 1 reflects the experienced self-efficacy to remember 18 out of 18 products, Level 2 reflects the experienced self-efficacy to remember 14 out of 18 products, etc.). Participants have to estimate, indicated by a percentage between 0 and 100, in steps of 10, how confident they are that they can perform each level (score range 0-100). Higher estimates indicate a higher confidence. In this study, the mean estimation across the four memory aspects and five difficulty levels were used.

The Questionnaire for Experiences of Attention Deficits (German: Fragebogen Erlebter Defizite der Aufmerksamkeit [FEDA]) is a 27-item rating scale aimed at assessing attention deficits in everyday situations (Zimmermann et al., 1991). Participants have to indicate on a 5-point scale how often they experience certain problems with attention. The scale ranges from never [0] to very frequently [4]. An example of an item is: “It is hard to concentrate when something is going on around me.” The FEDA consists of three subscales, representing Distractibility, Fatigue, and Motivation. In this study, the total score was used, based on the sum of the scores on all items (score range 0-108).

2.2.2. Personality

The NEO-Five Factor Inventory (NEO-FFI) is a 60-item rating scale that measures the Big Five personality factors Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism (Costa & McCrae, 1992; Hoekstra et al., 2007). On a 5-point scale, which ranges from completely disagree (1 or 5) to completely agree (5 or 1), participants have to indicate to what degree certain statements apply to them. For each personality factor, a total score is calculated (score range 12-60 per factor).

2.2.3. Symptoms of depression, anxiety, and stress

The Depression Anxiety Stress Scale (DASS-21) is a 21-item rating scale aimed at measuring negative emotions (De Beurs et al., 2001). Participants have to indicate on a 4-point scale how often the items apply to them. The scale ranges from never or not applicable (0) to very certainly or often applicable (3). The DASS-21 consists of three subscales: Depressive symptoms, Anxiety symptoms, and Stress. The DASS-21 is a shortened version of the original DASS consisting of 42 items (Lovibond & Lovibond, 1995). To be able to use the cutoff scores of

the original DASS, the scores on the three subscales of the DASS-21 are multiplied by two (score range 0-42 per subscale).

2.3. Procedure

All questionnaires and scales were accessible online (Qualtrics, Provo, UT) and completion took approximately 30 minutes. The survey started with the general questions regarding demographics. Subsequently, the BRIEF-A, MSEQ, FEDA, NEO-FFI, and DASS-21 were administered in this fixed order. It was possible to temporarily pause the survey and continue at a later time. Data was collected between October 2016 and March 2018.

2.4. Statistical analyses

For statistical purposes, the variables education level, marital status, and profession were recoded as low/intermediate/high, having a partner yes/no, and having a profession yes/no, respectively. In total, this study included 21 independent variables: age (in years), gender (male/female), educational level (low/intermediate/high), having a profession (yes/no), having a partner (yes/no), having children (yes/no), having pets (yes/no), income (6 categories), BMI (weight in kilograms/length in meters^2), hours of sleep per night, sleep quality (scale 0-10), self-rated health (scale 1-5), quality of life (scale 0-10), the NEO-FFI personality factors Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism, and the DASS subscales Depressive symptoms, Anxiety symptoms, and Stress. For data reduction purposes, five variables were merged into two overall scores: the total score of the DASS as a measure of negative emotional symptoms (i.e., the sum of the subscales Depressive symptoms, Anxiety symptoms, and Stress) and an overall score for sleep (i.e., average of the Z-scores for hours of sleep per night and sleep quality). Therefore, 18 independent variables were used for analysis.

In the current study, two types of analyses were performed. First, an exploratory analysis was performed to determine which of the 18 independent variables could predict the scores on the dependent variables BRIEF-A BRI, BRIEF-A MI, MSEQ, and FEDA. For this purpose, a two-step regression approach was applied to the data of 813 randomly selected participants (i.e., 2/3 of the total sample). In Step 1, simple linear regression analyses were performed in order to assess the predictive value of each independent variable for the dependent variables separately. Additionally, if one of the merged variables turned out to be significant, the predictive value of the variables on which the merged variable was based was also explored (e.g., if the DASS total score was found to be a significant predictor, the three separate subscales were also analyzed). In Step 2, multiple regression analyses (enter method) were

performed for the four dependent variables using the significant predictors from Step 1. To internally validate the results, bootstrapping with 1000 samples was used to derive 99% bias corrected accelerated (BCa) confidence intervals for the regression coefficients.

Second, a confirmatory analysis was performed in order to determine the robustness of the results from the exploratory analysis (i.e., independent validation). Again, the two-step regression approach as described above was performed, including the bootstrapping procedure, this time on the data of the remaining 406 participants (i.e., 1/3 of the total sample). The only difference here was that in Step 2 not only the significant predictors from Step 1 were used, but also the significant predictors from Step 2 in the exploratory analysis (if not already included).

Overall, due to multiple testing and the large sample sizes, a conservative *p*-value of ≤ .01 was used in order to reduce type I errors. In Step 2 of both the exploratory and confirmatory analyses, predictors were considered significant if both the *p*-value was ≤ .01 and the bootstrap BCa confidence interval (CI) did not include the value 0. Variables were considered relevant predictors if they were significant in both the exploratory and confirmatory regression analyses (i.e., consistent predictors across samples). Effect sizes were indicated by the percentage of explained variance (R^2) and interpreted as small (≤ .08), medium (.09-.24), or large (≥ .25) (Cohen, 1988). The squared semipartial correlation (sr^2) indicates the percentage of unique contribution of a specific independent variable to the total variation in the dependent variable. The sr^2 was interpreted as small (< .01), medium (.01-.059) or large (> .059) (Fritz et al., 2012). In case of missing values, participants were excluded listwise per analysis.

In both the exploratory and confirmatory sample, the data was checked for influential cases and the assumptions associated with linear regression analysis were tested. To check for the presence of influential cases Cook's distance was calculated. All values were below 1, indicating there were no influential outliers. Linearity was assessed by visual inspection of the partial plots. There was no evidence of a curved pattern in any of the plots. To test whether the residuals were normally distributed, the histograms and probability-probability plots were checked. Overall, the residuals showed a normal distribution. Some slightly skewed distributions were accepted as they are, since sample sizes bigger than 50 are considered to be robust against violations of normality (Casson & Farmer, 2014). For the assumption of homoscedasticity, the scatterplots of the Z-values of the residuals against those of the predicted values were visually checked and the Koenker test was used (Koenker, 1981). Any

violations of homoscedasticity were not corrected, as bootstrapping was additionally performed to determine the significance of a predictor (Hausman & Palmer, 2012). Finally, to test for multicollinearity, the variance inflation factor (VIF) was inspected. All VIF values were well below 10, indicating there were no problematic correlations between the independent variables in the multiple regression models (Belsley et al., 2005). All analyses were carried out using Statistical Package for the Social Sciences version 26.

3. RESULTS

3.1. Sample characteristics

Table 1 provides an overview of the scores on the dependent and independent variables of both the exploratory and confirmatory sample. There were no significant differences between the two samples regarding these variables.

When comparing the scores of individual participants to the BRIEF-A norms for adults aged 18-65 years old (Scholte & Noens, 2011), a large majority of participants in both samples was found to score in the very low to above average range (i.e., percentile < 90) on the two indexes (exploratory sample: BRI = 96.9% and MI = 95.6%; confirmatory sample: BRI = 96.6% and MI = 94.1%). This indicates that the majority of participants report a low to above average number of complaints on these indexes. There was, however, a small number of participants scoring in the high (i.e., percentile ≥90) or very high (i.e., percentile ≥98) range, indicating a high or very high number/severity of complaints. For the BRIEF-A BRI, in both samples 3.0% of participants scored in the high range and 0.1% and 0.5% of the exploratory and confirmatory sample, respectively, scored in the very high range. On the BRIEF-A MI, 3.7% of participants in the exploratory sample scored high and 0.7% very high and in the confirmatory sample 5.4% scored high and 0.5% very high. For the FEDA and the Dutch version of the MSEQ no normative data was available.

On the NEO-FFI, the majority of participants also scored in the average range (i.e., stanines 3-7) on the five personality factors compared to the normative data of people older than 50 years (Hoekstra et al., 2007). In the exploratory sample, this was 67.6% for Openness; 79.2% for Conscientiousness; 72.9% for Extraversion; 71.2% for Agreeableness; and 76.6% for Neuroticism. In the confirmatory sample, the percentages of participants that scored in the average range was as follows: Openness, 65.6%; Conscientiousness, 80.2%; Extraversion, 75.5%; Agreeableness, 70.0%; and Neuroticism, 75.1%. A small number of participants scored in the low range (i.e., stanines 1-2) or high range (i.e., stanines 8-9). In the exploratory sample, 2.9%, 8.9%, 5.2%, 4.8%, and 17.4% of participants scored low and 29.5%, 11.9%, 21.9%, 23.9%, and 6.0% of participants scored high, respectively, on the factors Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism. In the confirmatory sample, 5.6%, 7.6%, 6.1%, 8.7%, and 17.3% of participants scored low and 28.8%, 12.2%, 18.4%, 21.4%, and 7.6% of participants scored high, respectively, on the factors Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism.

Table 1. Demographic characteristics and scores on the dependent and independent variables of the exploratory and confirmatory sample. Note. [a] For Education level the information of four participants in the exploratory sample was missing. BRIEF-A BRI = Behavior Rating Inventory Executive Function - Adult version Behavioral Regulation Index; BRIEF-A MI = Behavior Rating Inventory Executive Function - Adult version Metacognition Index; MSEQ = Memory Self-Efficacy Questionnaire; FEDA = Questionnaire for Experiences of Attention Deficits; BMI = body mass index. Income is based on 6-point scale ranging from < €1000 to > €5000 per month, sleep quality is indicated by a grade between 0 and 10, self-rated health is based on a 5-point scale ranging from bad to excellent, and quality of life is indicated by a grade between 0 and 10.

	Exploratory sample (n = 813)			Confirmatory sample (n = 406)		
Continuous variables	*M* (*SD*)	Median	min-max	*M* (*SD*)	Median	min-max
BRIEF-BRI	40.3 (7.3)	39.0	30-75	40.7 (7.5)	40.0	30-73
BRIEF-MI	55.1 (9.9)	54.0	40-107	55.2 (10.4)	53.5	40-89
MSEQ	72.7 (15.7)	74.5	11-100	71.9 (16.9)	74.3	14.5-99.5
FEDA	20.7 (13.8)	19.0	0-82	21.7 (14.5)	19.0	0-72
Age	60.0 (11.4)	58.0	40-94	61.6 (11.0)	60.0	40-97
Income	2.7 (1.2)	3.0	1-6	2.7 (1.2)	3.0	1-6
BMI	26.4 (4.7)	25.7	17.9-58.6	26.4 (4.6)	25.7	17.4-57.2
Hours of sleep	7.1 (1.0)	7.0	3-10	7.0 (1.0)	7.0	2-10
Sleep quality	7.0 (1.6)	7.0	0-10	7.0 (1.7)	7.0	0-10
Self-rated health	3.2 (0.8)	3.0	1-5	3.2 (0.8)	3.0	1-5
Quality of life	7.7 (1.1)	8.0	2-10	7.7 (1.2)	8.0	1-10
Openness	37.7 (5.7)	37.0	22-55	37.1 (6.1)	37.0	16-55
Conscientiousness	46.3 (5.4)	46.0	27-60	46.1 (5.4)	46.0	26-60
Extraversion	40.6 (6.2)	41.0	14-58	40.1 (6.2)	40.0	20-58
Agreeableness	45.8 (5.1)	46.0	31-58	45.2 (5.4)	46.0	28-60
Neuroticism	28.1 (7.3)	28.0	12-57	28.8 (7.7)	28.0	12-53
Depressive symptoms	3.9 (5.3)	2.0	0-30	4.6 (6.2)	2.0	0-32
Anxiety symptoms	3.5 (4.5)	2.0	0-28	3.7 (4.7)	2.0	0-32
Stress	5.8 (5.8)	4.0	0-28	6.1 (6.2)	4.0	0-30
Categorical variables	n (%)			n (%)		
Gender (female)	442 (54.4%)			210 (51.7%)		
Education level (low/ intermediate/ high)	121 (14.9%) / 307 (37.8%) / 381 (46.9%) [a]			79 (19.5%) / 136 (33.5%) / 191 (47.0%)		
Partner (yes)	636 (78.2%)			307 (75.6%)		
Children (yes)	700 (86.1%)			343 (84.5%)		
Pets (yes)	358 (44.0%)			188 (46.3%)		
Profession (yes)	441 (54.2%)			203 (50.0%)		

Finally, on the DASS, most participants in both samples scored in the normal to moderate range on the subscales for Depressive symptoms (exploratory sample: 98.7%, confirmatory sample: 96.9%), Anxiety symptoms (both samples 97.2%), and Stress (exploratory sample: 99.5%, confirmatory sample: 99.2%). On the subscale Depressive symptoms, 0.9% of participants in the exploratory sample scored in the severe range and 0.4% in the extremely

severe range. In the confirmatory sample, this was slightly higher with 2.7% of participants scoring in the severe range and 1.0% in the extremely severe range. On the subscale Anxiety symptoms, 1.2% of the participants in the exploratory sample had a severe score and 1.4% an extremely severe score. For the confirmatory sample, this was 1.5% and 1.2%, respectively. Finally, on the subscale Stress, 0.5% of participants in the exploratory sample and 0.7% in the confirmatory sample scored in the severe range. None of the participants scored in the extremely severe range on this subscale.

3.2. Exploratory analysis

3.2.1. Step 1: Simple linear regression

Tables 2-5 show the results of the simple linear regression analyses. For the BRIEF-A BRI, BRIEF-A MI, and MSEQ, there were 12 significant predictors and for the FEDA 16 predictors. More complaints on the BRIEF-A indexes and FEDA and lower estimations of self-efficacy on the MSEQ were consistently found to be predicted by a lower self-rated health and quality of life, lower scores on Conscientiousness, Extraversion, and Agreeableness, and higher scores on Neuroticism, Depressive symptoms, Anxiety symptoms, and Stress. Additionally, more complaints on the BRIEF-A BRI were predicted by a lower income, less hours of sleep, and a lower sleep quality. For the BRIEF-A MI, more complaints were additionally predicted by a lower age, less hours of sleep, and a lower sleep quality. Lower estimations on the MSEQ were additionally found to be predicted by being male, a lower education level, and a lower score on Openness. Finally, more reported complaints on the FEDA were additionally found to be predicted by being female, a lower education level, not having a partner, not having children, a lower income, less hours of sleep, and a lower sleep quality.

3.2.2. Step 2: Multiple linear regression

In the second step, for each dependent variable the significant predictors from Step 1 were put into a multiple regression model using the enter method. For the purpose of internal validation bootstrapping was applied (Tables 2-5). More complaints on the BRIEF-A BRI were significantly predicted by a lower score on Agreeableness and higher scores on Neuroticism and Stress. The variable Stress had the highest sr^2; this variable could uniquely explain 6.0% of variance in the BRIEF-A BRI (i.e., large effect). For Agreeableness and Neuroticism, the uniquely explained variances were 1.6% and 3.6%, respectively (i.e., medium effects). Partly similar results were found for the BRIEF-A MI. Here, more complaints were significantly predicted by a lower age, a lower score on Conscientiousness, and higher scores on Agreeableness, Depressive symptoms,

and Stress. Within this context, the variable Conscientiousness had the highest unique contribution to the total variation, namely 13.4% (i.e., large effect). The other four predictors had small to medium sr^2 values between 0.6% and 2.3%. For the MSEQ, the variables gender (i.e., being male) and a lower score on Conscientiousness significantly predicted a lower confidence estimation. The personality factor Conscientiousness had the highest unique contribution and explained 2.4% of variance in the MSEQ (i.e., medium effect). For gender the uniquely explained variance was 0.9% (i.e., small effect). Finally, for the FEDA, more complaints were predicted by lower scores on Conscientiousness and Extraversion and higher scores on Neuroticism, Depressive symptoms, and Stress. Conscientiousness had again the highest unique contribution (i.e., 2.5%, medium effect). The sr^2 values for the other three significant predictors ranged between 0.9% and 1.6% (i.e., small to medium effects).

The total models for the BRIEF-A BRI, BRIEF-A MI, and FEDA were all significant and had large effect sizes, explaining 42% ($F(12, 740) = 44.252$, $p < .001$), 43% ($F(12, 740) = 46.702$, $p < .001$), and 52% ($F(17, 731) = 45.682$, $p < .001$) of the variance, respectively. The total model for the MSEQ was also significant and explained 14% of variance ($F(13, 736) = 9.494$, $p < .001$). This is considered to be a medium effect size.

3.3.1. Step 1: Simple linear regression

Tables 2-5 show the results of the simple linear regression analyses in the confirmatory sample. For both the BRIEF-A BRI and BRIEF-A MI, there were twelve significant predictors, for the MSEQ ten, and for the FEDA fourteen. More complaints on the two BRIEF-A indexes and FEDA and lower estimations of self-efficacy on the MSEQ were all predicted by a lower quality of life, lower scores on Conscientiousness and Extraversion, and higher scores on Neuroticism, Depressive symptoms, Anxiety symptoms, and Stress. Additionally, more complaints on the BRIEF-A BRI were predicted by a lower age and income, less hours of sleep, a lower sleep quality, and a lower score on Agreeableness. A higher number of complaints on the BRIEF-A MI was additionally found to be predicted by a lower age, having pets, having a profession, less hours of sleep, and a lower sleep quality. A lower confidence estimate on the MSEQ was additionally found to be predicted by a higher age, a lower education level, and not having a profession. Finally, for the FEDA more complaints could additionally be predicted by a lower education level, not having a partner, a lower income, less hours of sleep, a lower sleep quality, a lower self-rated health, and a lower score on Agreeableness.

Overall, the significant predictors in Step 1 for the confirmatory analysis were highly similar to the significant predictors of this step in the exploratory sample. However, a smaller number of variables reached statistical significance in the confirmatory sample. For the BRIEF-A BRI, this was self-rated health, for the BRIEF-A MI self-rated health and Agreeableness, for the MSEQ gender, self-rated health, Openness, and Agreeableness, and for the FEDA gender and having children. Additionally, there were some predictors that were statistically significant in the confirmatory analysis that were not statistically significant in the exploratory analysis. These were age for the BRIEF-A BRI and MSEQ, having a profession for the BRIEF-A MI and MSEQ, and having pets for the BRIEF-A MI.

3.3.2. Step 2: Multiple linear regression

Tables 2-5 show the results of the multiple regression analyses and bootstrapping for the four dependent variables using the significant predictors from Step 1. Additionally, for the BRIEF-A MI the variable Agreeableness and for the MSEQ the variable gender were added to the multiple regression models, as these were found to be significant predictors in Step 2 of the exploratory analyses. For the other two dependent variables no other variables were added.

For the BRIEF-A BRI, the variables Agreeableness, Neuroticism, and Stress were significant predictors, just as in the exploratory analysis. Additionally, the variables hours of sleep and sleep quality were found to be significant predictors in the confirmatory analysis. More complaints were predicted by fewer hours of sleep, a higher sleep quality, a lower score on Agreeableness, and higher scores on Neuroticism and Stress. Just as in the exploratory sample, Stress had the highest unique contribution to the total variation, namely 6.0% (i.e., large effect). For Neuroticism this was 3.5% and for Agreeableness 1.2% (medium effects); both are highly similar to the sr^2 values in the exploratory sample. Hours of sleep and sleep quality could both uniquely explain 1.3% (i.e., medium effects). For the BRIEF-A MI, the variables Conscientiousness, Agreeableness, and Depressive symptoms were again significant predictors. More complaints on the BRIEF-A MI could be predicted by a lower score on Conscientiousness and higher scores on Agreeableness and Depressive symptoms. Similar to the results of the exploratory analysis, Conscientiousness could uniquely explain 14.9% of variance (large effect). The unique contribution of Depressive symptoms was 2.3% and of Agreeableness 1.0% (medium effects). The variables age and Stress did not have the same significant predictive value here as they had in the exploratory analysis. For the MSEQ, none of the predictors was statistically significant in the confirmatory analysis, while in the exploratory analysis the variables gender and Conscientiousness were found to be significant predictors.

Overall, the significant predictors in Step 1 for the confirmatory analysis were highly similar to the significant predictors of this step in the exploratory sample. However, a smaller number of variables reached statistical significance in the confirmatory sample. For the BRIEF-A BRI, this was self-rated health, for the BRIEF-A MI self-rated health and Agreeableness, for the MSEQ gender, self-rated health, Openness, and Agreeableness, and for the FEDA gender and having children. Additionally, there were some predictors that were statistically significant in the confirmatory analysis that were not statistically significant in the exploratory analysis. These were age for the BRIEF-A BRI and MSEQ, having a profession for the BRIEF-A MI and MSEQ, and having pets for the BRIEF-A MI.

3.3.2. Step 2: Multiple linear regression

Tables 2-5 show the results of the multiple regression analyses and bootstrapping for the four dependent variables using the significant predictors from Step 1. Additionally, for the BRIEF-A MI the variable Agreeableness and for the MSEQ the variable gender were added to the multiple regression models, as these were found to be significant predictors in Step 2 of the exploratory analyses. For the other two dependent variables no other variables were added.

For the BRIEF-A BRI, the variables Agreeableness, Neuroticism, and Stress were significant predictors, just as in the exploratory analysis. Additionally, the variables hours of sleep and sleep quality were found to be significant predictors in the confirmatory analysis. More complaints were predicted by fewer hours of sleep, a higher sleep quality, a lower score on Agreeableness, and higher scores on Neuroticism and Stress. Just as in the exploratory sample, Stress had the highest unique contribution to the total variation, namely 6.0% (i.e., large effect). For Neuroticism this was 3.5% and for Agreeableness 1.2% (medium effects); both are highly similar to the sr^2 values in the exploratory sample. Hours of sleep and sleep quality could both uniquely explain 1.3% (i.e., medium effects). For the BRIEF-A MI, the variables Conscientiousness, Agreeableness, and Depressive symptoms were again significant predictors. More complaints on the BRIEF-A MI could be predicted by a lower score on Conscientiousness and higher scores on Agreeableness and Depressive symptoms. Similar to the results of the exploratory analysis, Conscientiousness could uniquely explain 14.9% of variance (large effect). The unique contribution of Depressive symptoms was 2.3% and of Agreeableness 1.0% (medium effects). The variables age and Stress did not have the same significant predictive value here as they had in the exploratory analysis. For the MSEQ, none of the predictors was statistically significant in the confirmatory analysis, while in the exploratory analysis the variables gender and Conscientiousness were found to be significant predictors.

Overall, the significant predictors in Step 1 for the confirmatory analysis were highly similar to the significant predictors of this step in the exploratory sample. However, a smaller number of variables reached statistical significance in the confirmatory sample. For the BRIEF-A BRI, this was self-rated health, for the BRIEF-A MI self-rated health and Agreeableness, for the MSEQ gender, self-rated health, Openness, and Agreeableness, and for the FEDA gender and having children. Additionally, there were some predictors that were statistically significant in the confirmatory analysis that were not statistically significant in the exploratory analysis. These were age for the BRIEF-A BRI and MSEQ, having a profession for the BRIEF-A MI and MSEQ, and having pets for the BRIEF-A MI.

3.3.2. Step 2: Multiple linear regression

Tables 2-5 show the results of the multiple regression analyses and bootstrapping for the four dependent variables using the significant predictors from Step 1. Additionally, for the BRIEF-A MI the variable Agreeableness and for the MSEQ the variable gender were added to the multiple regression models, as these were found to be significant predictors in Step 2 of the exploratory analyses. For the other two dependent variables no other variables were added.

For the BRIEF-A BRI, the variables Agreeableness, Neuroticism, and Stress were significant predictors, just as in the exploratory analysis. Additionally, the variables hours of sleep and sleep quality were found to be significant predictors in the confirmatory analysis. More complaints were predicted by fewer hours of sleep, a higher sleep quality, a lower score on Agreeableness, and higher scores on Neuroticism and Stress. Just as in the exploratory sample, Stress had the highest unique contribution to the total variation, namely 6.0% (i.e., large effect). For Neuroticism this was 3.5% and for Agreeableness 1.2% (medium effects); both are highly similar to the sr^2 values in the exploratory sample. Hours of sleep and sleep quality could both uniquely explain 1.3% (i.e., medium effects). For the BRIEF-A MI, the variables Conscientiousness, Agreeableness, and Depressive symptoms were again significant predictors. More complaints on the BRIEF-A MI could be predicted by a lower score on Conscientiousness and higher scores on Agreeableness and Depressive symptoms. Similar to the results of the exploratory analysis, Conscientiousness could uniquely explain 14.9% of variance (large effect). The unique contribution of Depressive symptoms was 2.3% and of Agreeableness 1.0% (medium effects). The variables age and Stress did not have the same significant predictive value here as they had in the exploratory analysis. For the MSEQ, none of the predictors was statistically significant in the confirmatory analysis, while in the exploratory analysis the variables gender and Conscientiousness were found to be significant predictors.

Table 2. Results of the simple linear regression analyses (Step 1) and multiple regression and bootstrap (Step 2) for the BRIEF-A BRI in the exploratory and confirmatory sample. Note. a and b are merged variables. If significant results were found for these merged variables, simple regression analysis were also performed for the separate variables these merged variables were based on. * Significant if $p \leq .01$. The rows marked bold represent variables that were significant in the simple and multiple regression analyses in the exploratory sample as well as in the confirmatory sample. BRIEF-A BRI = Behavior Rating Inventory Executive Function - Adult version Behavioral Regulation Index; BMI = body mass index; DASS = Depression Anxiety Stress Scales.

	Exploratory sample (n = 813)									
	Simple linear regression				*Multiple regression and bootstrap*					
Independent variables						BCa 99% CI				
	B	*t*	*p*	R^2	*B*	lower	upper	*t*	*p*	sr^2
Age	-.055	-2.446	.015	.007						
Gender	.860	1.683	.093	.003						
Education level				.006						
- Intermediate	-1.240	-1.590	.112							
- High	-1.683	-2.221	.027							
Partner	-.121	-.196	.845	< .001						
Children	-1.178	-1.601	.110	.003						
Pets	.561	1.092	.275	.001						
Profession	-.021	-.041	.968	< .001						
Income	-.868	-3.961	< .001*	.019	-.424	-.849	.040	-2.283	.023	.004
BMI	.009	.170	.865	< .001						
Sleep (overall)[a]	-1.488	-5.155	< .001*	.032						
Hours of sleep	-.918	-3.730	< .001*	.017	-.393	-.956	.242	-1.654	.098	.002
Sleep quality	-.833	-5.232	< .001*	.033	.127	-.340	.598	.754	.451	< .001
Self-rated health	-1.405	-4.656	< .001*	.026	.218	-.772	1.066	.708	.479	< .001
Quality of life	-1.687	-7.711	< .001*	.068	-.042	-.717	.568	-.160	.873	< .001
Openness	-.048	-1.053	.293	.001						
Conscientiousness	-.417	-9.177	< .001*	.099	-.098	-.208	.020	-2.162	.031	.004
Extraversion	-.266	-6.454	< .001*	.052	.089	-.008	.192	2.166	.031	.004
Agreeableness	**-.438**	**-8.974**	**< .001***	**.095**	**-.201**	**-.336**	**-.068**	**-4.544**	**< .001***	**.016**
Neuroticism	**.519**	**17.081**	**< .001***	**.277**	**.273**	**.156**	**.387**	**6.799**	**< .001***	**.036**
DASS total score[b]	.292	17.918	< .001*	.299						
Depressive symptoms	.656	14.967	< .001*	.229	.065	-.146	.260	1.037	.300	.001
Anxiety symptoms	.601	11.181	< .001*	.142	-.031	-.210	.174	-.500	.617	< .001
Stress	**.685**	**17.893**	**< .001***	**.298**	**.451**	**.317**	**.593**	**8.738**	**< .001***	**.060**

Table 2. Continued.

	Confirmatory sample (n = 406)									
	Simple linear regression				*Multiple regression and bootstrap*					
Independent variables						BCa 99% CI				
	B	*t*	*p*	R^2	*B*	lower	upper	*t*	*p*	sr^2
Age	-.095	-2.826	.005*	.019	-.040	-.114	.028	-1.402	.162	.003
Gender	.102	.136	.892	< .001						
Education level				.019						
- Intermediate	-.915	-.868	.386							
- High	-2.526	-2.535	.012							
Partner	-.036	-.041	.967	< .001						
Children	.737	.716	.474	.001						
Pets	1.318	1.770	.077	.008						
Profession	1.251	1.684	.093	.007						
Income	-1.169	-3.686	< .001*	.033	-.554	-1.342	.122	-2.097	.037	.006
BMI	.055	.680	.497	.001						
Sleep (overall)[a]	-1.576	-3.817	< .001*	.035						
Hours of sleep	-1.367	-3.700	< .001*	.033	-1.095	-1.944	-.139	-3.065	.002*	.013
Sleep quality	-.672	-3.054	.002*	.023	.677	.113	1.264	3.001	.003*	.013
Self-rated health	-1.008	-2.234	.026	.012						
Quality of life	-1.618	-5.290	< .001*	.065	.221	-.454	.919	.759	.448	.001
Openness	-.103	-1.643	.101	.007						
Conscientiousness	-.445	-6.679	< .001*	.102	-.097	-.271	.058	-1.463	.144	.003
Extraversion	-.242	-4.032	< .001*	.040	.156	-.013	.303	2.717	.007	.011
Agreeableness	**-.390**	**-5.801**	**< .001***	**.079**	**-.169**	**-.332**	**-.013**	**-2.894**	**.004***	**.012**
Neuroticism	**.523**	**12.502**	**< .001***	**.286**	**.275**	**.124**	**.418**	**4.971**	**< .001***	**.035**
DASS total score[b]	.295	14.271	< .001*	.346						
Depressive symptoms	.634	11.982	< .001*	.272	.144	-.100	.392	1.872	.062	.005
Anxiety symptoms	.664	8.840	< .001*	.169	-.040	-.263	.214	-.462	.644	< .001
Stress	**.725**	**14.540**	**< .001***	**.354**	**.456**	**.247**	**.674**	**6.450**	**< .001***	**.060**

Table 3. Results of the simple linear regression analyses (Step 1) and multiple regression and bootstrap (Step 2) for the BRIEF-A MI in the exploratory and confirmatory sample. Note. a and b are merged variables. If significant results were found for these merged variables, simple regression analysis were also performed for the separate variables these merged variables were based on. * Significant if $p \leq .01$. The rows marked bold represent variables that were significant in the simple and multiple regression analyses in the exploratory sample as well as in the confirmatory sample. BRIEF-A MI = Behavior Rating Inventory Executive Function - Adult version Metacognition Index; BMI = body mass index; DASS = Depression Anxiety Stress Scales.

	Exploratory sample (n = 813)									
	Simple linear regression				*Multiple regression and bootstrap*					
Independent variables						BCa 99% CI				
	B	*t*	*p*	R^2	*B*	lower	upper	*t*	*p*	sr^2
Age	-.136	-4.515	< .001*	.025	-.127	-.203	-.040	-4.992	< .001*	.019
Gender	1.063	1.528	.127	.003						
Education level				.006						
- Intermediate	-.750	-.708	.479							
- High	.946	.918	.359							
Partner	-1.145	-1.363	.173	.002						
Children	-2.260	-2.260	.024	.006						
Pets	.678	.970	.332	.001						
Profession	1.549	2.231	.026	.006						
Income	-.736	-2.454	.014	.007						
BMI	-.104	-1.401	.162	.002						
Sleep (overall)[a]	-1.979	-5.031	< .001*	.030						
Hours of sleep	-1.057	-3.148	.002*	.012	-.237	-1.174	.729	-.738	.460	< .001
Sleep quality	-1.213	-5.612	< .001*	.037	.003	-.640	.713	.012	.990	< .001
Self-rated health	-1.643	-3.987	< .001*	.019	.496	-.694	1.615	1.180	.238	.001
Quality of life	-2.003	-6.670	< .001*	.052	.201	-.838	1.231	.568	.570	< .001
Openness	.142	2.289	.022	.007						
Conscientiousness	**-.958**	**-17.174**	**< .001***	**.279**	**-.812**	**-1.022**	**-.645**	**-13.216**	**< .001***	**.134**
Extraversion	-.498	-9.024	< .001*	.097	-.093	-.221	.043	-1.663	.097	.002
Agreeableness	**-.280**	**-4.024**	**< .001***	**.021**	**.220**	**.075**	**.383**	**3.694**	**< .001***	**.010**
Neuroticism	.571	12.857	< .001*	.178	.048	-.078	.185	.879	.380	.001
DASS total score[b]	.345	14.676	< .001*	.222						
Depressive symptoms	**.862**	**14.175**	**< .001***	**.210**	**.245**	**.004**	**.476**	**2.889**	**.004***	**.006**
Anxiety symptoms	.718	9.568	< .001*	.108	.053	-.157	.294	.616	.538	< .001
Stress	.731	12.929	< .001*	.181	.382	.199	.569	5.452	< .001*	.023

Table 3. Continued.

	Confirmatory sample (n = 406)									
	Simple linear regression				*Multiple regression and bootstrap*					
Independent variables						BCa 99% CI				
	B	*t*	*p*	R^2	*B*	lower	upper	*t*	*p*	sr^2
Age	-.218	-4.773	< .001*	.053	-.097	-.248	.065	-1.823	.069	.004
Gender	.464	.450	.653	.001						
Education level				.004						
- Intermediate	-.547	-.373	.709							
- High	.980	.707	.480							
Partner	-1.039	-.868	.386	.002						
Children	1.155	.814	.416	.002						
Pets	2.840	2.779	.006*	.019	.409	-1.967	2.668	.481	.631	< .001
Profession	4.271	4.242	< .001*	.043	1.738	-1.042	4.768	1.603	.110	.003
Income	-.892	-2.014	.045	.010						
BMI	-.070	-.629	.530	.001						
Sleep (overall)[a]	-2.511	-4.432	< .001*	.046						
Hours of sleep	-1.813	-3.550	< .001*	.030	-1.206	-2.463	-.027	-2.472	.014	.008
Sleep quality	-1.287	-4.282	< .001*	.043	.299	-.510	1.094	.976	.330	.001
Self-rated health	-1.312	-2.106	.036	.011						
Quality of life	-2.473	-5.901	< .001*	.079	.001	-1.151	1.037	.001	.999	< .001
Openness	.058	.678	.498	.001						
Conscientiousness	**-1.082**	**-13.584**	**< .001***	**.321**	**-.943**	**-1.170**	**-.709**	**-10.430**	**< .001***	**.149**
Extraversion	-.472	-5.829	< .001*	.080	.083	-.172	.270	1.059	.290	.002
Agreeableness	**-.245**	**-2.565**	**.011**	**.017**	**.214**	**.042**	**.405**	**2.734**	**.007***	**.010**
Neuroticism	.616	10.176	< .001*	.209	.041	-.143	.233	.554	.580	< .001
DASS total score[b]	.328	10.543	< .001*	.224						
Depressive symptoms	**.799**	**10.602**	**< .001***	**.226**	**.426**	**.076**	**.765**	**4.054**	**< .001***	**.023**
Anxiety symptoms	.674	6.212	< .001*	.091	-.129	-.476	.276	-1.085	.279	.002
Stress	.748	9.743	< .001*	.198	.268	-.013	.567	2.769	.006	.010

Table 4. Results of the simple linear regression analyses (Step 1) and multiple regression and bootstrap (Step 2) for the MSEQ in the exploratory and confirmatory sample. Note. a and b are merged variables. If significant results were found for these merged variables, simple regression analysis were also performed for the separate variables these merged variables were based on. * Significant if $p \leq .01$. MSEQ = Memory Self-Efficacy Questionnaire; BMI = body mass index; DASS = Depression Anxiety Stress Scales.

	Exploratory sample (n = 813)									
	Simple linear regression				*Multiple regression and bootstrap*					
Independent variables						BCa 99% CI				
	B	*t*	*p*	R^2	*B*	lower	upper	*t*	*p*	sr^2
Age	-.119	-2.457	.014	.007						
Gender	3.161	2.864	.004*	.010	3.261	.056	6.497	2.793	.005*	.009
Education level				.023						
- Intermediate	6.949	4.152	< .001*		3.664	-.681	8.065	2.179	.030	.005
- High	6.273	3.855	< .001*		1.827	-2.812	6.567	1.050	.294	.001
Partner	2.848	2.132	.033	.006						
Children	1.113	.697	.486	.001						
Pets	1.500	1.349	.178	.002						
Profession	2.839	2.570	.010	.008						
Income	.762	1.592	.112	.003						
BMI	-.061	-.523	.601	< .001						
Sleep (overall)[a]	1.043	1.645	.100	.003						
Hours of sleep										
Sleep quality										
Self-rated health	2.652	4.043	< .001*	.020	-.689	-2.953	1.489	-.844	.399	.001
Quality of life	3.231	6.761	< .001*	.053	1.900	-.161	3.886	2.855	.004	.009
Openness	.318	3.235	.001*	.014	.157	-.132	.452	1.506	.132	.003
Conscientiousness	.825	8.230	< .001*	.082	.543	.278	.823	4.537	< .001*	.024
Extraversion	.633	7.076	< .001*	.062	.292	-.047	.617	2.670	.008	.008
Agreeableness	.450	4.061	< .001*	.021	-.066	-.392	.256	-.544	.586	< .001
Neuroticism	-.374	-4.877	< .001*	.030	.048	-.202	.316	.445	.656	< .001
DASS total score[b]	-.215	-5.174	< .001*	.034						
Depressive symptoms	-.614	-5.782	< .001*	.042	-.045	-.498	.370	-.273	.785	< .001
Anxiety symptoms	-.553	-4.449	< .001*	.026	-.242	-.763	.253	-1.456	.146	.003
Stress	-.326	-3.306	.001*	.014	.042	-.333	.476	.305	.760	< .001

Table 4. Continued.

	Exploratory sample (n = 813)									
	Simple linear regression				*Multiple regression and bootstrap*					
Independent variables						BCa 99% CI				
	B	*t*	*p*	R^2	*B*	lower	upper	*t*	*p*	sr^2
Age	-.232	-3.066	.002*	.023	-.148	-.447	.168	-1.411	.159	.004
Gender	3.453	2.068	.039	.010	2.268	-2.507	6.863	1.330	.184	.004
Education level				.027						
- Intermediate	7.735	3.276	.001*		4.437	-2.806	10.927	1.798	.073	.007
- High	6.187	2.771	.006*		2.529	-4.560	9.435	1.048	.295	.002
Partner	3.726	1.916	.056	.009						
Children	-1.128	-.487	.626	.001						
Pets	.020	.012	.990	< .001						
Profession	4.904	2.954	.003*	.021	1.106	-5.183	8.475	.495	.621	.001
Income	1.451	2.009	.045	.010						
BMI	-.079	-.433	.665	< .001						
Sleep (overall)[a]	-.978	-1.035	.301	.003						
Hours of sleep										
Sleep quality										
Self-rated health	2.398	2.364	.019	.014						
Quality of life	2.488	3.548	< .001*	.030	-.090	-1.841	1.754	-.113	.910	< .001
Openness	.356	2.570	.011	.017						
Conscientiousness	.737	4.844	< .001*	.057	.385	-.076	.905	2.101	.036	.010
Extraversion	.785	5.999	< .001*	.084	.373	-.078	.834	2.314	.021	.012
Agreeableness	.257	1.653	.099	.007						
Neuroticism	-.431	-3.982	< .001*	.039	-.016	-.430	.407	-.103	.918	< .001
DASS total score[b]	-.269	-4.870	< .001*	.058						
Depressive symptoms	-.757	-5.715	< .001*	.078	-.514	-1.130	.205	-2.369	.018	.013
Anxiety symptoms	-.806	-4.516	< .001*	.050	-.286	-1.028	.382	-1.133	.258	.003
Stress	-.367	-2.684	.008*	.018	.307	-.219	.847	1.535	.126	.005

Table 5. Results of the simple linear regression analyses (Step 1) and multiple regression and bootstrap (Step 2) for the FEDA in the exploratory and confirmatory sample. Note. a and b are merged variables. If significant results were found for these merged variables, simple regression analysis were also performed for the separate variables these merged variables were based on. * Significant if $p \leq .01$. The rows marked bold represent variables that were significant in the simple and multiple regression analyses in the exploratory sample as well as in the confirmatory sample. FEDA = Questionnaire for Experiences of Attention Deficits, BMI = body mass index, DASS = Depression Anxiety Stress Scales.

	Exploratory sample (n = 813)									
	Simple linear regression				*Multiple regression and bootstrap*					
Independent variables						BCa 99% CI				
	B	*t*	*p*	R^2	*B*	lower	upper	*t*	*p*	sr^2
Age	-.068	-1.598	.110	.003						
Gender	3.196	3.317	.001*	.013	1.884	-.377	4.512	2.322	.020	.004
Education level				.011						
- Intermediate	-4.383	-2.978	.003*		-.322	-3.095	3.043	-.291	.771	< .001
- High	-3.424	-2.393	.017		1.532	-1.606	4.658	1.367	.172	.001
Partner	-3.864	-3.323	.001*	.013	.002	-2.532	2.615	.002	.998	< .001
Children	-3.630	-2.610	.009*	.008	-1.019	-4.052	1.560	-.973	.331	.001
Pets	.836	.859	.391	.001						
Profession	-1.401	-1.447	.148	.003						
Income	-1.930	-4.668	< .001*	.026	.086	-.809	.975	.237	.813	< .001
BMI	.074	.713	.476	.001						
Sleep (overall)[a]	-3.413	-6.286	< .001*	.047						
Hours of sleep	-1.441	-3.081	.002*	.012	.318	-.898	1.444	.766	.444	< .001
Sleep quality	-2.338	-7.913	< .001*	.072	-.257	-1.253	.750	-.870	.385	< .001
Self-rated health	-5.248	-9.558	< .001*	.101	-.767	-2.081	.579	-1.420	.156	.001
Quality of life	-5.002	-12.768	< .001*	.167	-.845	-2.040	.466	-1.835	.067	.002
Openness	-.142	-1.648	.100	.004						
Conscientiousness	**-1.193**	**-14.870**	**< .001***	**.225**	**-.484**	**-.719**	**-.275**	**-6.105**	**< .001***	**.025**
Extraversion	**-1.032**	**-14.485**	**< .001***	**.216**	**-.359**	**-.592**	**-.155**	**-4.974**	**< .001***	**.016**
Agreeableness	-.641	-6.771	< .001*	.057	.056	-.144	.266	.698	.485	< .001
Neuroticism	**1.095**	**19.873**	**< .001***	**.341**	**.302**	**.090**	**.516**	**4.198**	**< .001***	**.012**
DASS total score[b]	.597	19.932	< .001*	.345						
Depressive symptoms	1.528	19.882	< .001*	.344	.413	.111	.744	3.779	< .001*	.009
Anxiety symptoms	1.378	14.049	< .001*	.207	.284	-.005	.585	2.583	.010	.004
Stress	1.147	15.089	< .001*	.232	.341	.123	.549	3.776	< .001*	.009

Table 5. Continued.

	Exploratory sample (n = 813)									
	Simple linear regression				*Multiple regression and bootstrap*					
Independent variables						BCa 99% CI				
	B	*t*	*p*	R^2	*B*	lower	upper	*t*	*p*	sr^2
Age	-.102	-1.549	.122	.006						
Gender	2.092	1.454	.147	.005						
Education level				.019						
- Intermediate	-5.333	-2.616	.009*		.183	-4.384	4.442	.112	.911	< .001
- High	-4.634	-2.404	.017		2.220	-2.939	6.562	1.299	.195	.002
Partner	-4.372	-2.626	.009*	.017	-.284	-4.398	3.254	-.219	.826	< .001
Children	.214	.107	.915	< .001						
Pets	2.343	1.626	.105	.007						
Profession	.936	.649	.516	.001						
Income	-2.774	-4.562	< .001*	.049	-1.084	-2.340	.079	-2.054	.041	.005
BMI	.132	.848	.397	.002						
Sleep (overall)[a]	-3.982	-5.050	< .001*	.059						
Hours of sleep	-2.960	-4.159	< .001*	.041	-2.328	-4.305	-.353	-3.465	.001*	.016
Sleep quality	-1.991	-4.750	< .001*	.053	.737	-.442	1.856	1.756	.080	.004
Self-rated health	-4.451	5.239	< .001*	.064	1.214	-.658	3.303	1.489	.137	.003
Quality of life	-4.500	-7.899	< .001*	.134	.150	-1.476	1.814	.242	.809	< .001
Openness	-.114	-.946	.345	.002						
Conscientiousness	**-1.408**	**-12.157**	**< .001***	**.274**	**-.697**	**-1.001**	**-.372**	**-5.604**	**< .001***	**.041**
Extraversion	**-1.027**	**-9.638**	**< .001***	**.192**	**-.321**	**-.570**	**-.022**	**-3.043**	**.003***	**.012**
Agreeableness	-.594	-4.497	< .001*	.049	.100	-.173	.386	.909	.364	.001
Neuroticism	**1.075**	**13.633**	**< .001***	**.322**	**.303**	**.025**	**.573**	**3.010**	**.003***	**.012**
DASS total score[b]	.569	14.239	< .001*	.345						
Depressive symptoms	1.268	12.589	< .001*	.292	.174	-.347	.570	1.217	.224	.002
Anxiety symptoms	1.556	11.304	< .001*	.249	.576	.162	1.022	3.478	.001*	.016
Stress	1.192	11.568	< .001*	.258	.320	-.033	.683	2.437	.015	.008

However, the variable Depressive symptoms could uniquely explain 1.3% of variance (medium effect) and showed a trend toward significance. Despite the lack of significant predictors, the total model of MSEQ was statistically significant. For the FEDA, the personality factors Conscientiousness, Extraversion, and Neuroticism were again found to be significant predictors. These variables uniquely explained 4.1%, 1.2%, and 1.2% of the variance in the FEDA, falling in the same medium range as in exploratory analysis (i.e., 2.5%, 1.6%, and 1.2%). Additionally, the variables hours of sleep and Anxiety symptoms were significant in the confirmatory analysis, both uniquely explaining 1.6% of variance in FEDA (i.e., medium effects). Overall, more complaints could be predicted by less hours of sleep, lower scores on Conscientiousness and Extraversion, and higher scores on Neuroticism and Anxiety symptoms. In contrast to the exploratory analysis, the variables Depressive symptoms and Stress were not found to significantly predict the scores on the FEDA.

The total models for the BRIEF-A BRI, BRIEF-A MI, and FEDA all had a large effect size and explained 47% ($F(12, 373) = 27.389$, $p < .001$), 49% ($F(13, 372) = 27.523$, $p < .001$), and 52% ($F(15, 370) = 26.811$, $p < .001$) of variance, respectively. The total model for the MSEQ explained 17% of variance ($F(12, 373) = 6.313$, $p < .001$), which is a medium effect size. These R^2 values are similar to those found in the exploratory analysis (i.e., maximum of 6% difference).

4. DISCUSSION

The current study examined a large community sample of adults aged 40 years and older in order to assess to what extent psychological factors contribute to the subjective experience of cognitive complaints in the domains of executive functioning, memory, and attention. Using a two-step regression approach with bootstrapping for internal validation, it was first examined which factors could predict the presence of complaints in the different cognitive domains in an exploratory sample and subsequently these results were independently validated in a second confirmatory sample.

The results of the present study indicate that for the domain of executive functioning, in both the exploratory and confirmatory sample, more complaints about the ability to appropriately regulate behavior and emotional responses (i.e., BRIEF-A BRI) were predicted by a lower level of agreeableness and higher levels of neuroticism and perceived stress. More complaints about the ability to actively solve problems in different circumstances (i.e., BRIEF-A MI) were predicted by a lower level of conscientiousness, higher levels of agreeableness, and more (severe) depressive symptoms. Regarding attention, more complaints in this domain were consistently found to be predicted by lower levels of conscientiousness and extraversion, together with a higher level of neuroticism. For the cognitive domain of memory, no significant predictors were consistently found across the exploratory and confirmatory samples. Other independent variables included in the study, such as age, gender, sleep, quality of life, perceived health, and other demographic factors, did not consistently predict complaints in any of the cognitive domains.

These results show that personality factors were consistently found to predict SCCs, in particular neuroticism, conscientiousness, agreeableness, and extraversion. Just as in previous studies, a higher level of neuroticism predicted more complaints (Kliegel & Zimprich, 2005; Reid & MacLullich, 2006). Research shows that people who score higher on neuroticism tend to experience higher levels of anxiety, worry more often, and are less able to cope with stress and frustration, in comparison to people with lower neuroticism scores (Hoekstra et al., 2007). Additionally, they are more likely to recall negative things, including cognitive complaints. As predicted, conscientiousness showed an inverse relation with SCCs (Slavin et al., 2010). It is assumed that people who score low on this factor are more messy and less dutiful, disciplined, and achievement-striving than people scoring high on this factor. They have lower levels of self-awareness related to their health and probably their cognitive

functioning, and are less likely to exhibit preventive health behaviors such as using mnemonics to prevent memory failures (Kliegel & Zimprich, 2005).

For the personality factors agreeableness and extraversion, there were no clear expectations as, according to our knowledge, they are not consistently mentioned as associated with SCCs in the literature. In this current study, however, lower levels of extraversion were found to be associated with SCCs in the domain of attention. A lower score on this personality factor points to introversion. Introverted people have been described to tend to focus their attention more often on their own feelings, thoughts, and activities, instead of being focused on their environment like extraverts do (Hoekstra et al., 2007). This could make them more aware of any SCCs earlier or more frequently than people who score higher on extraversion. For the factor agreeableness, findings were mixed regarding the two indexes of executive functioning. More complaints regarding the ability to regulate behavior and emotional responses (i.e., BRIEF-A BRI) were predicted by lower levels of agreeableness, while more complaints regarding actively solving problems in different circumstances (i.e., BRIEF-A MI) were predicted by a higher agreeableness level. It is important to note that for the latter executive functioning ability, the simple linear regression analysis in both samples indicated that more complaints were predicted by lower levels of agreeableness. This means that, in the multiple regression models this was reversed for the BRIEF-A MI. The exact reason for this is unclear, but it could be due to interactions between agreeableness and the other independent variables included in the models. In general, people who score high on agreeableness are relatively altruistic, helpful, friendly, and oriented toward the experiences, interests, and goals of others. Low scorers, conversely, are more antagonistic and egocentric, and their attitude is more competitive (Hoekstra et al., 2007). Previous studies did not find a relationship between agreeableness and subjective executive functioning in older adults (e.g., Bell et al., 2020). However, in children, there seems to be a positive association between agreeableness and effortful (or executive) control, which refers to the ability to use attentional resources and inhibit behavioral responses in order to regulate emotions and behaviors (Ode & Robinson, 2007). It has been suggested that effortful control is an important precursor for agreeableness in adulthood (e.g., Jensen-Campbell et al., 2002). In particular, this could explain the predictive value of lower levels of agreeableness for complaints regarding the ability to regulate behavior and emotional responses (i.e., BRIEF-A BRI).

With regard to negative affective states, the presence of self-reported depressive symptoms and stress was consistently found to predict subjective complaints regarding the ability to

actively solve problems in different circumstances (i.e., BRIEF-A MI) and the ability to appropriately regulate behavior and emotional responses (BRIEF-A BRI), respectively. Additionally, anxiety symptoms were close to reaching statistical significance for the prediction of complaints with regard to attention functioning (i.e., FEDA). Prior studies already reported a positive association between more (severe) depressive symptoms and self-reported complaints regarding executive functioning on the BRIEF-A (e.g., Meltzer et al., 2017; Rabin et al., 2006). It appears that people who report more symptoms of depression are relatively more likely to misconceive normal lapses in cognitive functioning as representing cognitive impairment and overrate any actual cognitive errors, while downplaying cognitive successes (Meltzer et al., 2017). Such misinterpretations can lead to an increased report of complaints regarding their cognitive functioning. A similar explanation is proposed for perceived stress; it creates attentional biases toward cognitive errors, promoting worrying and over-awareness of cognitive functioning (Bell et al., 2020). Additionally, people with higher levels of perceived stress are more likely than people with low levels of stress to ruminate negative events (Willis & Burnett, 2016), such as cognitive errors, which in turn magnifies the body's stress reaction (Zoccola & Dickerson, 2012). In sum, negative affective states, such as depressive symptoms and stress, are associated with biases toward a more unpleasant perception, attention, interpretation, and recall from memory of emotional information, including cognitive errors (Gomez et al., 2002).

In the final models, the included psychological factors could explain about half of the variance of the scores for subjective executive functioning and attention. This emphasizes the importance of these psychological factors in understanding the subjective experience of complaints in these cognitive domains. These findings fit with the biopsychosocial model of health (Engel, 1980), which states that both health and disease can be explained by a dynamic interaction between biological, psychological, and social factors. The results of this study imply that clinicians should take psychological factors into account when dealing with patients who present with SCCs. In particular, if standardized cognitive testing does not clearly indicate cognitive impairment, the assessment of psychological factors, such as personality factors and negative affective states, is indicated. If patients for instance show high levels of perceived stress, interventions for stress management have the potential to reduce SCCs and improve wellbeing and quality of life.

In general, the findings of this study suggest that both objective and subjective measures of cognition should be taken into account when conducting a neuropsychological assessment in

an individual subject. Previous studies indicated that there is only limited support for a link between SCCs and the concurrent level of objective performance on cognitive tests (e.g., Burmester et al., 2016; Fuermaier et al., 2015; Koerts et al., 2012). There might be several explanations for the lack of an association. First, different aspects of cognition might be measured with objective and subjective measures. Whereas objective measures of cognition often take a snapshot of behavior and require optimal performance, subjective self-report measures require subjects to evaluate their average or typical performance over a certain period of time (e.g., the last two months). Second, objective measures might lack ecological validity, since they are rather structured and often aim at measuring a single aspect of cognition. Subjective measures of cognition focus more often on everyday performance that requires the integration of multiple cognitive functions. Third, there might be differences in motivation when performing objective cognitive measures compared to performance in everyday life as measured with self-report measures. Fourth, unimpaired performance on objective cognitive tests could be the result of successful compensation by the subject while the subject still reports cognitive complaints on self-report measures. Finally, it is possible that subtle cognitive impairments are difficult to detect with objective cognitive measures due to a lack of sensitivity and specificity even though they are reported on self-report measures of cognition. Therefore, both objective measures of cognition and self-report measures of SCCs should be taken into account when integrating and interpreting the results of a neuropsychological assessment since both can provide valuable information.

Strengths of the current study were the recruitment of a large heterogeneous community sample of adults aged 40 years and older; the use of the BRIEF-A validity scales as exclusion criteria; the assessment of three different cognitive domains; the division of the total sample into exploratory and confirmatory samples, which allows independent validation; and the application of both *p*-values and bootstrapping to determine significant predictors, which allows internal validation. These strengths together make the results of this study reliable and generalizable to the general population.

However, the considerably lower percentage of explained variance for memory and the lack of significant predictors in this cognitive domain are noteworthy. Memory is probably a cognitive construct that is easier for people to understand and observe; therefore, it could be that participants had a better feeling of what memory failure is, making their self-evaluations more fitting and less influenced by other factors such as personality and negative affect states. In addition, the MSEQ does not directly measure the presence of memory complaints, but instead

assesses memory self-efficacy. This refers to an individual's belief or confidence in one's own capacity to remember different memory aspects (i.e., the location of objects, shopping list, names, important points from a story). In this regard, the MSEQ is different from the BRIEF-A and FEDA, as these questionnaires directly ask how often certain complaints regarding executive functioning or attention occur in daily life. The reason for using a measure of memory self-efficacy was that most memory questionnaires measure subjective memory complaints in relation to a specific disorder (e.g., Alzheimer's disease). These questionnaires assess rather severe memory complaints and cannot be applied to the normal population, as they would result in ceiling effects. One may therefore assume that the MSEQ measures subjective cognitive complaints in a different way than the other two questionnaires. An alternative for future research could be to use a questionnaire for relatively minor subjective memory complaints in the general population, such as for instance the Prospective Retrospective Memory Questionnaire (Crawford et al., 2003).

A limitation of this study is the fact that there were relatively few participants in the exploratory and confirmatory sample with (very) high scores on the BRIEF-A indexes and DASS scales (i.e., depressive symptoms, anxiety symptoms, and stress). This indicates that the participants in this study were relatively healthy regarding their cognitive and mental functioning. This could have influenced the results and the observed patterns may not be maintained in clinical samples with greater variability in cognitive and mental abilities. A recommendation for future research is, therefore, to conduct studies on SCCs in clinical samples. In this context, the number of factors that is explored can be reduced so that smaller samples can be used to examine explanatory hypotheses. Second, about 20% of the participants were excluded from the analysis because they did not fully complete the BRIEF-A, MSEQ, and FEDA. This may have resulted in a selection bias; participants with more cognitive and/or mental complaints could have had relatively more difficulties with completing the survey. Third, the study did not include objective measures of cognition. Therefore, an unknown number of participants might have had actual cognitive impairments; participants who should have been excluded from the present study. Fourth, regarding the independent variable hours of sleep per night, which we consider as a continuous variable, it is important to mention that more hours of sleep is not always better. Both too little and too much sleep can be unhealthy and could affect SCCs (e.g., Devore et al., 2014). A fifth limitation is that no causal conclusions can be drawn from the current study. Both dependent and independent variables could potentially overlap, share an underlying etiology, or simultaneously influence each other. Finally, there might be other confounding variables affecting SCCs that were not included in the study, such as social

support, previous life events, or neuropsychiatric symptoms (e.g., mild behavioral impairment, Rouse et al., 2021). Future research could focus on disentangling the differential effects of the independent variables on the cognitive domains and look into causality using a prospective longitudinal design. Other avenues worth exploring are the interactions between measures and the effects of confounding variables.

Conclusion

In sum, the results of this study highlight the role of psychological factors in the subjective experience of cognitive complaints. In particular, personality factors and negative affective states, such as perceived stress and depressive symptoms, seem to predict the presence of SCCs in the domains of executive functioning and attention.

Data availability statement

All data files are available from the dataverseNL database: https://doi.org/10.34894/QNVTOA.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethic Committee of the Faculty for Social Sciences, University of Groningen, Netherlands. The participants provided their written informed consent to participate in this study.

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Declaration of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Chapter 6

General discussion

GENERAL DISCUSSION

This thesis focuses on EFs, examining both objective and subjective aspects, with a specific emphasis on adults who self-report complaints in this cognitive domain in their daily lives (i.e., scoring at the 90th percentile or higher on the BRIEF-A questionnaire). Following the biopsychosocial model (Havelka et al., 2009), EFs are conceptually considered to be the result of a complex dynamic interplay of various biological, psychological, and social factors (see Figure 1). The objectives of this thesis were (i) to assess the biological neurophysiological markers underlying EFs in adults self-reporting EF complaints, (ii) to evaluate the effects of frontal-midline (FM) theta neurofeedback (NF) as a neuroscientific intervention for improving EFs in this (sub)clinical group, as well as its overall effectiveness in upregulating FM theta, and (iii) to identify psychological factors predicting subjective self-reported EFs in daily life. In this final discussion, I will reflect broadly on the main results from the preceding chapters and discuss potential directions for future research and implications and recommendations for clinical practice.

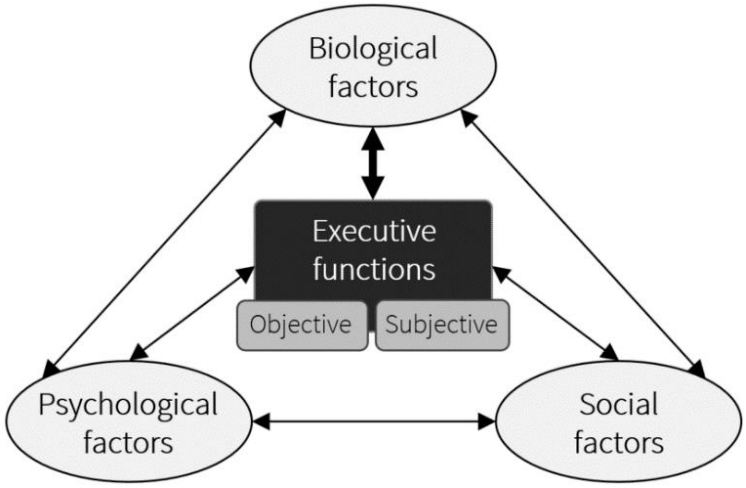

Figure 1. Biopsychosocial model of executive functions (after Havelka et al., 2009).

Neurophysiological markers of executive functions

In this thesis, we consider efficient underlying neural mechanisms as the primary biological determinant or prerequisite for adequate EFs in daily life. Chapter 2 assessed theta power and functional theta connectivity as underlying neurophysiological markers of the four core EFs in adults self-reporting EF complaints. The results showed that theta power dynamics over time

in the right frontolateral and FM regions were affected during conflict monitoring. In particular, the group self-reporting EF complaints and an ADHD diagnosis demonstrated lower power in the right frontolateral region during the critical time window for EFs and a slower reaction time compared to controls without EF complaints. This indicates reduced engagement of this region, potentially leading to impaired processing of conflicting or competing actions and therefore a slower response in this group. Overall, these findings showed the combined effect of both self-reported EF complaints and an ADHD diagnosis on the neurophysiological marker theta power underlying conflict monitoring. However, a possible confounding factor was medication use in this group, which was not an exclusion criterion in the study. Solely the presence of self-reported EF complaints, without a psychiatric disorder, does not appear to affect underlying theta power and connectivity at the sensor level of the superordinate network or behavioral performance on the objective tasks assessing the core EFs. This latter finding confirms the lack of an association between objective and subjective self-report EFs assessments in non-clinical samples (Buchanan, 2016). A next step in neurophysiological marker research is to move from the sensor level to the generator level (e.g., Pellegrini et al., 2023) in order to identify the specific brain regions in the superordinate network that are responsible for producing the observed patterns in the sensor data and to better understand the underlying neural mechanisms of EFs.

Effects of individualized frontal-midline theta neurofeedback

Given that EFs are essential for adaptive, independent, and goal-oriented behavior in everyday life, there is a need for interventions that can effectively address EF impairments and optimize EFs in the general population. The importance of research on interventions to improve EFs cannot be overstated, as EF impairments are common in clinical groups (e.g., Snyder et al., 2015; Chiaravalloti & DeLuca, 2008) and EF complaints are frequently self-reported in the general population (e.g., Stenfors et al., 2013; Slavin et al., 2010), and can have a (strong) negative impact on everyday life (Low et al., 2021; Diamond, 2013). As noted in the general introduction, most interventions for EFs typically produce only immediate, specific effects that do not generalize to other aspects of EFs or daily life (Diamond & Ling, 2016). FM theta NF is a promising alternative because it directly targets one of the neurophysiological markers underlying EFs (i.e., FM theta power), providing a solid biological basis for improving EFs. The main strength of this FM theta NF protocol is that it is one of the best validated protocols and there are strong indications for a causal relationship between theta power and EFs (e.g., Zhu et al., 2023; Polanía et al., 2012). Therefore, in Chapter 3, we examined the effectiveness of FM theta NF as a neuroscientific treatment approach to improve EFs in adults who self-report

complaints in this domain (with or without a psychiatric disorder). Enhancing FM theta power through FM theta NF with the purpose of improving objective EFs (Eschmann & Mecklinger, 2022; Enriquez-Geppert et al., 2014a), can potentially also translate into a reduction of self-reported EF complaints in this (sub)clinical group. In addition, in Chapter 4, we attempted to advance research on FM theta NF and address the issue of limited sample sizes by describing the learning curve based on pooled raw data from different FM theta NF studies in healthy and (sub)clinical samples.

Neurofeedback training effects

The mega-analytical findings of Chapter 4 showed that overall individualized FM theta NF is an effective neuromodulation technique to upregulate FM theta power. However, effects differed depending on whether the standard FM theta band (4-8 Hz) or the narrower individualized FM theta band was assessed, and also extended to the delta and beta frequency bands. When specifically evaluating the FM theta NF protocol in individuals self-reporting EF complaints in daily life (Chapter 3), the NF group showed an increase in individualized FM theta across and within sessions compared with the sham group, but only when non-responders were excluded from the analysis. This finding differed from studies conducted on healthy individuals (Eschmann & Mecklinger, 2022; Brandmeyer & Delorme, 2020; Enriquez-Geppert et al., 2014a; Wang & Hsieh, 2013) and suggests that individuals self-reporting EF complaints (with or without a psychiatric disorder) may exhibit relatively weaker NF learning. This finding is supported by the results in Chapter 4, indicating that self-reported EF complaints predict lower FM theta upregulation. Non-response is a common phenomenon in NF research, with approximately one-third of participants appearing to be unable to self-regulate brain activity (Alkoby et al., 2018; Haugg et al., 2021). The results from Chapters 3 and 4 both show that non-responders in the NF group had a significantly higher percentage of participants who reported having or suspecting a psychiatric disorder in comparison to responders. It is possible that factors related to specific psychiatric disorders, such as ADHD, interfere with the ability to learn from feedback and successfully self-regulate FM theta.

Overall, these findings have important implications for the (clinical) application of FM theta NF. First, it stresses the importance of identifying non-responders, as this can guide a tailored intervention strategy, where only those participants who exhibit a positive response to FM theta NF would be administered this intervention. Such a stratification can enhance overall treatment effectiveness (i.e., transfer effects on behavior and cognition), improve outcomes, and reduce costs. Unfortunately, there is currently a lack of consensus on how to exactly

identify non-responders and there is no widely accepted explanation for non-response. Although several psychological and neurophysiological factors have been identified as potential predictors (e.g. Alkoby, 2018), more research is needed to better understand and accurately identify NF non-response. Second, the findings of these two chapters emphasize the importance of personalizing and refining NF procedures to individual differences among responders in order to enhance upregulation success and transform non-responders into responders by customizing NF training elements. In the general introduction of this thesis, the five elements of the NF processing pipeline (i.e., data acquisition, online pre-processing, feature extraction, feedback generation, and the participant) were discussed. Optimization of these different elements could contribute to improving the learning process and NF outcomes. For example, implementing more advanced techniques for data acquisition and feature extraction (e.g., machine learning), identifying effective mental strategies to specifically manipulate the targeted brain parameter, adjusting the type and modality of feedback to the participant's cognitive/motivational profile, or dynamically adapting difficulty based on the evolving state and self-regulation skills over the course of the NF sessions (Batail et al., 2019; Alkoby et al., 2018; Enriquez-Geppert et al., 2017).

Furthermore, to better understand the outcomes of FM theta NF specifically in individuals self-reporting EF complaints with or without a psychiatric disorder, additional research is needed. Exploring the possible causes of relatively lower FM theta upregulation could lead to more targeted and effective NF interventions for this sub(clinical) population. For example, it might be necessary to adjust the intensity or duration of the NF sessions, increase the number of sessions to achieve a similar level of upregulation, use a more engaging type of feedback (e.g., 3D virtual reality-based feedback; Berger et al., 2022), or apply methods to increase neuroplasticity (e.g., psilocybin microdosing; Enriquez-Geppert et al., 2023).

Finally, future NF studies could assess FM theta upregulation ability and the effectiveness of this protocol in individuals with objective EF impairments. In our current sample of adults self-reporting EF complaints, it is unknown whether participants have objective EF impairments, as the computerized objective tests used are sensitive and valid to assess the core EFs, but unfortunately have no established normative data. In Chapter 2, it was found that individuals self-reporting EF complaints did not significantly differ in the underlying mechanisms of EFs (i.e., theta power and connectivity) in the frontal-midline compared to controls without EF complaints. However, individuals with verified objective EF impairments may exhibit

abnormalities in theta power and connectivity (McLoughlin et al., 2021), which could affect NF learning and subsequently the effectiveness of FM theta NF on improving EFs.

Neurofeedback transfer effects

It is of crucial importance to assess the cognitive/behavioral transfer effects of NF training that can be expected based on the relationship between targeted brain characteristic and cognitive function. The results of Chapter 3 suggest that in our (sub)clinical sample self-reporting EF complaints, the transfer effect of FM theta NF to behavioral performance on objective EF tasks takes longer to manifest post-NF training compared to healthy individuals, who exhibited immediate NF-specific improvements in proactive EF tasks (Eschmann & Mecklinger, 2022; Brandmeyer & Delorme, 2020; Enriquez-Geppert et al., 2014a; Wang & Hsieh, 2013). This delay may be directly related to the finding in Chapter 4 that the presence of self-reported EF complaints predicts lower FM theta upregulation relative to healthy individuals. The NF-specific behavioral improvements in working memory updating (i.e., faster reaction time) and conflict monitoring (i.e., lower reaction time variability) six months after NF training in our (sub)clinical sample can be attributed to neuroplastic changes induced by NF training that take time to fully manifest (Ros et al., 2014). However, FM theta NF did not appear to significantly affect FM theta power during EF task performance (Chapter 3). This could suggest that the NF training influenced other neural mechanisms underlying EFs, such as improved theta connectivity or frequency coupling (Enriquez-Geppert et al., 2014a). To better understand the exact underlying mechanisms at play and their contribution to immediate and long-term behavioral improvement following NF training, additional research is needed. To advance the theta NF protocol, an interesting future direction could involve adopting a network approach and assess the effectiveness of NF targeting theta connectivity within the superordinate network, rather than focusing on the MCC as a single hub.

In addition to objective transfer effects after FM theta NF training, the immediate and long-term effects on subjective self-reported EFs in daily life were assessed for the first time in Chapter 3, and were found to be non-specific. Both the NF group and sham group self-reported improvements in EFs immediately and six months after completing the NF training. These non-specific factors can be related to the NF context (e.g., learning to sit still, mindfulness-related effects), placebo effects, repetition-related improvements, or natural fluctuations (Ros et al., 2020; Micoulaud-Franchi & Fovet, 2018; Garcia Pimenta et al., 2021). Moreover, various other psychological factors, whether related to the NF training or not, such as personality factors and

negative affective states (Chapter 5), along with social factors (e.g., support from a trainer or family), may have contributed to a reduction of self-reported EF complaints after NF training.

Overall, it seems that FM theta NF has a specific effect on improving long-term objective EF performance (potentially due to its effect on underlying neural mechanisms other than FM theta power), while the overall experience of participating in a NF training exerts a more significant non-specific influence on self-reported EFs. This suggests that psychological and/or social factors in the context of a NF training play a more substantial role than biological factors in improving subjective self-reported EF complaints as compared to enhancing objective EF performance. Since subjective EF improvements are as important as objective EF improvements with respect to functioning in daily life, interventions aimed at improving EF should take into account the influence of psychological and social factors and take advantage of these effects, and not solely focus on improving the underlying (biological) neural mechanisms of EFs. On the one hand, psychological and social factors could be more purposefully integrated within the context of FM theta NF training, for example through the use of therapist guidance, family involvement, a robotic learning companion (Pillette et al., 2019), peer support, or even group sessions. On the other hand, NF training can be combined with other interventions that focus on improving psychological/social factors, for instance an intervention to enhance the psychological factor self-esteem (Niveau et al., 2021). Moreover, such interventions can be applied as stand-alone treatment if the main aim is to reduce self-reported EF complaints (for instance in NF non-responders). More research is needed to fully understand the scope and potential of these integrated treatment approaches.

Psychological predictors of self-reported executive functions

As self-reported EFs complaints are not solely determined by biological factors according to the biopsychosocial model (Havelka et al., 2009), Chapter 5 examined whether self-reported psychological factors could predict subjectively experienced EFs (and other cognitive functions) in a large community sample aged 40 years and older (n = 1219). The results show that psychological factors, particularly personality factors and negative affective states, are strong predictors of self-reported EFs in daily life. Personality significantly shapes how we perceive, interpret, and respond to the world around us, affecting decision making, emotion regulation, and social interactions (Burger, 2014). Previous studies already consistently linked low levels of conscientiousness and high levels of neuroticism to more self-reported complaints about EFs (Buchanan, 2016; Meltzer et al., 2017; Roye et al., 2022). In fact, the constructs conscientiousness and EF share similarities and there is overlap between the items

of their self-report scales. Interestingly, both conscientiousness and neuroticism are linked to brain regions known to be involved in EFs, such as the DLPFC and MCC (e.g., Forbes et al., 2014; DeYoung et al., 2010). In contrast, the personality factors extraversion and agreeableness have not been consistently associated with self-reported EFs, but in the case of introversion and low levels of agreeableness, their self-centered focus may make individuals more aware of EF difficulties. Negative affective states predicting a higher number of self-reported EF complaints is consistent with previous studies (e.g., Balash et al., 2013). Perceived stress and depressive symptoms are both linked to attentional biases towards everyday EF failures (Bell et al., 2020) and can result in rumination and intrusive thoughts that compete for cognitive resources (e.g., Boals & Banks, 2012). Hence, they can contribute to both self-reported EF complaints as well as impaired objective EF performance.

As previously noted, self-reported EFs in daily life do not necessarily align with objective EF performance measured by standardized tests in the general population (e.g., Buchanan, 2016; Meltzer et al., 2017) and clinical samples (e.g., Vlagsma et al., 2017; Ingulfsvann Hagen et al., 2021). Thus, self-report measures of EFs cannot serve as a reliable proxy for objective EF performance as assessed by these standardized tests. The lack of an association between the two types of measures may be because they assess different aspects of EFs. Objective measures offer a snapshot of EFs under optimal conditions in a highly structured environment. Such performance-based tasks may not engage the same EFs needed in naturalistic settings, given that these conditions bear little resemblance to the real world (Burgess, 1997). In contrast, self-report measures assess the application of EFs in daily life and require individuals to rate their average/typical everyday EF performance, providing greater ecological validity than objective EF measures, as they tap into the complex and multidimensional nature of EFs (Meltzer et al., 2017). However, the reliability of self-report measures depends on their accuracy in reflecting actual EFs in everyday life, rather than psychological factors such as personality traits. Moreover, objective EF performance is also linked to traits such as neuroticism and may even predict it (Williams et al., 2010; Murdock et al., 2013). Further research is needed to understand the complex relationship between self-reported EFs, objective EF test performance, and psychological factors such as personality traits and negative affective states.

The findings of Chapter 5 have important implications for clinical practice when it comes to individuals self-reporting EF complaints in daily life. First, the use of both objective and subjective self-report EF measures in neuropsychological assessments is crucial because each type of measure provides unique information about an individual's EFs and can help gain a

more comprehensive understanding. The use of objective standardized tests to assess EFs is already common practice today. It is recommended to administer multiple objective EF tests to adequately and reliably capture the multifaceted construct of EFs (e.g., Suchy et al., 2017). Moreover, clinicians should use tests with proper normative data that measure core EFs (i.e., set-shifting, working memory updating, response inhibition, and conflict monitoring) rather than the more traditional tests that involve multiple (core) EFs and non-EF cognitive processes in order to improve validity (e.g., Randolph & Chaytor, 2022). The use of subjective self-report EF measures is needed to assess the extent of experienced EF difficulties in daily life and an individual's self-awareness of EF failures. Moreover, self-reported EF complaints in older adults may indicate subtle underlying neurodegenerative changes even before statistically significant changes manifest in objective EF measures (Rabin et al., 2006; Jessen, et al., 2014; Saykin et al., 2006). In this group, the use of subjective self-report EF measures may help identify early clinical signs that indicate increased susceptibility to developing mild cognitive impairment or a neurodegenerative disease.

Second, clinicians are advised to additionally assess psychological factors, such as personality factors and negative affective states (i.e., perceived stress and symptoms of depression and anxiety) to help identify potential underlying factors that may contribute to the self-reported EF complaints and inform an appropriate treatment strategy. For example, if an individual exhibits high levels of perceived stress, interventions for stress management (e.g., meditation or improving sleep) may improve self-reported EFs as well as wellbeing and quality of life. In addition, there are psychological interventions that can improve the level of neuroticism, which are associated with a range of beneficial treatment outcomes (e.g., Sauer-Zavala et al., 2017). Altogether, by taking into account both objective and subjective self-report EFs measures as well as psychological factors, such as personality and negative affective states, clinicians can assess EFs more reliably and improve the overall effectiveness of interventions and help individuals achieve better outcomes.

Concluding remarks

The studies presented in this thesis contribute to our understanding of EFs, both objectively and subjectively assessed, particularly in adults self-reporting EF complaints in everyday life. EFs are conceptually viewed as the result of a complex interplay of various biological factors (e.g., underlying neural functioning; Chapter 2), psychological factors (e.g., personality factors and negative affective states; Chapter 5), and social factors (e.g., social support; Mueller et al., 2023). However, the relevance and contribution of biological, psychological, and social factors

appear to vary depending on whether EFs are measured objectively through computerized tasks or subjectively by self-report measures, as these two assessment methods capture different aspects of EFs. NF is an effective neuromodulation technique capable of enhancing FM theta upregulation (i.e., directly affecting an essential biological factor underlying EFs) and has potential to induce long-term behavioral improvements in objective EF performance, but has a non-specific positive effect on self-reported EF complaints (Chapters 3 and 4). Subjective self-reported EFs thus seem to depend more on psychological and/or social factors that are indirectly influenced by participation in a NF training (see Figure 2). Overall, our findings underscore the critical importance of tailoring EF interventions to each individual's specific treatment goals (e.g., improving objective EFs or subjective self-reported EFs, or both) and personal characteristics such as the presence or absence of objective EF impairments, self-reported EF complaints, psychiatric disorders, depressive symptoms, perceived stress, ability to self-regulate brain activity, etc. This personalized approach to interventions is the cornerstone for maximizing treatment effectiveness and achieving the desired outcomes.

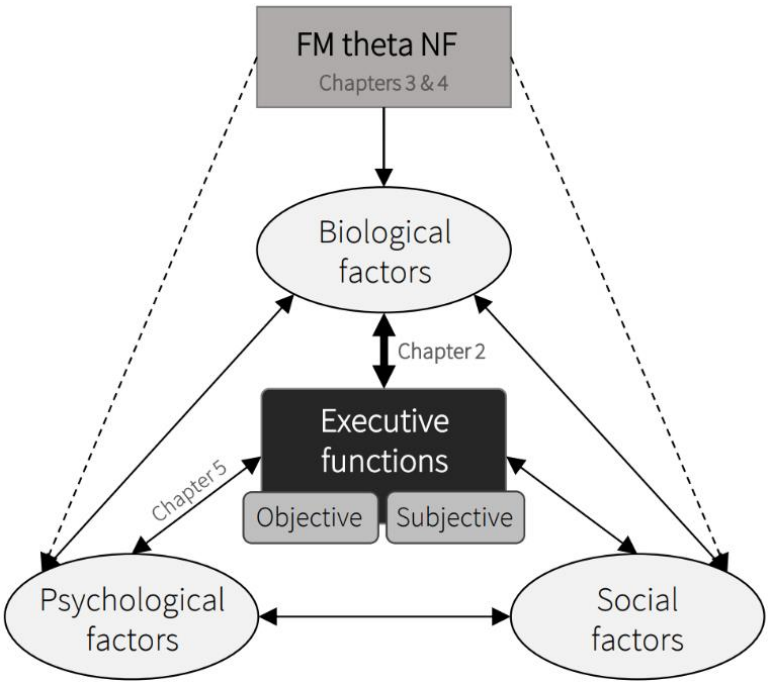

Figure 2. Biopsychosocial model of executive functions and the specific and unspecific effects of frontal-midline theta neurofeedback (after Havelka et al., 2009).

Chapter 7

Addenda

- Summary
- Nederlandse samenvatting (Dutch summary)
- References
- Co-author affiliations
- About the author
- List of publications
- Acknowledgements - Dankwoord

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SUMMARY

Executive functions (EFs) is an umbrella term for higher cognitive (control) processes that are crucial for independent, adaptive, and goal-oriented behavior in everyday life. Despite its broad nature, four core EFs have been identified: working memory updating, set-shifting, response inhibition, and conflict monitoring. Impairments in these EFs are common in psychiatric and neurological disorders, as are self-reported EF complaints in the general population, and can negatively affect functioning in various areas of life. EFs can be assessed using standardized objective tests or by subjective self-report measures. Interestingly, these two types of measures appear to assess different aspects of EFs and there is only limited support for a direct link between objective and subjective self-reported EFs. Therefore, self-reported EF complaints do not necessarily correspond to impaired performance on standardized EF tests and vice versa.

EFs rely on a superordinate brain network involving the midcingulate cortex, dorsolateral prefrontal cortex, and parietal cortex. The synchronization of neural oscillations (i.e., brain waves) is one fundamental mechanism of communication within brain networks enabling cognitive processes. For EFs, theta oscillations (4-8 Hz) are of particular importance as they are generated in response to events requiring cognitive control. In particular, two neurophysiological markers of EFs related to theta oscillations have been identified: (i) theta power at the frontal-midline and (2) functional theta connectivity within the superordinate network. Neuroscientific interventions such as neurofeedback offer the possibility to directly target these underlying (pathophysiological) neural mechanisms, making it a promising intervention to improve EFs.

Despite the crucial importance of efficient underlying neural mechanisms for adequate EFs in everyday life, EFs are thought to be the result of a complex dynamic interaction between various biological, psychological, and social factors. Overall, the three aims of this thesis were to (i) examine the neurophysiological theta markers underlying EFs in adults self-reporting EF complaints, (ii) assess the effects of frontal-midline theta neurofeedback as a neuroscientific intervention for improving EFs in this group, as well as the overall effectiveness of this neurofeedback protocol in upregulating frontal-midline theta, and (iii) identify psychological predictors of subjective self-reported EFs.

In Chapter 2, we assessed theta power in different (sensor space) regions related to the superordinate network, as well as functional theta connectivity between them, while performing computerized tasks assessing the four core EFs. This was done in three groups: adults self-reporting EF complaints and a diagnosis of ADHD (n = 27), adults self-reporting EF complaints without any diagnosis (n = 22), and controls without self-reported EF complaints (n = 21). The results show only strong indications for group differences in neurophysiological

markers during conflict monitoring. Specifically, the groups differ significantly in theta power dynamics over time in the right frontolateral and frontal-midline sensor space regions after the presentation of a stimulus. Post-hoc testing indicates that during the critical time window for EFs (i.e., 200-400 ms after stimulus onset), the group self-reporting EF complaints with an ADHD diagnosis demonstrates lower theta power in the right frontolateral region and slower reaction times in comparison to controls without EF complaints. This suggests that during conflict monitoring, there is less engagement of right lateral frontal brain regions, such as the dorsolateral prefrontal cortex, which is involved in directing attention to the task and processing of target information. Consequently, efficient processing of conflicting or competing actions may be hindered, potentially resulting in the slower reaction times. This is supported by the finding that across all groups, lower theta power in both the right and left frontolateral and frontal-midline sensor space regions during the critical time window for EFs is associated with slower reaction times in the conflict monitoring task. Additionally, lower power in the right frontolateral region is associated with more subjective complaints about conflict monitoring in daily life. In contrast, functional theta connectivity is similar between the three groups during conflict monitoring, indicating that this marker is not affected by the presence of self-reported EF complaints. Furthermore, no (convincing) group differences in theta activity are found for set-shifting, working memory updating, or response inhibition.

There is a need for effective interventions that can alleviate EF complaints and optimize EFs across non-clinical samples. Therefore, in Chapter 3, we evaluated the effectiveness of frontal-midline theta neurofeedback as a neuroscientific intervention to improve EFs in a sample of 58 adults self-reporting EF complaints in daily life (with or without a psychiatric disorder). A well-validated neurofeedback protocol was used targeting theta oscillations in the frontal-midline, which includes the midcingulate cortex; a primary generator of task-related theta oscillations, and thus directly targeting a neurophysiological marker underlying EFs. Using a pre/post/follow-up design with an active sham group, the effects of an 8-session individualized frontal-midline theta neurofeedback training were assessed. Outcome measures were the degree of frontal-midline theta upregulation during the neurofeedback sessions, as well as transfer to objective tasks measuring the four core EFs, frontal-midline theta power during these tasks, and self-reported EFs in daily life immediately after the training and at 6-month follow-up. The results indicate that there are only differences in frontal-midline theta upregulation between the neurofeedback group and sham group when non-responders are excluded from the analysis. Regarding behavioral transfer effects, neurofeedback-specific improvements are found in working memory updating reaction time and conflict monitoring reaction time variability at 6-month follow-up, but not immediately after the training. Frontal-midline theta power during the EF tasks did not change immediately after neurofeedback training and remained consistent six months later. However, both groups experienced a significant reduction in the number of self-reported complaints based on BRIEF-A outcomes

immediately after neurofeedback training that persisted six months later. Thus, the effects on subjective self-reported changes in daily life are not specific to neurofeedback training.

To advance neurofeedback research, the overall effectiveness of frontal-midline theta neurofeedback on the upregulation of frontal-midline theta during the sessions was assessed in Chapter 4. Using a mega-analysis, the raw data from multiple studies applying frontal-midline theta neurofeedback in healthy and (sub)clinical samples was combined creating a larger sample size (n = 149) and thus more power and accuracy. The results show that in the common six sessions of various frontal-midline theta neurofeedback studies training the individualized theta band, the neurofeedback group displays significantly higher upregulation of standard theta amplitudes compared to the sham group, but not of individualized theta amplitudes. After exclusion of non-responders in the neurofeedback group, higher upregulation is found in both the standard and individualized frontal-midline theta bands in comparison to the sham group. When comparing the first and last sessions of each study, the neurofeedback group shows higher upregulation only in the individualized frontal-midline theta band compared to the sham group, even when non-responders are excluded. Furthermore, the presence of self-reported EF complaints in daily life predicts less successful frontal-midline theta upregulation and non-responders are more likely to report a psychiatric disorder.

Although efficient underlying neural functioning is essential for adequate EFs, they are not solely determined by this biological foundation, but are rather the result of a complex interplay between various biological, psychological, and social factors. Therefore, in Chapter 5, we explored which psychological factors best predict self-reported EFs in daily life in a large community sample of (older) adults (n = 1219). It turned out that personality traits and negative affective states like depressive symptoms and perceived stress were strong psychological predictors of self-reported EFs.

Taken together, the findings in this thesis suggest that neurofeedback is overall an effective neuromodulation technique in upregulating frontal-midline theta and has potential for inducing long-term (i.e., 6-month period) improvements in performance on objective EF meas6ures. However, the effect on self-reported EF complaints in daily life is non-specific. Psychological and social factors in the context of the neurofeedback training (e.g., perceived stress, beliefs and expectations, social support of neurofeedback trainers, etc.) may have a greater influence on the subjective experience of EF complaints compared to biological neural mechanisms underlying EF, which were (largely) unaffected in adults self-reporting EF complaints. Overall, these results underscore the need to adopt an individualized approach for enhancing EFs, personalize interventions such as neurofeedback to the characteristics of the individual, identify neurofeedback non-responders who are unable to self-regulate their brain activity, and take the effect of psychological (and social) factors into account.

Addenda

- Summary
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NEDERLANDSE SAMENVATTING (DUTCH SUMMARY)

Executieve functies (EFs) is een overkoepelende term voor hogere cognitieve (controle) processen die cruciaal zijn voor onafhankelijk, adaptief en doelgericht gedrag in het dagelijks leven. Ondanks het brede karakter zijn er vier kern EFs geïdentificeerd: updaten van het werkgeheugen, set-shifting, respons inhibitie en conflict monitoring. Stoornissen in deze EFs komen vaak voor bij psychiatrische en neurologische aandoeningen, net als zelfgerapporteerde EF klachten in de algemene bevolking, en kunnen het functioneren op verschillende levensgebieden negatief beïnvloeden. EFs kunnen worden beoordeeld met behulp van gestandaardiseerde objectieve tests of door subjectieve zelfrapportage. Interessant genoeg lijken deze twee soorten metingen verschillende aspecten van EFs te beoordelen en is er slechts beperkte ondersteuning voor een direct verband tussen objectieve en subjectieve zelfgerapporteerde EFs. Daarom komen zelfgerapporteerde EF klachten niet noodzakelijkerwijs overeen met een verminderde prestatie op gestandaardiseerde EF tests en vice versa.

EFs zijn afhankelijk van een superordinate hersennetwerk waarbij de midcingulate cortex, dorsolaterale prefrontale cortex en pariëtale cortex betrokken zijn. De synchronisatie van neurale oscillaties (d.w.z. hersengolven) is een fundamenteel communicatiemechanisme binnen hersennetwerken die cognitieve processen mogelijk maken. Voor EFs zijn theta oscillaties (4-8 Hz) van bijzonder belang omdat ze worden gegenereerd als reactie op gebeurtenissen die cognitieve controle vereisen. Er zijn twee neurofysiologische markers van EFs geïdentificeerd die gerelateerd zijn aan theta oscillaties: (i) theta power in de frontale-middellijn en (ii) functionele theta connectiviteit in het superordinate netwerk. Neurowetenschappelijke interventies zoals neurofeedback bieden de mogelijkheid om deze onderliggende (pathofysiologische) neurale mechanismen direct te beïnvloeden, waardoor het een veelbelovende interventie is om EFs te verbeteren.

Ondanks het cruciale belang van efficiënte onderliggende neurale mechanismen voor adequate EFs in het dagelijks leven, wordt verondersteld dat EFs het resultaat zijn van een complexe dynamische interactie tussen verschillende biologische, psychologische en sociale factoren. De drie doelen van dit proefschrift waren: (i) het onderzoeken van de neurofysiologische theta markers die ten grondslag liggen aan EFs bij volwassenen die zelf EF klachten rapporteren, (ii) het beoordelen van de effecten van frontale-middellijn theta neurofeedback als een neurowetenschappelijke interventie voor het verbeteren van EFs in deze groep, evenals de algehele effectiviteit van dit neurofeedback protocol in het upreguleren van frontale-middellijn theta en (iii) het identificeren van psychologische voorspellers van subjectieve zelfgerapporteerde EFs.

In Hoofdstuk 2 hebben we de theta power beoordeeld in verschillende (sensor ruimte) regio's die gerelateerd zijn aan het superordinate netwerk, evenals de functionele theta connectiviteit tussen deze regio's, tijdens het uitvoeren van computertaken die de vier kern EFs meten. Dit werd gedaan in drie groepen: volwassenen die zelf EF klachten rapporteerden en een ADHD-diagnose (n = 27), volwassenen die zelf EF klachten rapporteerden zonder diagnose (n = 22), en controles zonder zelfgerapporteerde EF klachten (n = 21). De resultaten tonen alleen sterke aanwijzingen voor groepsverschillen in neurofysiologische markers tijdens conflict monitoring. Specifiek verschillen de groepen significant in theta power dynamiek over tijd in de rechter frontolaterale en frontale-middellijn sensor ruimte regio's na de presentatie van een stimulus. Post-hoc testen wijzen uit dat tijdens het kritieke tijdsinterval voor EFs (d.w.z. 200-400 ms na het begin van de stimulus), de groep die zelf EF klachten rapporteerde en een ADHD-diagnose een lagere theta power in de rechter frontolaterale regio laat zien en een langzamere reactietijd in vergelijking met controles zonder zelfgerapporteerde EF klachten. Dit suggereert dat tijdens conflict monitoring er minder betrokkenheid is van rechter frontale hersengebieden, zoals de dorsolaterale prefrontale cortex, die betrokken is bij het richten van de aandacht op de taak en het verwerken van doelinformatie. Bijgevolg kan een efficiënte verwerking van conflicterende of concurrerende acties worden belemmerd, wat mogelijk resulteert in de tragere reactietijd. Dit wordt ondersteund door de bevinding dat over alle groepen een lagere theta power in zowel de rechter- en linker frontolaterale en frontale-middellijn sensor ruimte regio's tijdens het kritieke tijdsinterval voor EFs geassocieerd is met een langzamere reactietijd in de conflict monitoring taak. Bovendien is een lagere power in de rechter frontolaterale regio geassocieerd met meer subjectieve klachten over conflict monitoring in het dagelijks leven. Daarentegen is de functionele theta connectiviteit vergelijkbaar tussen de drie groepen tijdens conflict monitoring, wat aangeeft dat deze marker niet wordt beïnvloed door de aanwezigheid van zelfgerapporteerde EF klachten. Verder zijn er geen (overtuigende) groepsverschillen in theta activiteit gevonden voor set-shifting, updaten van het werkgeheugen of respons inhibitie.

Er is behoefte aan effectieve interventies die EF klachten kunnen verminderen en EFs kunnen optimaliseren in niet-klinische groepen. Daarom evalueerden we in Hoofdstuk 3 de effectiviteit van frontale-middellijn theta neurofeedback als een neurowetenschappelijke interventie om EFs te verbeteren in een steekproef van 58 volwassenen die zelf EF klachten rapporteerden in het dagelijks leven (met of zonder psychiatrische stoornis). Dit goed gevalideerde neurofeedback protocol richt zich op theta oscillaties in de frontale-middellijn, die de midcingulate cortex omvat; een primaire generator van taakgerelateerde theta oscillaties, en richt zich dus direct op een neurofysiologische marker die ten grondslag ligt aan EFs. Door gebruik te maken van een pre/post/follow-up design met een actieve sham groep, werden de effecten van een 8 sessies durende geïndividualiseerde frontale-middellijn theta neurofeedback training beoordeeld. Uitkomstmaten waren de mate van frontale-middellijn theta upregulatie tijdens de neurofeedback sessies, evenals de transfer naar objectieve taken

die de vier kern EFs meten, frontale-middellijn theta power tijdens deze taken en zelfgerapporteerde EFs in het dagelijks leven direct na de training en na 6 maanden follow-up. De resultaten geven aan dat er alleen verschillen zijn in frontale-middellijn theta upregulatie tussen de neurofeedback groep en de sham groep wanneer non-responders worden uitgesloten van de analyse. Wat betreft transfer effecten naar gedrag worden neurofeedback-specifieke verbeteringen gevonden in reactietijd voor werkgeheugen updaten en reactietijd variabiliteit voor conflict monitoring na 6 maanden follow-up, maar niet direct na de training. Frontale-middellijn theta power tijdens EF taken verandert niet direct na de neurofeedback training en blijft consistent 6 maanden later. Beide groepen ervaren wel een significante vermindering in het aantal zelfgerapporteerde klachten gebaseerd op BRIEF-A uitkomsten direct na de neurofeedback training die 6 maanden later aanhield. De effecten op subjectieve zelfgerapporteerde veranderingen in het dagelijks leven zijn daarmee niet specifiek voor de neurofeedback training.

Om het neurofeedback onderzoek te bevorderen, werd in Hoofdstuk 4 de algehele effectiviteit van frontale-middellijn theta neurofeedback op de upregulatie van frontale-middellijn theta tijdens de sessies beoordeeld. Met behulp van een mega-analyse zijn de ruwe gegevens van meerdere onderzoeken naar frontale-middellijn theta neurofeedback in gezonde en (sub)klinische groepen gecombineerd, waardoor een grotere steekproefomvang (n = 149) en dus meer power en nauwkeurigheid werd gecreëerd. De resultaten tonen aan dat in de gemeenschappelijke 6 sessies van verschillende frontale-middellijn theta neurofeedback studies die de geïndividualiseerde theta band trainden, de neurofeedback groep significant hogere upregulatie van standaard theta amplitudes laat zien vergeleken met de sham groep, maar niet van geïndividualiseerde theta amplitudes. Na uitsluiting van non-responders in de neurofeedback groep wordt een hogere upregulatie gevonden in zowel de standaard als de geïndividualiseerde frontale-middellijn theta banden in vergelijking met de sham groep. Bij het vergelijken van de eerste en laatste sessies van elke studie, vertoont de neurofeedback groep alleen een hogere upregulatie in de geïndividualiseerde frontale-middellijn theta band in vergelijking met de sham groep, zelfs wanneer non-responders worden uitgesloten. Bovendien voorspelt de aanwezigheid van zelfgerapporteerde EF klachten in het dagelijks leven minder succesvolle frontale-middellijn theta upregulatie en rapporteren non-responders vaker een psychiatrische stoornis.

Hoewel efficiënt onderliggend neuraal functioneren essentieel is voor adequate EFs, worden ze niet alleen bepaald door deze biologische basis, maar zijn ze eerder het resultaat van een complexe wisselwerking tussen verschillende biologische, psychologische en sociale factoren. Daarom hebben we in Hoofdstuk 5 onderzocht welke psychologische factoren zelfgerapporteerde EFs in het dagelijks leven het beste voorspellen in een grote populatie steekproef (oudere) volwassenen (n = 1219). Het blijkt dat persoonlijkheidskenmerken en

negatieve emotionele gemoedstoestanden zoals depressieve symptomen en ervaren stress sterke psychologische voorspellers zijn van zelfgerapporteerde EFs.

Samengenomen suggereren de bevindingen in dit proefschrift dat neurofeedback over het algemeen een effectieve neuromodulatietechniek is voor het upreguleren van frontale-middellijn theta en dat het potentie heeft om op de lange termijn (d.w.z. na 6 maanden) verbeteringen te induceren in de prestatie op objectieve EF taken. Het effect op zelfgerapporteerde EF klachten in het dagelijks leven is echter niet specifiek. Psychologische en sociale factoren in de context van de neurofeedbacktraining (bv. ervaren stress, overtuigingen en verwachtingen, sociale steun van neurofeedback trainers, etc.) hebben mogelijk een grotere invloed op de subjectieve ervaring van EF klachten dan de biologische neurale mechanismen die ten grondslag liggen aan EF, welke (grotendeels) onveranderd zijn bij volwassenen die zelf EF klachten rapporteerden. Over het geheel genomen onderstrepen deze resultaten de noodzaak voor een geïndividualiseerde behandelaanpak voor het verbeteren van EFs, het personaliseren van interventies zoals neurofeedback op basis van de kenmerken van het individu, het identificeren van neurofeedback non-responders die niet in staat zijn om hun hersenactiviteit zelf te reguleren en het rekening houden met het effect van psychologische (en sociale) factoren.

Addenda

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- **References**
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Diede Smit was born on September 19, 1993 in Groningen and grew up in Bedum, a village near Groningen. In 2011, she completed her pre-university education at H. N. Werkman College in Groningen. That same year, she began her bachelor's degree in Psychology at the Faculty of Behavioural and Social Sciences of the University of Groningen and graduated cum laude in 2014. She then pursued her interest in neuropsychology and completed the master's program Neuropsychology in 2016 as well as the research master's program Clinical Neuropsychology in 2018, both cum laude, at the University of Groningen. During these master's programs, she did clinical internships at the Department of Medical Psychology of Wilhelmina Hospital Assen and at the Center for Neuropsychiatry of GGZ Friesland. During the research master's program, Diede wrote her thesis under the supervision of Dr. Stefanie Enriquez-Geppert. This work served as the basis for her PhD research proposal, which was funded by a Faculty Scholarship grant from the University of Groningen. In September 2018, Diede started her PhD project under the supervision of Prof. Oliver Tucha, Dr. Janneke Koerts, and Dr. Stefanie Enriquez-Geppert. She submitted her dissertation to the reading committee in January 2024.

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Conference contributions

Oral presentation at the Society of Applied Neuroscience conference in Thessaloniki, Greece (2022). Title: FM theta neurofeedback in a subclinical group

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Poster presentation at the Dutch Neuroscience meeting in Lunteren, the Netherlands (2019). Title: Towards the development of frontal-midline theta neurofeedback as therapeutic tool for executive dysfunctions

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Poster presentation at the Heymans Symposium in Groningen, the Netherlands (2019). Title: Assessing theta neurofeedback training as therapeutic tool to improve executive functioning: A pilot study

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