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EXPLORING PERSONALIZED APPROACHES FOR NEUROFEEDBACK OPTIMIZATION

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Declaration

I hereby declare that, the contents and organization of this dissertation constitute my own original work and does not compromise in any way the rights of third parties, including those relating to the security of personal data.

Arif Sinan Uslu

2023

To my parents, Şule and Coşkun,

and to the beloved memory of my grandfather Ahmet Güldütuna.

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Abstract

Neurofeedback is an intervention which is designed to alter cognitive-behavioral functions by inducing neural activity. Despite the growing evidence supporting its validity in healthy and clinical populations, there is current debate on its underlying mechanisms and its limited efficacy in mediating lasting changes to cognitive-behavioral outcomes. Recent neurofeedback studies suggest that inter-individual variations in neurophysiological and psychological factors may explain some of the heterogenous findings and may, further, inspire the individual adaptation of neurofeedback protocols. In a series of studies, we investigated how tailoring specific parameters of neurofeedback interventions may increase the overall efficacy in mediating changes to both neurophysiological and cognitive outcomes.

In study 1, we assessed the effect of self-pacing training-time during neurofeedback on cognitive outcomes and how the learning-rate of gaining control over the targeted neural feature related to changes in neurophysiological and cognitive functions measured before and after a single session of neurofeedback. Our results indicate that handing healthy participants the ability to adapt the training-time to their needs improved higher cognitive functions more than externally-pacing the training. We, further, observed that the more successful healthy participants were in regulating their brain activity, the more they increased their neurophysiological and cognitive-behavioral functions from before to after neurofeedback.

Next, we assessed person-specific neural correlates of mental rotation in study 2 by applying a machine learning approach. Modelling the time of correct responses as a function of preceding EEG activity in a mental rotation task revealed inter-individual differences in the importance of spectral and spatial EEG features for the prediction on the one hand and similar group-based EEG features as reported in previous studies on the other hand. More specifically, our findings highlighted the relevance of alpha and beta band-related activity as well as left frontal and right parieto-occipital activity for mental rotation.

In study 3, we finally investigated the efficacy of personalized target feature specification in a neurofeedback intervention by applying the methodology detailed in study 2. Our results suggest that compared to sham feedback, participants receiving personalized neurofeedback improved their mental rotation performance significantly more. Furthermore, the mediated effect of neurofeedback training was specific to mental rotation and did not transfer to other cognitive functions.

The results from the conducted neurofeedback studies provide partial support for the notion that adapting neurofeedback protocols to user characteristics increases the efficacy of neurofeedback interventions in mediating changes to neurophysiological and cognitive-behavioral functions. Future studies are required to overcome some of our limitations also related to the spatial resolution of the chosen brain imaging technique, our adaptation of the mental rotation task, and the specificity of neurofeedback as an intervention to exclusively induce changes to the targeted neural feature.

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Abbreviations

ADHD	Attention Deficit / Hyperactivity Disorder
Ag/AgCl	ArGentum (silver) / ArGentum ChLoride
BCI	Brain-Computer Interface
CI	Confidence Interval
EEG	ElectroEncephaloGraphy
ERD	Event-Related Desynchronization
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-Infrared Spectroscopy
(G)LMM	(Generalized) Linear Mixed Model
HPDI	Highest Posterior Density Interval
ICA	Independent Component Analysis
IUA	Individual Upper Alpha

M	Mean
MAE	Mean Absolute Error
MEG	MagnetoEncephaloGraphy
PET	Positron Emission Tomography
RCT	Randomized Controlled Trial
RT	Reaction Time
SCP	Slow Cortical Potentials
SD	Standard Deviation
SHAP	SHapley Additive exPlanations
SMR	SensoriMotor Rhythm
SNR	Signal to Noise Ratio
SPoC	Source POwer Comodulation
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
TMT	Trail Making Task

CHAPTER 1

Scientific Background

In this chapter we will review the scientific background of neurofeedback – that is an iterative learning process to regulate one's own brain activity (see section 1.2.2) – and, further, carve out current limitations of neurofeedback research to, finally, outline our studies which we have designed to investigate personalized approaches to overcome some of the introduced limitations. For the review, we will begin with literature concerning the mapping of brain activity and cognitive-behavioral outcomes (i.e., neural correlates) which has received attention from both within and outside the field of neurofeedback research. Due to their relevance for the studies carried out in the context of this thesis, we highlight background information on EEG based neurofeedback and neural correlates of visuo-spatial working memory throughout this introductory chapter. Subsequently, the focus will be set on neurofeedback itself with a definition of the paradigm, followed by a description of parameters inherent to neurofeedback training protocols and a note on the heterogeneity observed in the efficacy of neurofeedback interventions to induce changes in brain activity and potentially mediate modifications in concomitant cognitive and behavioral functions. After having covered background information on neural correlates and neurofeedback, we will introduce machine learning approaches to enrich research on the two aforementioned domains as the third area relevant for the contextualization of methodology and findings reported in the studies carried out (i.e., chapters 2, 3, and 4). Finally, we will summarize the current limitations of neurofeedback research and formulate approaches based on the reviewed literature to partly explain the heterogenous patterns observed in traditional neurofeedback protocols on the one hand and to further enhance the efficacy of neurofeedback interventions on the other hand.

1.1 Neural correlates

A critical prerequisite of neurofeedback is the link between neural activity and cognitive-behavioral outcome measures. While neurofeedback studies are one approach to investigate this link, we will also present other methodological procedures not less important for fostering the connection between brain activity and behavior. Neural correlates can be described as neural biomarkers providing such a mapping (Biomarkers Definition Working Group, 2001). Since the early observations of functional impairments in patients suffering from severe brain damage, a wide range of techniques has been developed to investigate such functional relations in the absence of traumatic brain injury. These techniques include imaging methods (e.g., fMRI), neural stimulation techniques (e.g., TMS; see section 1.1.1), and have more recently been extended by machine learning approaches enabling person-specific calibration of brain activity-behavioral outcome mappings (Porter et al., 2023). Neural correlates have enriched research in several domains some of which are related to neurofeedback such as neural correlates of cognitive processes and neural correlates predicting the success rate of neurofeedback trainings. Mental rotation, a cognitive operation during which a mental representation of an image is rotated around an axis, is one such cognitive process that has garnered considerable popularity in the field (Borst, 2013; Veldema et al., 2021; Zacks, 2008).

1.1.1 Methodological approaches

Brain imaging techniques such as EEG, MEG, fMRI, and fNIRS have provided substantial insights into how neural processes relate to mental processes and, further, how brain activity relates to behavioral outcomes. EEG and MEG devices provide a low latency for signal acquisition (i.e., below one millisecond). Both assess the electric current (the latter via the concomitant magnetic field) of pyramidal cells perpendicular to the scalp (Murakami & Okada, 2006; Thibault et al., 2016). Further imaging techniques include fNIRS and fMRI both of which probe hemodynamic changes in the brain following neural activation due to neurovascular coupling. Due to this indirect measure of brain activity, both imaging techniques provide a higher signal acquisition latency compared to EEG and MEG. While fMRI provides the highest spatial resolution of active brain regions out of the four introduced imaging techniques, fNIRS provides similarly to EEG a more portable means to assess brain activity and is less affected by electric noise. Although the introduced imaging techniques provide information on the correlations between electrical and hemodynamic properties of neural processes associated with ongoing oscillatory activity and activity in specific brain regions on the one hand and some task performance on the other hand, these methods do not answer questions concerning the causal relationship between brain activity and cognitive-behavioral outcomes.

Non-invasive brain stimulation techniques such as TMS and tDCS alter neural processes directly and, hence, are suitable for investigations of brain activity causally involved in the generation of behavioral output. Previously discussed neuroimaging techniques are well suited to inform these stimulation techniques regarding associated brain regions assisting the definition of the target activity for the stimulation procedure.

Another approach to validate neural correlates is realized by applying a neurofeedback paradigm involving an experimental condition to modulate the neural feature of interest and a control condition. However, this approach poses significant limitations, primarily concerning potential unspecific modulation not only of the targeted neural feature but also of other neural features, thus raising the risk that the intended neural feature may not be modulated at all. As a result, careful planning of experimental designs and the implementation of appropriate statistical analyses are imperative to address and mitigate these concerns effectively.

1.1.2 Behavioral outcome

Studies utilizing fMRI to investigate brain regions specifically implicated in mental rotation processes have yielded heterogeneous activity patterns. This variability in findings is likely attributable to differences in experimental procedures across studies (Zacks, 2008). Nonetheless, an increase in hemodynamic activity in the right posterior parietal cortex and the left frontal lobe has been more consistently observed across mental rotation studies, suggesting that these regions may be less susceptible to the variations in applied experimental designs (Veldema et al., 2021; Zacks, 2008).

Furthermore, some studies have observed inter-individual and context-dependent variance in the neurophysiological response suggesting that task-related neural activity may partly be explained by person-specific characteristics. In a study adopting the oddball paradigm to assess the reliability of neural face discrimination response amplitude and topography, the EEG response patterns varied depending on stimulus-, person-, and time-specific characteristics suggesting that such variations may be masked in aggregated estimates (Stacchi et al., 2019). Although some have argued that inter-individual differences merely represent noise and should be treated as such, others have pointed out the potential use of inter-individual variations for person-specific interventions (Cooper et al., 2019; Madden et al., 2021).

One common assumption in neurofeedback training is that modifications of neural activity transfer to changes in associated cognitive and behavioral functions. Reviews and meta-analyses have addressed numerous studies investigating the efficacy of neurofeedback training to alter neural activity and to change cognitive or behavioral functions in both clinical and healthy populations (Alkoby et al., 2018; Gruzelier, 2014; Patil et al., 2023; Veldema et al., 2021). They have extensively demonstrated the treatment efficacy of neurofeedback in various clinical conditions including anxiety disorders (Schoenberg & David, 2014), in ADHD (Lin et al., 2022; Van Doren et al., 2019), major depressive disorder and depressive symptomology (Fernández-Alvarez et al., 2022; Patil et al., 2023), stroke (Renton et al., 2017), tinnitus (Güntensperger et al., 2017), emotional disorders, chronic pain, autism spectrum disorder, epilepsy, addiction, and insomnia. Furthermore, there is evidence that neurofeedback further improves behavioral and cognitive functions in healthy populations including motor performance (e.g., speed, and accuracy) (Gruzelier, 2014; Onagawa et al., 2023) and cognitive functions (e.g., episodic, long-term, and working memory) (Matsuzaki et al., 2023). Thus, neurofeedback may foster the bridging between neural activity and both cognitive and behavioral outcomes.

1.2 Neurofeedback

In the following, we will outline the history and define the concept of neurofeedback including the training parameters to be defined for an intervention. Despite the various imaging techniques available to assess brain activity, we will focus here on EEG based neurofeedback interventions due to the vast amount of studies applying this protocol and due to their relevance for the upcoming chapters on the completed studies for this thesis (i.e., chapters 2, 3, and 4).

1.2.1 A brief history of neurofeedback

Neurofeedback emerged mainly from two scientific discoveries in the 20th century, namely electrical activity in the brain (Niedermeyer & da Silva, 2005) and operant conditioning (McSweeney & Murphy, 2014). The demonstration of electrical currents in mammal’s brains when placing two recording electrodes on the cortex or one on the surface of the skull and one on the cortex later led to EEG recordings in humans (Brazier, 1963). In 1929, EEG recordings of humans were published for the first time, notably showing prominent alpha activity in relaxed wakefulness, and within a decade all major brainwaves had been identified (Collura, 2014). Parallel to these advances in psychophysiology, principles explaining changes in behavior based on environmental antecedents and consequences were formulated (McSweeney & Murphy, 2014). Operant conditioning refers to a type of learning modifying the frequency of a behavior by either reinforcement or punishment (Skinner, 1938). In the 1960s, neurofeedback research began with a discrimination training to detect the onset of bursts in alpha activity (Kamiya, 2011). Prior to the training, the experimenter instructed participants to indicate upon each ding of a bell which appeared half the time in phase with alpha bursts whether alpha activity was increased. During the training, the experimenter reinforced correct responses by calling ‘correct’ and thereby providing an auditive feedback. Not only did the participants learn to accurately indicate the presence or absence of alpha bursts upon the bell ding, but they also further demonstrated in a follow-up experiment their ability to accurately indicate bursts in alpha activity without any cue from the bell ding.

1.2.2 Definition

Neurofeedback, sometimes also referred to as EEG biofeedback, is the iterative process of self-regulating neural activity based on external feedback reinforcing correct regulation. Commonly, this iterative process involves (1) measuring, (2) processing, and (3) feeding back neural activity (see Figure 1). Since neurofeedback teaches users to interact with a system which provides the feedback by using neural activity and not peripheral nerves or muscular activity, it can be considered as a specific type of BCI application (Wolpaw et al., 2000). In contrast to neural stimulation techniques such as TMS and tDCS, neurofeedback relies on the principles of self-regulation in the absence of external sources targeting the stimulation of neural activity.

To measure changes in targeted outcomes, instructors commonly assess the user’s performance prior to any training (i.e., at baseline) and after each session. In research, controlled experiments have been established to investigate the efficacy of neurofeedback and, further, to rule out non-specific factors (Sorger et al., 2019). For example, in sham-controlled studies one condition involves participants receiving sham feedback (e.g., based on the neural activity of another participant) while keeping constant other parameters of neurofeedback training such as the training duration. Active controls represent another type of control where participants receive a different type of feedback based on their own neural activity (e.g., activity from a different brain region).

1.2.3 Parameters

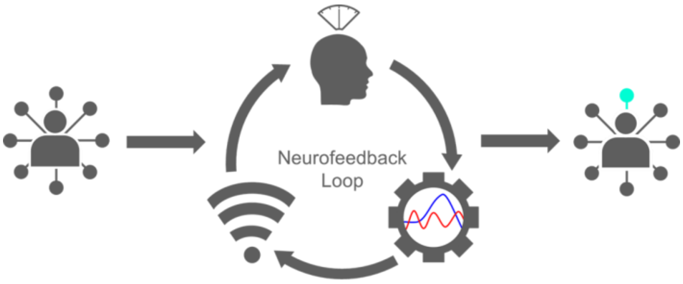

Figure 1. Illustration of neurofeedback loop. Neurofeedback encompasses several parameters that warrant clear definition including the imaging technique measuring neural activity (Nicolas-Alonso & Gomez-Gil, 2012), the type of feedback, the number of training sessions, the neural feature used for feedback and the targeted behavioral outcome measure.

1.2.3.1 Imaging techniques

EEG and MEG based neurofeedback provide a low latency for feedback generation (i.e., below 50 ms up to hundreds of ms depending on the complexity of feature extraction and available computing resources). While both assess the electric current, neurofeedback in humans began with EEG based neurofeedback and has yielded a broad landscape of relevant literature whereas MEG based neurofeedback is a more recently applied imaging method and has improved the spatial resolution of the recorded signals (Murakami & Okada, 2006; Thibault et al., 2016). Further imaging techniques applied for neurofeedback include fNIRS and fMRI both of which provide a higher feedback latency compared to EEG and MEG based neurofeedback. More recently, multimodal systems have provided insight into electrical and vascular functionality of neural activity fostering the bridge between multimodal information (Thibault et al., 2016).

1.2.3.2 *Feedback modality*

The feedback modality is another parameter to be defined for neurofeedback training and may rely on visual, auditory, and haptic sensory information to be processed (Jones & Sarter, 2008; Kitson et al., 2018; Nicolas-Alonso & Gomez-Gil, 2012). These feedback modalities provide tangible and accessible means for individuals to perceive and engage with their neurophysiological activity during the neurofeedback intervention.

With designs applying a visual feedback of neurophysiological signals, users commonly learn to alter a visual representation of their neural activity either on a 2D-screen or in a more immersive virtual reality environment. Visual representations of neural activity include shapes, colors, textures, and positions all of which may evoke a range of affective states (Pinilla et al., 2021). In neurofeedback research, successful regulations have been visualized by changes in the properties of abstract objects such as modifying the height of horizontal bars (Hsueh et al., 2016), changing the saturation and color of squares (Brandmeyer & Delorme, 2020; Enriquez-Geppert et al., 2014; Hanslmayr et al., 2005; Smit et al., 2023), and alternating the direction of a curve (Scharnowski et al., 2015), and, further, by property changes of real-world objects such as accelerating rollercoasters (Eschmann et al., 2020), increasing the temperature as indicated by a thermometer (Al-Wasity et al., 2021; Gordon et al., 2020; Kim et al., 2019; Paret et al., 2016; Y. Wang et al., 2020), and moving a basketball (S. He et al., 2020).

Designs providing auditory feedback have utilized variations in tone pitch (Sidhu & Cooke, 2021; Tseng et al., 2021), bird chirps (Nan et al., 2020), and changing the tone volume (Faller et al., 2019; Grosselin et al., 2021; Ozga et al., 2019; Ramirez et al., 2015). Some studies provided both auditory and visual feedback (Cheng et al., 2015; Mirifar et al., 2019; Wang & Hsieh, 2013) or additionally tactile feedback (Jensen et al., 2007) during the training supporting the development of multimodal feedback systems. There is evidence that the efficacy of neurofeedback partly depends on the feedback modality applied to regulate neural activity (Yeh et al., 2022).

1.2.3.3 Training frequency

As already indicated, neurofeedback trainings also differ in the number of sessions and the training duration per session with most studies applying a single session design (Ciccarelli et al., 2023). Although changes in neural activity and cognitive-behavioral outcomes have been demonstrated even after a single session of neurofeedback (typically around 30 minutes), it is more common to apply neurofeedback over multiple sessions, especially in clinical settings where neurofeedback treatments may well contain 20 training sessions or more. During training, the feedback is provided shortly after the signal has been processed as feedback latency is crucial for reinforcement learning. In EEG based neurofeedback, artificially delaying the feedback delivery after finished processing affected induced changes in neural activity (Belinskaia et al., 2020). Despite the necessity to investigate the impact of training frequency as mentioned in several reviews (Alkoby et al., 2018; Patil et al., 2023), it however remains sparsely explored how the duration, the number and the frequency of training sessions relate to successful control of the targeted neural feature and potentially to long-lasting cognitive-behavioral variables.

1.2.3.4 Neural features and targeted outcomes

Finally, neurofeedback trainings are also parameterized by their targeted neural feature ideally mediating changes in cognitive-behavioral outcome measures. In EEG based neurofeedback designs, this parameter is commonly specified by the targeted frequency band and to a lesser degree by the associated brain region estimated inter alia through source localization techniques. As the power in the frequency representation of human EEG is well approximated by a 1/frequency function, most energy is concentrated in lower frequencies and higher frequencies of the EEG are associated with a lower SNR (He, 2014).

Targeted oscillatory activity at specific frequency ranges include SCP (0.5-2Hz), delta (2-4Hz), theta (4-7Hz), alpha (8-12Hz), beta (12-30Hz), and gamma (30-100Hz) (Rogala et al., 2016). There is evidence that SCP indicate monitoring and allocation of attentional resources for information processing (Elbert, 1993). In clinical populations with impaired attentional control such as in ADHD, the modulation of SCP commonly at the centrally placed Cz electrode during neurofeedback mediated behavioral improvements and reductions in clinical symptoms (Mayer et al., 2013). However, the current body of research lacks medication or sham-controlled studies that would further validate the efficacy of neurofeedback in these populations. Only a few studies have applied delta feedback most of which combined it with other frequency bands for instance to reduce delta activity and thereby the impact of associated signal artifacts (Kravitz et al., 2006; Wang & Hsieh, 2013). Depending on the electrode positions chosen to calculate the feedback signal, theta neurofeedback has mediated changes in executive functions and memory processes (Gruzelier, 2014). While some studies have applied multi-band feedback protocol to increase the specificity of the training and reduce the risk of altering oscillatory activity in other bands, others have concluded that training multiple bands was less likely to induce expected changes in neural activity compared to single band protocols (Rogala et al., 2016).

Alpha neurofeedback has been shown to mediate enhancements in visuo-spatial information processing and working memory as involved in mental rotation when applied over frontal and parieto-occipital regions (Gruzelier, 2014; Viviani & Vallesi, 2021; Yeh et al., 2022). Since the distribution of the EEG signal in the frequency domain contains person-specific features, some studies have adapted alpha neurofeedback protocols by specifying the feedback band based on the frequency associated with the peak in the alpha range (Escolano et al., 2014; Hanslmayr et al., 2005). Studies applying a beta neurofeedback protocol commonly observed a decrease in impulsivity after training patients diagnosed with ADHD and, furthermore, demonstrated enhanced response inhibition when applied in a healthy population (Egner & Gruzelier, 2001; Viviani & Vallesi, 2021). While some researchers have linked up-regulation of gamma band activity over occipital and frontal regions to memory processes including the retrieval of episodic information (Keizer et al., 2010), others have failed to replicate this finding and applied a gamma protocol as an active control condition instead (Kober et al., 2017; Staufenbiel et al., 2014).

To summarize, the targeted frequency band is commonly specified based on the behavioral outcome measure it is thought to mediate. Albeit some studies applying multi-band feedback protocols, single-band protocols have proven higher success rates in inducing changes in neural oscillatory activity. Person-specific characteristics have inspired some researchers to take these variations into account when defining a training protocol rather than dismissing them as noise.

1.2.4 Neurofeedback success

To overcome substantial differences in success rates of neurofeedback trainings, a recent review has detailed several neurophysiological and psychological candidates associated with successful regulation of targeted neural features despite the various measures quantifying success in neurofeedback trainings (Alkoby et al., 2018). As already noted earlier, the number of frequency bands targeted during trainings had a negative effect on neurofeedback success rate and, furthermore, success rates substantially differed between targeted frequency bands with alpha and theta band activity being more susceptible to neurofeedback than beta band related activity (Rogala et al., 2016). Given the large amount of data recorded during such neuropsychological experiments, more advanced analysis techniques may be useful to gain new insights into how training parameters relate to outcome measures.

1.3 Machine learning

Despite recent advances in the field with deep learning techniques, we will restrict our review to classical machine learning approaches due to their popularity in the domain of neurophysiology and the higher degree of interpretability classical machine learning methods provide in contrast to deep learning models (Usman et al., 2021).

1.3.1 Definition

Machine learning algorithms refer to computer programs written to perform either classification or regression tasks while learning from their performance in these tasks. In contrast to more traditional methodologies, these algorithms enable the processing of large volumes of data as collected during neurophysiological recordings (Hrovat et al., 2014). While adaptive models are trained to assign an input to a finite number of discrete categories in the context of classification problems, they provide continuous outcome variables for regression problems. Furthermore, problems are either referred to as supervised learning problems if the targeted outcome value is known or otherwise referred to as unsupervised learning problems for instance when exploring similarities between data points to form groups (i.e., clustering). By adopting a machine learning approach, only a subset of the available data set is used to tune the parameters of a model (i.e., a training set) and another, independent subset (i.e., a hold-out set) is used to assess the generalizability of the model when generating predictions based on new data. Commonly, the input data are transformed during a pre-processing phase which happens prior to the training of model parameters or the generation of predictions and may for instance improve the SNR in the raw data.

1.3.2 Applications in neuropsychology

The extraction of features enabling the detecting of medical or psychiatric conditions is another area where machine learning methods such as SVM or random forest have been applied. Although some studies have reported that models using resting state fMRI signals to classify major depressive disorder from healthy controls perform at chance level, most studies have trained the models to perform significantly above chance level and identified most discriminative features fostering the classification accuracy in prefrontal-limbic areas of the brain (Bondi et al., 2023). In epilepsy research, machine learning models have substantially improved the detection and localization of pathological cortical lesions providing crucial information for neurosurgeons (Yuan et al., 2022).

Only a few studies have investigated the potential use of machine learning in the context of neurofeedback (Hossain & Yaacob, 2022). In multimodal recordings, machine learning approaches have enriched the connections between various imaging techniques for instance when electrical activity is related to hemodynamic properties of neural processes by using only EEG signals to predict feedback values of simultaneous fMRI-EEG neurofeedback (Lioi et al., 2020; Perronnet et al., 2017). Besides investigating the mapping of multimodal imaging techniques, machine learning approaches have further been applied to adapt the feedback threshold to person-specific characteristics (Han et al., 2016). Amidst the plethora of reviews and meta-analyses proposing the integration of machine learning approaches to individually tailored training protocols, up until now only a few studies have explored the potential of machine learning methods in this domain (Alkoby et al., 2018; Hossain & Yaacob, 2022; Jeunet et al., 2018).

1.4 Research aims

After having reviewed the literature concerning neurofeedback along with related research from the wider field investigating neural correlates and applications of machine learning methods to gain new insights, we will now summarize the main limitations of neurofeedback interventions and describe potential solutions yielding the basis for the experimental and methodological investigations carried out in the context of this thesis. For potential solutions, we will take adaptable training parameters into account as presented in section 1.2.3, some of which have already been shown as relevant for neurofeedback success. These parameters include (a) task-specific, (b) cognitive and motivational, and (c) technology-acceptance related factors (Jeunet et al., 2018).

1.4.1 Current limitations

Although a wide range of factors has been shown to be related to learning success during neurofeedback, RCTs investigating the efficacy of these factors on training outcome measures are rare, thus impeding potential conclusions about their causal role. Despite several reviews highlighting training frequency as a key factor for training success, in some studies participants were not able to regulate their brain activity even after multiple training sessions suggesting that other factors may play an important role. One other factor discussed in the literature is the sense of agency experienced during the training and its impact on motivational components, which in turn is crucial for successful learning. Due to heterogenous findings of neurofeedback training on enhancing targeted cognitive-behavioral variables, some researchers have hypothesized that the lack of precise and relevant brain regions used for feedback generation may have limited the mediation of targeted outcomes through neural features regulated in the context of neurofeedback training and, hence, have proposed to target functionally related and accurately estimated neural sources during neurofeedback (Rogala et al., 2016).

1.4.2 Outline of studies

Given the large inter- and intraindividual differences observed in the efficacy of neurofeedback, one approach to overcome this limitation is adapting neurofeedback parameters to the situational context and user characteristics.

As motivation plays a critical role in reinforcement learning (Dayan & Balleine, 2002), an effect of motivation on neurofeedback learning was expected. As an increase in the degree of control is associated with enhanced motivation to perform in human-machine interactions (Eitam et al., 2013), one approach to individually tailor neurofeedback training paradigms is by handing users more control over the timing of their training. Therefore, we investigated in our first study how self-paced training – where users freely distribute their training time – relates to neurofeedback outcomes in comparison to externally-paced training during which all users receive the same traditional block design.

Recent reviews have proposed machine learning to adjust neurofeedback parameters to user characteristics (Fernández-Alvarez et al., 2022). Hitherto, machine learning approaches have provided evidence for person-specific task-related mental states supporting the need for individually adjusted neural features (Porter et al., 2023). In our second study we therefore explored person-specific neural correlates of cognitive-behavioral variables applying a machine learning approach to make generalizable predictions using neural activity. We finally validated our person-specific machine learning approach extracting neural correlates by applying a neurofeedback procedure relying on the individually specified neural features taking person-specific topographic patterns into account for feedback generation.

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CHAPTER 2

Self-agency and learning in neurofeedback

After having introduced the concepts of neural correlates, neurofeedback and machine learning, we now focus on the studies carried out to overcome some of the limitations detailed in the previous chapter. In study 1, we investigated the effect of control over neurofeedback systems on neurocognitive and neurophysiological outcomes. This study resulted in a poster presented at the 47th annual “Psychologie und Gehirn” (psychology and brain) conference in Freiburg (Germany) and an article published in the journal Frontiers in Human Neuroscience (https://doi.org/10.3389/fnhum.2023.1077039).

Abstract

Real time electroencephalogram (EEG) based neurofeedback has been shown to be effective in regulating brain activity, thereby modifying cognitive performance and behavior. Nevertheless, individual variations in neurofeedback learning rates limit the overall efficacy of EEG based neurofeedback. In the present study we investigated the effects of learning rate and control over training realized by self-pacing on cognitive performance and electrocortical activity. Using a double-blind design, we randomly allocated 60 participants to either individual upper alpha (IUA) or sham neurofeedback and subsequently to self- or externally paced training. Participants receiving IUA neurofeedback improved their IUA activity more than participants receiving sham neurofeedback. Furthermore, the learning rate predicted enhancements in resting-state activity and mental rotation ability. The direction of this linear relationship depended on the neurofeedback condition being positive for IUA and negative for sham neurofeedback. Finally, self-paced training increased higher-level cognitive skills more than externally paced training. These results underpin the important role of learning rate in enhancing both resting-state activity and cognitive performance. Our design allowed us to differentiate the effect of learning rate between neurofeedback conditions, and to demonstrate the positive effect of self-paced training on cognitive performance in IUA neurofeedback.

2.1 Introduction

Neurofeedback is a neurocognitive intervention which enables users to regulate their brain activity via a three-step iterative loop: (1) measuring brain activity, (2) processing it and (3) feeding it back to the user. The learning of this regulation relies on the principles of operant conditioning by providing rewarding feedback whenever the user successfully regulated the brain activity and, furthermore, it is conceptualized in the context of control-theoretical models involving neurophysiological processes and the dual-process theory including automated processes (for a review see Enriquez-Geppert et al., 2017). This reinforcement and increase in successful regulation are finally intended to change cognitive and behavioral outcomes, which are related to the targeted brain activity (Enriquez-Geppert et al., 2017). In electroencephalography (EEG) based neurofeedback, training protocols typically target the regulation of frequency bands by decomposing the EEG signal during neurofeedback training.

Many studies have demonstrated the efficacy of neurofeedback to regulate brain activity and, thereby, to modify cognitive performance and behavior in both clinical (Garcia Pimenta et al., 2021) and healthy samples (Escolano et al., 2014; Nan et al., 2012; Navarro Gil et al., 2018). In clinical populations, neurofeedback has been shown to enable patients to regulate their brain activity and thereby to influence their symptoms. For example, in attention deficit hyperactivity disorder (ADHD) the treatment efficacy of neurofeedback was comparable to those of other intervention types and further improved when personalized by selecting the brain activity feature to modulate based on EEG characteristics measured prior to neurofeedback (for a review see Garcia Pimenta et al., 2021). In their review the authors further discussed heightened reward sensitivity in children diagnosed with ADHD as a non-specific factor contributing to the training effect on clinical outcomes (Garcia Pimenta et al., 2021). While neurofeedback applications in clinical populations have focused on restoring cognitive and behavioral functionality, studies with non-clinical samples have concentrated on enhancing cognitive performance. Across varying training protocols, many studies could show cognitive improvements after regulating the alpha frequency range from the EEG spectrum (Gruzelier, 2014). For example, participants performing a single session of individual upper alpha (IUA) neurofeedback over occipitoparietal regions improved their IUA activity during training more than participants receiving sham neurofeedback (Escolano et al., 2014). Furthermore, participants receiving IUA neurofeedback also increased their higher-level cognitive skills measured with part B of the trail making task (TMT) more than participants receiving sham feedback, however, without differences in resting-state activity between the two groups. Even when participants underwent multiple sessions of IUA neurofeedback they did not show an increased IUA activity during a resting-state period compared to a waiting-list control group (Navarro Gil et al., 2018). In addition to enhancing cognitive performance, IUA neurofeedback also led to better short-term memory performance when compared to a non-neurofeedback waiting-list control group (Nan et al., 2012). The evidence from these studies also suggests that the increase in performance positively correlates with an increase in IUA activity (Nan et al., 2012; Navarro Gil et al., 2018).

Notably, the efficacy of neurofeedback varies across participants with some of them not increasing the targeted brain activity at all (Alkoby et al., 2018). While some researchers separate their analyses for participants who were successful in regulating their brain activity, hereafter referred to as “responders,” and for those who were not, hereafter referred to as “non-responders” (Autenrieth et al., 2020; Eschmann et al., 2022; Hsueh et al., 2016), other researchers have investigated the association between learning rate and outcome measures in a continuous manner (Naas et al., 2019; Nan et al., 2012; Navarro Gil et al., 2018). To explain these variations between participants, previous studies have assessed psychological (Thibault et al., 2016) and neurophysiological factors (Scheinost et al., 2014; Zhao et al., 2021) as predictors of improvements in behavioral and neurophysiological outcomes. In terms of neurophysiological factors, previous studies have used both measures of connectivity (Scheinost et al., 2014) and gray matter volume in resting-state fMRI as indicators of learning success (Zhao et al., 2021). For EEG based neurofeedback, researchers have demonstrated in a study in which all participants performed individual alpha band neurofeedback that resting-state relative alpha band power was positively correlated with the learning rate during training (Wan et al., 2014). Regarding psychological factors, researchers have investigated mental strategies participants used to regulate their brain activity (Kober et al., 2013), and the control beliefs participants had while dealing with technology (Witte et al., 2013). Participants reported different strategies after neurofeedback also depending on the targeted frequency band (Kober et al., 2013). For example, after sensory motor rhythm (SMR) based neurofeedback participants who reported not to have used a specific strategy enhanced their SMR activity more than participants reporting a strategy. Hence, up-regulation of SMR activity might depend on implicit associative learning mechanisms (Gruzelier, 2014). Some researchers have thus hypothesized that conscious efforts during neurofeedback interfere with non-conscious learning processes and may in turn decrease the learning rate (Witte et al., 2013). To summarize, both psychological and neurophysiological factors contributed to the overall efficacy of neurofeedback training and the findings suggest that those factors interact with the targeted feature of brain activity and, furthermore, depend on user characteristics.

In alpha neurofeedback the conscious pursuit of mental strategies positively influenced IUA band activity (Naas et al., 2019; Nan et al., 2012) and the individual adjustment of feedback levels yielded a wider range of feedback realized during training (Han et al., 2016). Participants were asked to pursue any mental strategy for a neurofeedback trial, but to stick to it during the trial (Nan et al., 2012). They were allowed to change strategies between trials. Reports gathered after neurofeedback indicated that positive strategies (e.g., thinking about friends) yielded increased activity in the IUA band compared to neutral (e.g., thinking about numbers) or negative strategies (e.g., thinking about accidents) (Nan et al., 2012). To control for non-specific factors, another study extended this methodology to a sham-controlled experiment (Naas et al., 2019). Interestingly, the learning rate was comparable between the groups indicating that appropriate mental strategies may be sufficient to enhance IUA activity. Nevertheless, hitherto no study has investigated the efficacy of mental strategies on IUA neurofeedback performance in a randomized controlled trial. Another approach to increase the efficacy of neurofeedback is focused on individually tailoring the training paradigm. For instance, the peak alpha frequency as a neurophysiological correlate of cognitive processes (Klimesch et al., 1993) enabled the individual adjustment of the targeted frequency range in neurofeedback training paradigms (Gruzelier, 2014). The mental rotation performance increased after stimulating participants with a transmagnetic stimulation frequency based on the individual alpha peak (Klimesch et al., 1993). In alpha neurofeedback studies, both the mental rotation task and TMT performance increased after the session (Escolano et al., 2014; Hanslmayr et al., 2005). Other parameters than the neurophysiological activity at resting-state which allow for individual adaptation include feedback thresholds (Han et al., 2016) and pacing of the training. Self-paced training would grant users more control over the distribution of their training time and allow them to explore mental strategies on their own pace.

The main goal of the current study was to extend previous research by estimating the effect of learning rate on resting-state IUA activity and cognitive performance after a single session of IUA neurofeedback and to investigate the efficacy of control over training to enhance cognitive performance. To give participants control over the neurofeedback training, we allowed some of them to freely distribute their training and rest time during the session, whereas others received neurofeedback in an externally paced manner. Importantly, only the distribution of the rest time varied between conditions keeping the rest, training and overall time constant across all participants. To control for non-specific factors, we included a sham-control condition with the pre-recorded feedback from another participant not further involved in this study. We assessed the mental rotation ability, visual search skills, and higher-level cognitive skills task before and after neurofeedback. To estimate the efficacy of neurofeedback we conducted a series of mixed models analyses taking variations between participants into account.

Based on previous findings, we expected to observe (1) an effect of neurofeedback on relative IUA activity (see section 2.2.8 for more technical details), (2) a transfer effect of neurofeedback and pacing on cognitive outcomes (i.e., a negative effect on changes in error rate and response time), and (3) an association between learning rate during neurofeedback and changes in cognitive outcomes (see Figure 2). We first of all expected to observe a greater increase in IUA activity for participants in the IUA neurofeedback group compared to participants receiving sham neurofeedback after a single neurofeedback session. Additionally, we hypothesized that (2a) all participants increase their cognitive performance from pre to post-neurofeedback due to practice, (2b) participants receiving IUA neurofeedback increase their cognitive performance more than participants receiving sham neurofeedback, (2c) that participants who pace neurofeedback training on their own enhance their cognitive performance more than participants training in an externally paced manner, and (2d) that this pacing effect is more dominant in the real neurofeedback group compared to the sham neurofeedback group. Finally, we expected to observe an effect of neurofeedback learning rates on (3a) cognitive outcomes and (3b) resting-state activity specifically for participants in the real neurofeedback group.

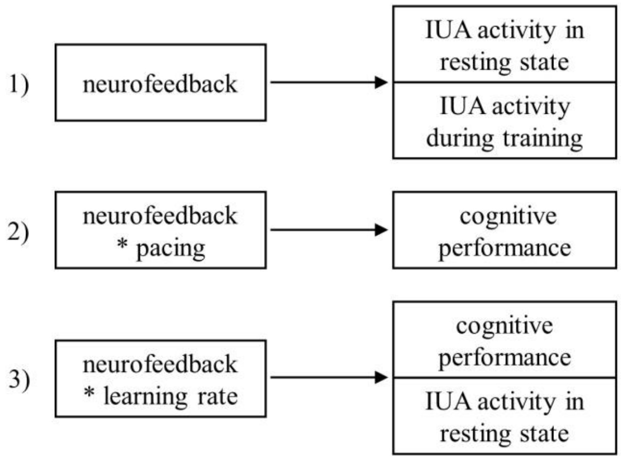

Figure 2. Summary of the hypotheses. The asterisk operator denotes factor crossing.

2.2 Materials and methods

This study followed a sham-controlled, randomized, double-blind design to investigate these factors in enhancing both resting-state relative IUA activity and cognitive performance. As we expected larger differences between IUA and sham neurofeedback than between the two pacing conditions within IUA neurofeedback, we required a larger sample size in both IUA neurofeedback pacing conditions to detect smaller effects. Therefore, we randomly allocated participants on a 2:1 basis to either IUA or sham neurofeedback and subsequently on a 1:1 ratio to either self- or externally paced training using the Fisher-Yates algorithm.

2.2.1 Participants

The sample consisted of N = 60 healthy young adults (42 females, mean age: 24.65 years, age range: 18–35 years) who underwent the same procedure except for type of neurofeedback and the type of pacing. All participants had normal or corrected-to-normal vision.

2.2.2 Mental rotation task

The computerized mental rotation task contained 96 trials and was administered pre- and post-neurofeedback training. Each trial displayed one object pair: a baseline object on the left half of the screen and a target object on the right half of the screen (see Figure 3). The target object was the same as the baseline object (but rotated) for half of the trials and horizontally flipped for the remaining trials. For each participant, time point (pre, post) and rotation angle (0, 50, 100, 150°) we randomly sampled the 3D object pairs without replacement from a stimulus pool (Ganis & Kievit, 2015). Object pairs used for practice trials were excluded from the stimulus pool.

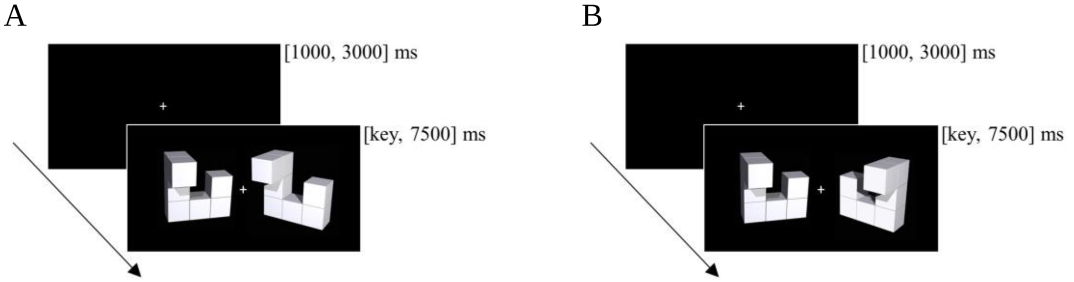

Figure 3. Trial from the mental rotation task. (A) The figure presented right to the fixation cross is the same as the figure on the left (correct response is “Y”). (B) The figure presented right to the fixation cross is not the same as the figure on the left as it is mirrored (correct response is “N”).

All experimental trials started with a fixation cross. An object pair appeared subsequently until participants responded. If participants did not respond within 7500 ms, the next trial continued. The duration of the fixation cross varied randomly between 1000 and 3000 ms to minimize expectancy effects. Participants were instructed to respond as quickly and as accurately as possible by using the “Y” (same, but rotated objects) and the “N” key (horizontally flipped objects).

2.2.3 Trail making test

The TMT consists of two parts: (A) 25 encircled numbers from “1” to “25” and (B) a total of 25 encircled numbers, from “1” to “13,” and letters, from “A” to “L” (Bowie & Harvey, 2006). We administered a paper pencil version and instructed participants to connect the series of circles in ascending order without lifting the pencil from the paper as fast as they can. For part B participants had to alternate between numbers and letters (i.e., 1-A-2-B etc.). Each part started with a practice trial with a total of eight circles to ensure that participants understood and adhered to the instructions. While the completion time for part A measured visual search and motor speed skills, the completion time for part B assessed higher-level cognitive skills including mental flexibility.

2.2.4 EEG recording

The EEG signals were amplified by a BrainAmp system (Brain Products, Gilching, Germany). Its output was digitized with a resolution of 16 bit and sampled at a rate of 1000 Hz via the lab streaming layer protocol. For data acquisition, we mounted a set of 32 Ag/AgCl electrodes according to the 10/20-system and referenced it to FCz. To capture horizontal eye movements, we placed two additional electrodes on the external canthi of both eyes. We kept the impedances below 20 kΩ with the ground and the reference electrode below 5 kΩ throughout the recording.

2.2.5 Neurofeedback

We implemented a neurofeedback software to acquire, process and visualize electrophysiological signals in Python, which will be made available upon reasonable request. Configuration recordings prior to neurofeedback training provided gradient and amplitude artifact detection thresholds calibrated for each participant. A 5-min eyes open resting-state recording prior to the neurofeedback training determined the IUA frequency range (individual alpha peak frequency + 2 Hz) and its related power. We did not disclose successful mental strategies to increase IUA activity to participants before neurofeedback. Some researchers have argued that this reduces the risk of participants enhancing their IUA activity when receiving sham feedback (Naas et al., 2019). Others have pointed out that only the use of mental strategies might increase the targeted brain activity and thus this mental rehearsal should be controlled (Sorger et al., 2019). Nevertheless, the implicitness of some mental strategies complicates the applicability of such a control condition and an explicit instruction might even interfere with the targeted brain activity (Kober et al., 2013). For IUA neurofeedback, we did not find studies experimentally varying the content of mental rehearsal strategies to investigate their efficacy in a randomized controlled trial. For fMRI neurofeedback, studies applying a mental rehearsal control condition typically instructed participants to choose a strategy and to stick to it throughout the session (for a review see Sorger et al., 2019).

During neurofeedback training the IUA band power was averaged across P3, Pz, P4, O1, and O2 (Escolano et al., 2014). The difference of current and resting-state IUA power standardized by the resting-state IUA power standard deviation determined the height of a bar plot. For participants receiving sham feedback we used the same pre-recorded EEG activity. To ensure that the technician carrying out the recording was blinded, he was separated by a mounted wall from the participant and, hence, could not monitor the feedback the participant received. Additionally, the technician only viewed the actual recording presented on the monitor (and not the sham recording). We instructed participants to keep the bar above a line which corresponded to their resting-state IUA power. Whenever the signal exceeded the individually adjusted artifact detection threshold, the word “NOISE” appeared at the center of the screen and the feedback was halted until the signal decreased below the threshold. For online processing, we applied a sliding Fast Fourier Transform performed on a 1 s Hanning window with an overlap of 75% resulting in an update rate of 4 Hz. To increase the frequency resolution to 0.5 Hz, we zero-padded the time windows. To facilitate alpha peak identification and to smooth the spectral data, we additionally applied a Savitzky–Golay filter with window size 11 and polynomial order 2 (Savitzky & Golay, 1964). Participants in the sham condition received the feedback from another participant not involved in the study.

2.2.6 Procedure

Participants took part in individual laboratory sessions at the University of Luxembourg. They received course credits or 20€ in vouchers as reimbursement for the 2 h lasting procedure (see Figure 4). After giving their informed, written consent, all participants completed a questionnaire capturing socio-demographic data. We then administered the TMT (pre-neurofeedback) including practice trials and recorded the completion time. Next, we started the EEG recording and continued with the mental rotation task.

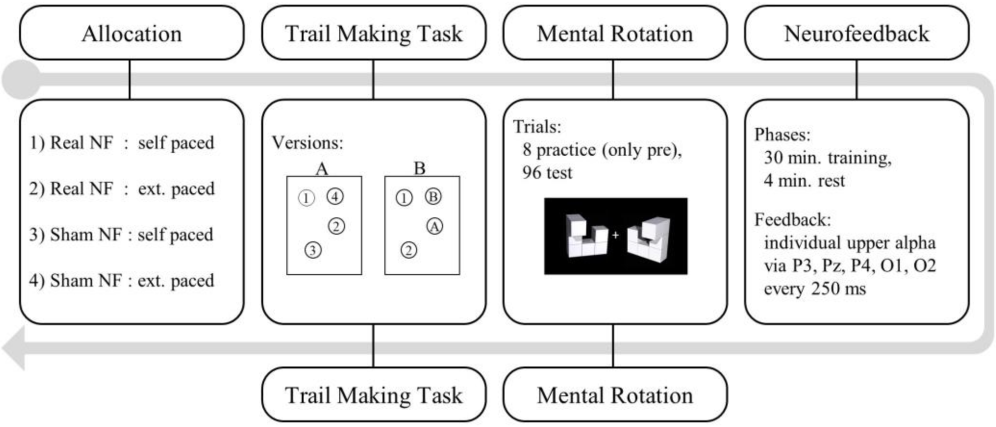

Figure 4. Study procedure: Trial making task (TMT) and mental rotation task were administered pre- and post-neurofeedback.

To prepare the neurofeedback training, we first calibrated the artifact detection thresholds. Therefore, we recorded three epochs of 10 s each prior to which we instructed participants (1) not to blink, (2) to blink, and (3) to activate other facial muscles. Next, we recorded the baseline IUA activity in resting-state. The single session neurofeedback training procedure had a total duration of 34 min (30 min training + 4 min rest). For sham feedback we provided the same pre-recorded feedback to Participants in the self-paced condition distributed the resting minutes themselves whereas for participants in the externally paced condition five training blocks were interspersed with 1 min resting epochs. When self-pacing the training, resting phases immediately followed upon pressing the spacebar. To continue with the training, we instructed participants in the self-paced condition to press the spacebar again. The bar plot reappeared after a delay of 3 s to reduce the impact of muscle activity on the feedback signal. After the training we administered the post-neurofeedback TMT and mental rotation task without any practice trials. Finally, we debriefed all participants about the allocation of some participants to a control condition receiving sham neurofeedback and about our hypotheses.

2.2.7 EEG pre-processing

We used the MNE library version 0.23.0 (Gramfort et al., 2013) in Python version 3.7.3 (Python Software Foundation, DE, USA) to process all EEG data. For each participant we imported the EEG data into the MNE framework and added all required information (e.g., sampling rate, definition of stimulus channels). We analyzed the data separately for resting states and neurofeedback training. In both cases, we first re-referenced the signal to the average for further analysis. For outlier and artifact detection, we then segmented the continuous EEG data into consecutive, non-overlapping epochs with a duration of 10 s each. Next, we identified and treated outliers either by channel interpolation or by epoch removal. For detection, we estimated for each channel and each epoch the strength of high-frequency components by first calculating the power between 70 and 130 Hz, normalizing it by total power and finally applying a log-transformation for a conversion into decibel. We defined a median absolute deviation threshold of 3 to detect outliers. After raw data inspection, we bandpass filtered the remaining EEG signal between 0.2 and 100 Hz with a finite item response filter (FIR) to improve the following independent component analysis (ICA) performance. In detail, we applied a one-pass, non-causal, zero phase, Hamming-windowed FIR filter (lower half-amplitude cut-off = 0.1 Hz, upper half-amplitude cut-off = 112.5 Hz, passband ripple = 0.0194 dB, stopband attenuation = 53 dB). To attenuate line noise, we additionally notch filtered the signal at 50 Hz. We then performed an ICA decomposition with the FastICA algorithm (Hyvärinen & Oja, 2000) to detect and remove components representing eye- and muscle-artifacts. For artifact detection we relied on the visual inspection of each component’s time signal, its power spectral density distribution and its topographical activity. After the artifact cleaning procedure, we applied the ICA solution back on the EEG data and estimated the power spectral density for each epoch. Only for the resting state phases before and after neurofeedback, we averaged the estimates across all epochs.

2.2.8 Statistical analyses

We carried out all statistical analyses in R version 4.1.3 (R Core Team, 2022). To estimate mixed models, we mostly used the lme4 package version 1.1.28 (Bates et al., 2015) but also used the nlme package version 3.1.155 (Pinheiro et al., 2022) to additionally include autoregressive residuals. For hypothesis testing we performed both model comparisons based on the likelihood ratio test and multiple contrast tests. By default, we determined restricted maximum likelihood estimates of model parameters which produce unbiased parameter estimates and are preferred for unbalanced data (Searle & McCulloch, 2001). Exclusively for model comparisons, we estimated model parameters using maximum likelihood. Since we tested some of our hypotheses with multiple contrast tests, we calculated simultaneous confidence intervals at a 95% significance level with the multcomp package version 1.4.19 which control the family wise error rate (Hothorn et al., 2008).

We fitted a series of mixed models to estimate the fixed effect of time (contrast: post = 0.5, pre = −0.5; continuous for within neurofeedback changes), neurofeedback (IUA = 0.5, sham = −0.5), pacing (self = 0.5, external = −0.5) and their interactions on outcome measures. Depending on the nature of the data we either applied linear mixed models (LMMs) or generalized linear mixed models (GLMMs). For both, we first fitted null models only including random effects to estimate the variance explained by level 1 predictors such as participant or angular disparity (exclusively for the mental rotation task). To calculate point-estimates, we then fitted a full model including all fixed effects; and to estimate the contribution of each fixed effect to the overall model fit, we compared a model including the fixed effect of interest to a corresponding reference model without that effect. Finally, we tested our a priori contrasts in the full model including all fixed effects by estimating 95% simultaneous confidence intervals for the specified hypotheses. This procedure corrected the inflated family wise error rate associated with multiple testing. To test our first hypotheses, we evaluated pre vs. post-resting-state and within neurofeedback changes of relative IUA power. For both pre and post-neurofeedback, we calculated the relative IUA power by dividing IUA power by the total power of frequencies up to 49 Hz. Hereby we excluded potential biases due to notch filtering at 50 Hz. For within neurofeedback, we calculated the relative IUA power in the same manner but additionally expressed the change over the 10 s epochs in percentage change from resting-state relative IUA power measured before neurofeedback. To test our second hypotheses, we considered errors and reaction time (only in trials with correct response) for the mental rotation task and completion time for the TMT. For the number of errors, we fitted a GLMM to predict correct and incorrect responses by using a binomial distribution with the logit link function. For both reaction time in the mental rotation task and completion time in the TMT we applied LMMs. Only for the mental rotation task, we additionally included angular disparity as a crossed random effect in the random effects structure to estimate its contribution compared to participants' characteristics. To test our third hypothesis, we fitted linear models predicting participant level averaged change scores with neurofeedback, pace, learning rate and their interactions. We estimated the learning rate for each participant as the slope in a linear model predicting the change in relative IUA power over neurofeedback training epochs.

2.3 Results

We grouped the results section by the administered tasks and begin with the results on the effect of neurofeedback on IUA in resting state activity and IUA activity during neurofeedback training (hypotheses 1 and 3b). Next, we focus on the behavioral outcomes and report the results for the mental rotation task and the TMT. For each task we report both the crossed effects of neurofeedback and pacing and the crossed effects of neurofeedback and learning rate on performance (hypotheses 2 and 3a). For the descriptive statistics of the mental rotation task and the TMT please refer to Tables 1, 2.

Group	**RT**		**Error rate**	
	pre mean (SE)	post mean (SE)	pre mean (SE)	post mean (SE)
Real, self-paced NF (n=19)	7.90 (0.06)	7.71 (0.06)	16.19 (2.18)	12.14 (2.01)
Real, ext.-paced NF (n=20)	7.89 (0.04)	7.67 (0.04)	13.79 (1.45)	10.34 (1.30)
Sham, self-paced NF (n=10)	7.98 (0.07)	7.80 (0.06)	12.58 (2.26)	9.51 (1.57)
Sham, ext.-paced NF (n=10)	8.00 (0.09)	7.79 (0.09)	16.67 (3.79)	11.39 (3.41)

Table 1. Central tendency and variability of the mental rotation task performance measured as reaction time (RT) in log(ms) for trials with correct response and error rate in ratio of incorrect of trials with any response. First, we aggregated the mean of the measures per participant and time point. Then, we aggregated the mean and standard error (SE) of those aggregates. Participants were either allocated to real or sham neurofeedback (NF) and subsequently to either self- or externally-paced (ext.-paced) NF. We excluded one participant from the analyses whose overall error rate was above 80%.

Group	Version A		Version B	
	pre mean (SE)	post mean (SE)	pre mean (SE)	post mean (SE)
Real, self-paced NF (n=20)	3.20 (0.07)	2.91 (0.07)	3.99 (0.07)	3.74 (0.09)
Real, ext.-paced NF (n=19)	3.07 (0.07)	2.82 (0.05)	3.88 (0.07)	3.77 (0.09)
Sham, self-paced NF (n=10)	3.14 (0.12)	2.92 (0.08)	3.89 (0.06)	3.62 (0.09)
Sham, ext.-paced NF (n=10)	3.16 (0.09)	3.01 (0.09)	3.93 (0.06)	3.87 (0.09)

Table 2. Central tendency and variability of the trail making task (TMT) performance measured as completion time in s. We aggregated the mean (and standard error) of completion times per TMT version (A, B) group and time point. Participants were either allocated to real or sham neurofeedback (NF) and subsequently to either self- or externally-paced (ext.-paced) NF. We excluded one participant from the analyses due to non-compliance with the instructions.

2.3.1 Neurofeedback

First, we estimated the interaction effect of time and neurofeedback condition on resting-state relative IUA power in a linear mixed model. To estimate the effect of learning rate, we then calculated the relative IUA power change score for each participant and included the learning rate in a linear model. For the analysis of the learning rate during neurofeedback training, we finally estimated percentage changes from pre-neurofeedback resting-state relative IUA power over 10 s epochs in a series of linear mixed models.

2.3.1.1 Resting-state activity

The null model only including a random intercept for participants revealed that participants’ characteristics explained most of the variance ($\rho = 0.81$) in the relative IUA power measured before and after neurofeedback. A full model including fixed effects for neurofeedback, pacing, time, and their interactions failed to outperform the null model [X2(7) = 12.04, $p = 0.1$]. This suggests that the incorporated fixed factors did not have sufficient explanatory power and we found no support for changes between pre and post-neurofeedback regarding the relative IUA activity. To estimate the link between learning rate and alterations in resting-state activity, we predicted the difference in relative IUA activity measured during resting-state (post–pre) in a linear model including neurofeedback, pacing, learning rate and their interactions as independent variables. As expected, we observed a positive interaction effect for neurofeedback and learning rate [$b = 0.18$, $t(52) = 2.10$, $p < 0.05$] indicating that the link between learning rate and resting-state relative IUA activity was stronger for participants receiving IUA neurofeedback. A follow-up trend analysis revealed that the more participants increased their IUA activity during neurofeedback, the more they increased their relative IUA activity from pre to post-neurofeedback in the resting-state [$b = 0.09$, $t(52) = 2.69$, $p < 0.01$]. These results indicate that the learning rate plays a crucial role in alternating resting-state activity.

2.3.1.2 Training activity

To investigate changes during neurofeedback, we estimated parameters of a multilevel growth model including time as a continuous predictor. The time variable represented the ith epoch where each epoch contained 10 s of EEG data during the training phases (the relative IUA power of which we predicted in our models). During pre-processing of the EEG data, we excluded 144 epochs due to artifacts resulting in a total of 10656 remaining epochs. We defined three models (1) a null model with a random intercept for participants, (2) an intermediate model additionally including fixed effects for neurofeedback, pacing, time, and their interaction, and (3) a full model with an additional first order autoregressive, AR(1), within-participant residual. The null model revealed a sufficient intraclass correlation ($\rho = 0.28$) indicating the adequateness of applying a multilevel model. Our intermediate model outperformed the null model [X2(7) = 181.31, $p < 0.001$] but out of the three competing models the final model fitted the data best [X2(1) = 548.33, $p < 0.001$]. As expected, model comparisons to estimate the contribution of each fixed effect revealed a positive main effect for time and a positive interaction effect for time and neurofeedback (see Table 3). After correction for multiple tests by estimating one-sided lower bounds of simultaneous confidence intervals with a 95% family wise confidence level both the main and the interaction effect remained significant. This suggests that although all participants increased their relative IUA power over time, participants in the real neurofeedback group improved their relative IUA power more than participants in the sham neurofeedback group.

Fixed effects				
	***B* (SE)**	**Likelihood ratio test**		**95% SCI-LB**
		$X^2(1)$	*p*	
Intercept	84.191 (3.867)	-	-	-
Neurofeedback	-2.497 (7.734)	0.186	.67	-
Pacing	-0.367 (7.734)	0.171	.68	-
Time	0.093 (0.011)	100.441	< .001	0.070
Neurofeedback x pacing	-18.117 (15.467)	1.292	.26	-
Neurofeedback x time	0.064 (0.022)	8.557	< .01	0.017
Pacing x time	0.003 (0.022)	0.059	.81	-
Neurofeedback x pacing x time	0.011 (0.043)	0.068	.79	-0.081
Random effects				
	***σ*²**		**phi**	
Participant (intercept)	728.195		-	
Residual	1921.776		-	
Time x participant	-		.226	

Table 3. GLMM for percentage changes in relative IUA power over neurofeedback training epochs. The unstandardized estimates (B) and their standard error (SE) listed for each fixed effect, variance (σ^2) and auto-correlation (phi) for random effects incorporated in the full model. For completeness, likelihood ratio test result is reported for each fixed effect by comparing a model including the effect to a corresponding reduced model. For final multiple contrast tests, we relied on the lower bound of one sided 95% simultaneous confidence intervals (95% SCI-LB).

A follow-up trend analysis showed that the slope for participants receiving IUA neurofeedback [b = 0.13, t(10592) = 9.98, p < 0.001] was twice as high as the slope for participants receiving sham neurofeedback [b = 0.06, t(10592) = 3.44, p < 0.001]. While participants in the IUA neurofeedback condition increased their relative

IUA power by 22.48% over the 180 10 s epochs during training, participants in the sham neurofeedback condition increased their relative IUA power only by 11.02%.

2.3.2 Mental rotation task

We fitted a series of models to estimate the effects of neurofeedback and pacing on changes in mental rotation task performance (i.e., reaction time and errors). From the 11520 trials (192 per participant) we excluded trials from one participant whose overall accuracy during the mental rotation task was below 20% and all trails without a response yielding the remaining 11169 trials. Only for reaction time analysis we additionally excluded trials with incorrect responses after which 9732 trials remained. The central tendency and variability of the outcome measures aggregated over participants and across time (i.e., pre and post) were comparable to results from the validation study (Ganis & Kievit, 2015). As expected, error rates and reaction times increased with angular disparity (see Table 4). To test our hypotheses, we first fitted null models with crossed random intercepts for participant and angular disparity to predict the respective outcome measure. Then, we estimated linear mixed models including the crossed random effects from the null model and the fixed effects for neurofeedback, pacing, time, and their interactions. Finally, we estimated a linear model including individual learning rates during neurofeedback to predict change scores (post–pre) in outcome measures.

Angle	**RT**	**Error rate**
	Mean (SE)	Mean (SE)
0°	2072.03 (72.07)	6.25 (0.99)
50°	2693.48 (87.24)	9.29 (0.92)
100°	3306.65 (94.15)	15.20 (1.32)
150°	3456.22 (95.94)	20.97 (1.46)

Table 4. Central tendency and variability of mental rotation task performance per angle measured as reaction time (RT) in ms for trials with correct response and error rate in percentage incorrect of trials with response. We aggregated both measures over participants and across time points (i.e., pre and post neurofeedback).

2.3.2.1 Response errors

The estimation of the null model revealed a similar intraclass correlation for participants' characteristics ($\rho = 0.10$) as for the angular disparity of the stimulus itself ($\rho = 0.08$). Comparisons with the likelihood ratio test estimating the explanatory contribution of each fixed effect revealed a negative main effect for time (see Table 5). Hence, the error rate decreased from pre to post-neurofeedback training independent of the neurofeedback condition participants were assigned to. To test our a priori contrasts, we then estimated one-sided 95% simultaneous confidence intervals. The main effect for time remained significant after correcting the inflated family wise error rate. There was no other main effect indicating that the overall error rate was similar across different conditions. Furthermore, the difference in the change of error rate (post vs. pre) between neurofeedback conditions (IUA vs. sham) was negligible. Similarly, we found no three-way interaction effect of time, pacing and neurofeedback.

To account for individual learning rates during neurofeedback, we additionally estimated a linear model predicting the change scores of error rate with neurofeedback, pacing, learning rate and their interactions as independent variables. Therefore, we aggregated the difference in number of incorrect responses (post–pre) for each participant over all trials. The model showed a positive interaction effect for neurofeedback and learning rate indicating that the linear relationship between error rate and learning rate was more negative for participants receiving IUA neurofeedback than for participants receiving sham neurofeedback [$b = -17.97$, $t(51) = -1.73$, $p < 0.05$]. To investigate whether the linear relationship between the error rate and the learning rate was significantly less than zero for participants in the real neurofeedback group, we performed a follow-up trend analysis. This revealed that the more participants in the IUA neurofeedback condition increased their relative IUA power during neurofeedback the less errors they made in the mental rotation task [$b = -7.36$, $t(51) = 1.85$, $p < 0.05$]. To conclude, the effect of learning rate on reductions in errors differed between the neurofeedback groups with a stronger negative linear relationship for the real than for the sham neurofeedback group.

Fixed effects				
	***B* (SE)**	**Likelihood ratio test**		**95% SCI-UB**
		$X^2(1)$	*p*	
Intercept	-2.179 (0.296)	-	-	-
Neurofeedback	0.068 (0.189)	0.103	.75	-
Pacing	-0.049 (0.189)	0	1	-
Time	-0.392 (0.063)	41.808	< .001	-0.250
Neurofeedback x pacing	0.320 (0.378)	0.760	.38	-
Neurofeedback x time	0.062 (0.127)	0.271	.60	0.346
Pacing x time	0.076 (0.127)	0.129	.72	0.359
Neurofeedback x pacing x time	-0.184 (0.253)	0.517	.47	0.383
Random effects				
				σ^2
Participant (intercept)				0.413
Angular disparity (intercept)				0.314
Residual				3.290

Table 5. GLMM for errors in the mental rotation task. The unstandardized estimates (B) and their standard error (SE) listed for each fixed effect incorporated in the full model. For completeness, likelihood ratio test result is reported for each fixed effect by comparing a model including the effect to a corresponding reduced model. For final multiple contrast tests, we relied on the lower bound of one sided 95% simultaneous confidence intervals (95% SCI-LB).

2.3.2.2 Reaction time

To reduce the skewness of the distribution, we first log-transformed reaction times. The null model revealed that the variance between participants was greater than the variance between angles. Hence, the logarithmic reaction times depended more on participant’s characteristics than on angular disparity. Like the full model predicting errors, we only found a main effect for time suggesting that all participants reduced their reaction time from pre to post-neurofeedback (see Table 6). However, the groups did not differ in their reduction of reaction time.

Fixed effects				
	B **(SE)**	**Likelihood ratio test**		**95% SCI-UB**
		$X^2(1)$	*p*	
Intercept	7.857 (0.134)	-	-	-
Neurofeedback	-0.097 (0.062)	2.525	.112	-
Pacing	0.014 (0.062)	0.120	.740	-
Time	-0.204 (0.009)	632.731	< .001	-0.185
Neurofeedback x pacing	0.031 (0.124)	0.066	.797	-
Neurofeedback x time	-0.016 (0.017)	0.905	.341	0.022
Pacing x time	0.030 (0.017)	4.054	.044	0.068
Neurofeedback x pacing x time	0.016 (0.034)	0.208	.648	0.092
Random effects				
				$\boldsymbol{\sigma^2}$
Participant (intercept)				0.050
Angular disparity (intercept)				0.068
Residual				0.159

Table 6. LMM for log reaction time in the mental rotation task. The unstandardized estimates (B) and their standard error (SE) listed for each fixed effect incorporated in the full model. For completeness, likelihood ratio test result is reported for each fixed effect by comparing a model including the effect to a corresponding reduced model. For final multiple contrast tests, we relied on the upper bound of one sided 95% simultaneous confidence intervals (95% SCI-UB).

When incorporating learning rates into a linear model to predict change scores of logarithmic reaction time (post–pre) we found a negative interaction effect between neurofeedback and learning rate [$b = -1373.45$, $t(51) = -1.94$, $p < 0.05$]. This suggests that the linear relation between learning rate and changes in reaction time was more negative for IUA neurofeedback. A follow-up trend analysis did not show that the linear relationship was significantly lower than zero for the real neurofeedback group [$b = -71.35$, $t(51) = -0.26$, $p = 0.40$]. In conclusion, the difference in the linear link between learning rate and reaction time was more driven by participants in the sham neurofeedback group who responded slower with increasing learning rate than by participants in the real neurofeedback group who responded faster with increasing learning rate.

2.3.3 Trail making test

To estimate the effects of neurofeedback and pacing on TMT completion time, we fitted a series of models analogously to the analyses of mental rotation task performance. We excluded one participant from our analyses due to non-compliance and ran the models separately for part A and B of the TMT. To reduce the skewness of the completion time distribution, we log-transformed the outcome measure before we fitted the models. First, we fitted a null model with a random intercept for participants. Next, we estimated the full linear mixed models including the fixed effects for neurofeedback, pacing, time, and their interactions.

2.3.3.1 Part A

The ICC of the null model was high and confirmed the adequateness of a mixed model because 67.7% of the variance in logarithmic completion time was explained by participants' characteristics. Our model comparisons estimating the contribution of each fixed effect showed a negative main effect for time (see Table 7). This effect remained significant after adjusting for the family wise error. Hence, all participants, irrespective of their group, reduced their logarithmic completion time from pre to post-neurofeedback. The interaction effect of neurofeedback and time as well as the interaction effect of pacing and time were negative but failed to reach significance. When taking the learning rate into account to predict change scores (post–pre) of logarithmic completion time, we did not observe the expected negative interaction between neurofeedback and learning rate. These results suggest that there was no other effect on logarithmic completion time in part A of the TMT except for the practice effect.

Fixed effects				
	***B* (SE)**	**Likelihood ratio test**		**95% SCI-UB**
		$X^2(1)$	p	
Intercept	3.030 (0.038)	-	-	-
Neurofeedback	-0.057 (0.076)	0.578	.447	-
Pacing	0.025 (0.076)	0.527	.468	-
Time	-0.229 (0.030)	48.590	< .001	-0.162
Neurofeedback x pacing	0.165 (0.152)	1.250	.264	-
Neurofeedback x time	-0.077 (0.059)	1.754	.185	0.056
Pacing x time	-0.056 (0.059)	0.824	.364	0.077
Neurofeedback x pacing x time	0.037 (0.119)	0.104	.747	0.303
Random effects				
				σ^2
Participant (intercept)				0.064
Residual				0.023

Table 7. LMM for log completion time in part A of the trail making task. The unstandardized estimates (B) and their standard error (SE) listed for each fixed effect incorporated in the full model. For completeness, likelihood ratio test result is reported for each fixed effect by comparing a model including the effect to a corresponding reduced model. For final multiple contrast tests, we relied on the upper bound of one sided 95% simultaneous confidence intervals (95% SCI-UB).

2.3.3.2 Part B

For part B of the TMT the logarithmic completion times varied substantially between participants within the null model ($\rho = 0.55$). In line with findings for part A, model comparisons showed a negative main effect for time indicating that all participants reduced their logarithmic completion time from pre to post-neurofeedback (see Table 8). Furthermore, the comparisons revealed a negative interaction effect for pacing and time. This suggests that participants in the self-paced group reduced their logarithmic completion time more than participants in the externally paced groups. Both the main effect for time and the negative interaction effect for pacing and time remained significant after adjusting for the family wise error rate with the estimation of simultaneous confidence intervals. Similar to part A, a linear model including the learning rates did not show the expected interaction effect of neurofeedback and learning rate on logarithmic completion time.

Fixed effects				
	B **(SE)**	**Likelihood ratio test**		**95% SCI-UB**
		$X^2(1)$	*p*	
Intercept	3.835 (0.039)	-	-	-
Neurofeedback	0.021 (0.079)	0.078	.780	-
Pacing	-0.051 (0.079)	0.082	.775	-
Time	-0.170 (0.039)	18.577	< .001	-0.084
Neurofeedback x pacing	0.187 (0.157)	1.497	.221	-
Neurofeedback x time	-0.009 (0.077)	0.014	.905	0.164
Pacing x time	-0.176 (0.077)	5.189	.023	-0.002
Neurofeedback x pacing x time	0.065 (0.155)	0.188	.665	0.411
Random effects				
				σ^2
Participant (intercept)				0.062
Residual				0.040

Table 8. LMM for log completion time in part B of the trail making task. The unstandardized estimates (B) and their standard error (SE) listed for each fixed effect incorporated in the full model. For completeness, likelihood ratio test result is reported for each fixed effect by comparing a model including the effect to a corresponding reduced model. For final multiple contrast tests, we relied on the upper bound of one sided 95% simultaneous confidence intervals (95% SCI-UB).

2.4 Discussion

We designed this study to investigate the effects of learning rate and control over training on cognitive performance and electrocortical activity. We randomly assigned participants either to IUA or sham neurofeedback and subsequently to a self- or externally paced single training session using a double-blind design. Before and after neurofeedback all participants performed the mental rotation task and the TMT to measure changes in neurocognitive performance. In line with previous research, we expected that (1) IUA neurofeedback increases IUA activity more than sham neurofeedback. Additionally, we hypothesized that, (2) IUA neurofeedback and self-paced training increase the performance in behavioral tasks to a greater extent than sham neurofeedback and externally paced training. Finally, we expected that, and (3) the neurofeedback learning rate relates to performance increase within the real neurofeedback group. To test these hypotheses, we fitted a series of mixed models and tested the fixed effects with a priori contrasts.

We first expected to observe an effect of neurofeedback on relative IUA activity and our analyses demonstrated that participants receiving real neurofeedback increased their IUA activity during training by more than twice as much as participants receiving sham neurofeedback. Regarding resting state IUA activity measured before and after neurofeedback training, we did not find any group differences. This is in line with previous work usually showing differences during training but not in resting-state activity (Escolano et al., 2014). Even studies applying IUA neurofeedback for multiple sessions, did not find changes in resting-state activity between the experimental and a control group (Nan et al., 2012; Navarro Gil et al., 2018). Therefore, it seems unlikely that repeated sessions per se would have yielded more pronounced group differences in resting-state activity. More research is needed to specify how changes in brain activity during training relate to behavioral changes measured after the training. One potential explanation is that resting-state alterations depend on the magnitude of IUA power change achieved during neurofeedback (Wan et al., 2014). Our results emphasize the importance of the magnitude of change (i.e., learning rate) to increase the targeted brain activity in resting-state. The more participants increased their IUA activity during neurofeedback, the more they increased their resting-state IUA activity. As an extension of previous findings, we additionally controlled for non-specific factors by comparing this association between the IUA neurofeedback group and a control group receiving sham neurofeedback. This comparison revealed that the positive linear relationship between learning rate and resting-state activity was specific to the real neurofeedback group indicating that participants receiving sham neurofeedback did not increase their IUA activity sufficiently to yield measurable changes when in resting-state. Another potential explanation is that different processes are involved for increased IUA activity through sham feedback compared to real feedback. Nevertheless, future studies applying IUA based neurofeedback should take the learning rate during training as a predictor of differences in resting-state activity into account.

Both the increase in IUA activity from pre-neurofeedback resting-state IUA observed during neurofeedback and during resting-state after neurofeedback are crucial determinants of plasticity induction (Ros et al., 2014). Therefore, we further investigated whether these induced alterations in electrocortical activity transferred to improvements in cognitive performance. Nevertheless, neither for the mental rotation task nor for the TMT were there performance differences between participants receiving IUA neurofeedback and participants receiving sham neurofeedback regarding their improvements from pre to post-training. This finding is in line with the results from another study in which researchers did not observe a significant difference in improvements in mental rotation task performance between those groups after a single session of IUA neurofeedback (Escolano et al., 2014). In contrast to our results, however, the real neurofeedback group decreased their completion time in part B of the TMT more than the sham neurofeedback group. As for changes in electrocortical activity one could argue that a single session of neurofeedback training was not sufficient to yield large improvement differences in cognitive performance between real and sham neurofeedback. In another study with 20 sessions of IUA neurofeedback participants receiving real neurofeedback improved their short-term memory performance more than the control group (Navarro Gil et al., 2018). Importantly, the researchers reported a strong correlation ($r > 0.5$) between the increase in IUA activity from the first to the last session and the increase in short-term memory performance. However, they compared the effects of real neurofeedback to a waitlist control condition which does not rule out non-specific effects and thus might exaggerate the efficacy of IUA neurofeedback (Sorger et al., 2019). We applied a double-blind, sham-controlled design to minimize non-specific effects and our results support the notion of a correlation between the magnitude of change in IUA activity and an increase in cognitive performance. Compared to sham neurofeedback, participants receiving real neurofeedback showed a more positive association between performance gains in the mental rotation task and learning rate. This association, however, was absent in the TMT following the mental rotation task. Compared to the mental rotation task where we administered 96 trials before and after neurofeedback, the TMT consisted of only two parts. Hence, change scores based on the TMT yield less accurate estimates than change scores based on mental rotation task scores which we aggregated for each participant. In summary, our results did not demonstrate an enhanced performance increase under IUA neurofeedback compared to sham neurofeedback, but our results indicate an important role for learning rate for explaining changes in behavioral outcomes.

One of our objectives was to investigate whether self-paced training improved cognitive performance more than externally paced training. As indicated by the positive link between mental strategies and IUA activity as well as the links between self-paced activities and executive functions (Holgado & Sanabria, 2021), we expected to observe increased performance gains for participants self-pacing their training. Our results support this hypothesis demonstrating that self-paced training increased higher-level cognitive skills more than externally paced training. However, the effect of pacing was comparable between IUA and sham neurofeedback indicating that there was no synergistic effect of the combination of IUA neurofeedback and self-paced training. Furthermore, we only found a pacing effect in part B of the TMT which may be explained by the relatively fast completion times in part A implying a ceiling effect. In the mental rotation task, participants who self-paced their training did not improve their performance more than participants receiving externally paced training indicating a task-dependent effect. One conceptual difference between the TMT and the mental rotation task is the degree of self-pacing involved. While participants were not limited in their completion time for the TMT and were allowed to connect the circles at their own pace, we imposed a time limit of 7.5 s per trial in the mental rotation task yielding an externally paced trial procedure if participants did not respond. Furthermore, participants could not influence the presentation duration of the fixation cross throughout the mental rotation task limiting the extent of self-pacing. Future studies are needed to investigate the association of self-pacing involved in both training and cognitive tasks. One way to assess the involvement of conscious and automated processes in self-paced activity would be asking participants to report strategies on how they distributed their rest time during neurofeedback.

Finally, our study has some important limitations regarding the validity of IUA activity as a predictor of resting-state activity and cognitive performance. We designed our neurofeedback procedure to enhance IUA activity during training and based our assumption that this increases cognitive performance on previous studies. Nevertheless, we did not assess whether participants' IUA activity was a valid indicator of performance in the mental rotation task or the TMT. Furthermore, we did not estimate the change in other frequency bands close to the IUA band, which may have contributed more to the changes in cognitive performance and resting-state activity. Future studies are required to assess the validity of the targeted frequency band to increase a related cognitive function. One approach would be to extract features of neurophysiological signals based on their correlation with cognitive processes to increase the specificity of neurofeedback training and take individual variations into account (Enriquez-Geppert et al., 2017).

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CHAPTER 3

Person-specific neural correlates of mental rotation

In the previous chapter we demonstrated the validity of our implemented neurofeedback system for inducing changes to the specified neural feature and, further, the impact of having control over training-pace during neurofeedback on higher cognitive functions. As another potential parameter for neurofeedback optimization, we focus in this chapter on inter-individual differences in neural correlates of mental rotation. Therefore, we applied a machine learning approach in which we individually trained regression models to predict the time of correct responses in a mental rotation task based on preceding neural activity. This manuscript was presented in form of a poster at the 45th annual international conference of the IEEE Engineering in Medicine and Biology Society in Sydney (Australia) and is currently under review in the journal PLOS ONE (https://doi.org/10.1101/2023.07.12.548729).

Abstract

Using neurophysiological measures to model how the brain performs complex cognitive processes such as mental rotation is a promising way towards precise predictions of behavioral responses. Up until now, research on neural correlates of mental rotation largely focused on group analyses yielding models with features common across people. Here, we propose an individually tailored machine learning approach to identify person-specific patterns of neural activity during mental rotation. Therefore, we trained ridge regressions to predict the reaction time of correct responses in a mental rotation task using task-related electrocortical activity of the same person. When tested on independent data of the same person, the ridge regression predicted the reaction times more accurately than when only the average reaction time was used for prediction. When tested on another person's data, the predictions were less accurate compared to within-person predictions. Further analyses revealed that considering person-specific reaction time and topographical activity patterns substantially improved a model's generalizability. Our results indicate that a more individualized approach towards neural correlates can improve their predictive performance of behavioral responses, particularly when combined with machine learning.

3.1 Introduction

Neural correlates quantify the relationship between neurophysiological properties and behavioral variables. Many studies have investigated the neural underpinnings of mental rotation. The mental rotation task has frequently been used to invoke complex cognitive processes including visuospatial representations and visual working memory. Neuroscience techniques such as positron emission tomography (PET scan), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG) have provided insights into task-ongoing brain activity (Veldema et al., 2021). They have consistently revealed an increased bilateral activity in several cortical areas including posterior parietal and frontal regions when performing mental rotations (Zacks, 2008). More recent findings suggest that further differentiation of activation patterns based on stimulus characteristics such as angular disparity (Gogos et al., 2010) and whether or not body parts were represented (Tomasino & Gremese, 2016) could benefit the identification of neural activity important for spatial manipulation. Additionally, the dorsal frontoparietal network was proposed as a neural substrate connecting motor and cognitive processes (Ptak et al., 2017). These investigations based on PET scans and fMRI yielded insights regarding the localization of neural processes but to a lesser degree about when the processing occurred. To extend these findings, studies recording task-ongoing EEG activity to capture temporal dynamics have revealed oscillatory activities involved in mental rotation and notably demonstrated the suppression of alpha (8–13 Hz) and beta (13–22 Hz) oscillatory activity with increasing demands for cognitive processing (i.e., event-related desynchronization – ERD; Boiten et al., 1992; Ozga et al., 2019). This body of findings indicates that mental rotation invokes consistent changes in neurophysiological activity which are stable across participants.

Furthermore, mental rotation performance and corresponding activity of its neural correlates changed in the presence of clinical deficits (Veldema et al., 2021). Compared to healthy participants, patients suffering from a major depressive disorder showed a reduced mental rotation performance (Chen et al., 2014). Additionally, the performance decreased proportionally to an increase in depressive symptom severity (Oshiyama et al., 2018). In schizophrenia, an increase in mental imagery accompanied enhanced visuospatial imagery but did not reliably translate to mental rotation task performance with some studies observing an increase and others a decrease in performance (Agarwal et al., 2015; Thakkar & Park, 2012). After bilateral stroke damaging the posterior parietal cortex, patients often showed impairments in visuospatial attention and own body awareness (Whitlock, 2017). In attention-deficit hyperactivity disorder, transcranial direct current stimulation demonstrated that increasing cortical excitability in the right posterior parietal cortex improved the attentional orienting network compared to a sham control (Salehinejad et al., 2019, 2020). To sum up, mental rotation in the clinical population is found altered and the identification of neural substrates represents a promising approach for neurophysiological stimulation studies to finally restore impaired behavioral functionality.

Since early neurophysiological studies which observed behavioral changes after brain injuries researchers have applied various approaches to assess neural underpinnings of behavior (Savoy, 2001). One approach to investigate the neurophysiological basis of cognitive performance involved the identification of differences in neurophysiological properties for individuals with superior and for those with inferior performance: the neural efficiency hypothesis emerged stating that for identical task demands individuals requiring less neural resources outperform those requiring more resources (Haier et al., 1992; Neubauer & Fink, 2009). To classify participants into a binary performance representation, applied methods included (a) the median split where the classification is based on the relative position of a participant’s task performance to the median performance derived from all participants and (b) contrasting neurophysiological activity between the participants with the highest and lowest performances (Haier et al., 1992; Kosslyn et al., 1996; Rypma et al., 2006). Another approach to extract neural correlates was realized by investigating the continuous association between behavior and neurophysiological phenomena. Quantifying the link between neural activity and cognitive performance in a continuous manner revealed for instance that less ERD in alpha oscillatory activity was related to faster mental rotation (Riečanský & Katina, 2010). Furthermore, machine learning approaches modelling behavioral responses as a function of preceding EEG frequency band activity achieved a mean absolute error between 100 and 600 ms (Binias et al., 2020; Rahman et al., 2022). The overwhelming majority of the studies investigating neural correlates commonly assumed the feasibility to estimate generalizable associations between brain activity patterns and some task performance which were stable across participants (Porter et al., 2023).

In a recent application of advanced algorithms for extracting neural activity patterns of mental states, researchers have extended previous approaches by making generalizable predictions on an individual level (Porter et al., 2023). When training individual models to classify mental states based on fMRI recordings, they found person-specific features accurately identifying brain states. To be specific, they demonstrated that the accuracy decreased when classifying brain states using a model trained on the fMRI data from another person. For EEG studies, algorithms to identify associations between electrocortical activity and behavioral measures included the supervised spatial filtering methods Common Spatial Patterns (CSP) and Source POwer Comodulation (SPoC; Dähne et al., 2014) which allow to obtain individual linear combinations of multi-channel EEG and magnetoencephalography recordings that have an increased signal to noise ratio compared to the original channels. As a common pre-processing step, frequency filter banks decomposed the EEG signals into defined frequency bands (Ang et al., 2008; Blanco-Diaz et al., 2022). While CSP addresses classification problems, SPoC extends this approach to continuous labels. For example, individual spatial filters resulting from SPoC related oscillatory rhythms to motor task performance in a continuous manner (Dähne et al., 2014; Meinel et al., 2015). These approaches took person-specific characteristics into account and notably increased the generalizability of predictions by carefully avoiding overfitting.

In this paper we present a machine learning approach to extract person-specific neural correlates of mental rotation. Therefore, we recorded the EEG activity in eyes-open resting state and when performing the mental rotation task with varying difficulty levels (i.e., angular disparity). We then removed artifacts and extracted EEG features preceding correct responses in the mental rotation task. To quantify the relationship between EEG features and reaction time (of correct responses), we trained a ridge regression model and finally evaluated its performance based on data not used for training (i.e., the hold-out set). For feature importance, we estimated SHapley Additive exPlanations (SHAP) values (Lundberg & Lee, 2017) in the hold-out set and thereby measured the contribution of each feature to the final prediction. Finally, we discuss the relevance and the limitations of our findings for application in personalized neurophysiological interventions.

3.2 Materials and methods

3.2.1 Participants

We collected the data in the context of a larger study for which we invited 40 participants each to a single 2-hour laboratory assessment at the University of Luxembourg. To approximate a homogenous sample regarding visuo-spatial working memory performance, participants had to be between 18 and 35 years of age, have normal or corrected-to-normal vision and have no history of psychiatric or neurological illnesses in order to be eligible to participate (Kronovsek et al., 2021). The Ethics Review Panel of the University of Luxembourg approved the study and all participants gave their written informed consent prior to participation (ERP 20-068). For reimbursement, participants received gift vouchers worth 10€ per hour.

3.2.2 Mental Rotation Task

As part of the study, we assessed the performance of participants in a computerized mental rotation task with a total of 192 trials (Ganis & Kievit, 2015). We will make the implementation of the mental rotation task available upon reasonable request. Each trial consisted of (1) a fixation cross which appeared on the center of the screen for a random duration between 1000 ms and 3000 ms, and (2) the two three-dimensional (3D) figures which appeared either until a response was given or for a maximum duration of 7500 ms. We used the lab-streaming layer (LSL; see section 3.2.3) to synchronize markers defining the onset of a new phase or event (i.e., fixation cross, 3D figures, response) with the EEG stream. The two figures could depict either mirrored or unmirrored 3D objects with varying degrees of angular disparity. We instructed participants to press the “Y” key on a QWERTZ keyboard whenever the presented 3D figures were unmirrored (i.e., rotationally invariant) and to press the “N” key otherwise (i.e., when the 3D figures were mirrored). For each participant we randomly sampled without replacement 192 object pairs out of a pool with a total of 384 object pairs and stratified the sampling by angular disparity (i.e., 0°, 50°, 100°, and 150°) and by rotational invariance (i.e., mirrored, unmirrored). We instructed participants to choose a strategy for responding (i.e., either slower and more accurate or faster and less accurate) and to stick to it throughout the task.

3.2.3 EEG recording

To capture electrocortical activity we mounted 32 Ag/AgCl electrodes according to the 10/20 system on the participants' head and referenced them to FCz. A BrainAmp system then amplified and digitized the signals with a resolution of 16 bit and a sampling rate of 1 kHz (Brain Products, Gilching, Germany). To stream the data and to synchronize input timestamps from other sources (e.g., keyboard, stimuli) we used the lab streaming layer protocol (Kothe, 2014). We then accessed the lab streaming layer from within Python 3.7.3 (Rossum & Drake, 2009) using the PyLSL library version 1.14.0 (Kothe, 2014). We implemented custom scripts based on the MNE library version 0.23.0 (Gramfort et al., 2013) for offline EEG processing and used SciPy library version 1.7.3 (Virtanen et al., 2020) for machine learning. Prior to the EEG recording in the mental rotation task, we recorded a 1-minute, eyes-open, resting-state segment prior to which we instructed participants to horizontally move their eyes in the first 5 seconds.

3.2.4 Data analysis

We trained a ridge regression model to predict the reaction time of correct responses in the mental rotation task based on features extracted from the EEG data (see section 3.2.4.3) prior to the response. First, we pre-processed the EEG data which involved removal of artifacts, bandpass filtering, the epoching of the continuous EEG signal and the removal of epochs with a duration of less than 700 ms. We then split the remaining data chronologically into a training set (consisting of the first 75% of epochs) and a hold-out set (with the remaining 25% of epochs). Based on the training data we performed a 3-fold sliding window cross-validation to optimize the regularization intensity lambda. Finally, we trained our model with the specified lambda using all training data and evaluated its generalizability on the hold-out set. For model interpretation we relied on SHAP values.

3.2.4.1 Pre-processing

Based on the one-minute resting-state recording we identified independent components, which contain artifacts (e.g., muscular activity, eye movements). Prior to training the fastICA implementation of the MNE toolbox, we applied a high-pass filter at 1 Hz (Hyvärinen & Oja, 2000; Winkler et al., 2015). After visually inspecting the components’ topographical activities, power spectral densities and time courses, we removed components representing artifacts. Using the spatial filters obtained based on the resting-state recording, this recording but also the EEG signals obtained during the mental rotation task could be cleaned by first zeroing out the corresponding columns in the unmixing matrix before applying the final unmixing matrix back to the raw, unfiltered EEG signals.

To prepare the extraction of bandpower features from the cleaned EEG signals, we applied ten non-overlapping, consecutive frequency filters (width: 4 Hz) that extracted the central frequencies at [2, 6, 10, 14, 18, 22, 26, 30, 34] Hz (Ang et al., 2008; Planke et al., 2021). Markers defining the start and end of each presentation phase in the mental rotation task yielded a total of 384 epochs (i.e., 192 epochs with a fixation cross presentation and 192 epochs with 3D figures presented). From these epochs we removed those during which (a) the fixation cross appeared, (b) the given response was incorrect, and finally (c) not sufficient amount of data was recorded. After (a) and (b) we removed the final 200 ms from each of the remaining epochs to reduce the impact of motor preparation. As the application of SPoC to extract spatial filters required epochs of equal size, we exclusively kept the initial 500 ms from each epoch and removed epochs with less data available. This procedure yielded on average across all participants 163 epochs (min = 105, max = 186 epochs) with 5000 x 32 samples per epoch.

3.2.4.2 Cross-validation

To calibrate the regularization parameter lambda towards minimization of the mean absolute error (MAE) for unseen data, we performed a chronological sliding window cross-validation procedure based on the first 75% of the available epochs (see Figure 5). Candidate values for lambda were exponentially spaced between 10^{-1} and 10^{3} with each of which we trained and evaluated the model in all windows. In each window we trained the model with the initial 55% of epochs and evaluated its performance with the remaining 45% of epochs. For each lambda we stored the average of all three windows' MAE. Finally, the value for lambda with the lowest average MAE score was chosen for further processing.

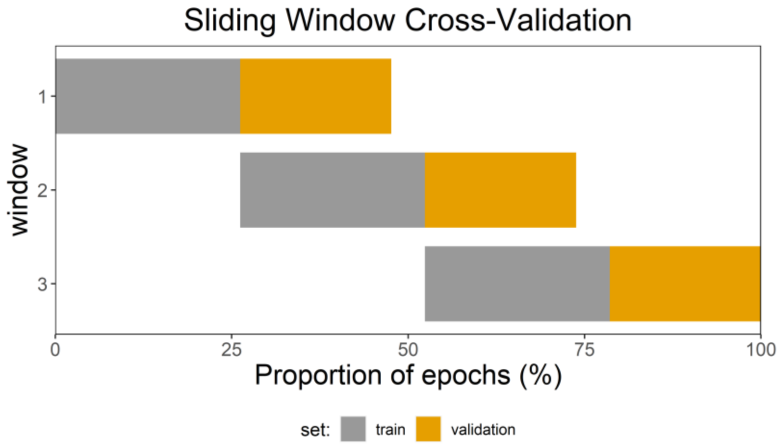

Figure 5. Procedure of sliding window cross-validation. For each participant, the train set was split into three consecutive windows of equal size. In each window, the model was trained with a pre-specified lambda on the initial 55% of the window's samples and, then, tested on the remaining 45% samples (i.e., the validation set). After assessing the predictive performance in all windows, we finally averaged the model's performance across the windows' validation sets.

3.2.4.3 Feature extraction

We applied a series of transformations to the reaction time labels in order to finally extract the features based on bandpass filtered EEG signals (see Figure 6). We log-transformed the reaction times to approximate a Gaussian distribution. Exclusively in the train set we then calculated the median absolute deviation of log-transformed reaction time labels per angle (i.e., 0°, 50°, 100°, 150°) and removed on average 12 epochs which we considered as outliers (i.e., if the label was beyond a threshold of 1.5 x MAD). This procedure yielded a final set of 110 epochs on average (min = 76, max = 138 epochs) with 5000 x 32 samples each which we used for training the regression models. Since the reaction time varied as a function of angular disparity and, hence, as a function of the degree to which mental rotation was involved to process the 3D figures, it was vital for the interpretability of our model to take this relationship into account. For example, a reaction time of 800 ms may be considered as a) a relatively slow response if the 3D figures were rotated by 0 degrees, or b) a relatively fast response if the 3D figures were rotated by 150 degrees. To take the varying difficulty levels based on angular disparity into account, we standardized the log-transformed reaction times per angular rotation. For hold-out and validation sets, we applied the means and standard deviations from the corresponding training set to standardize the reaction times, and to avoid data leakage.

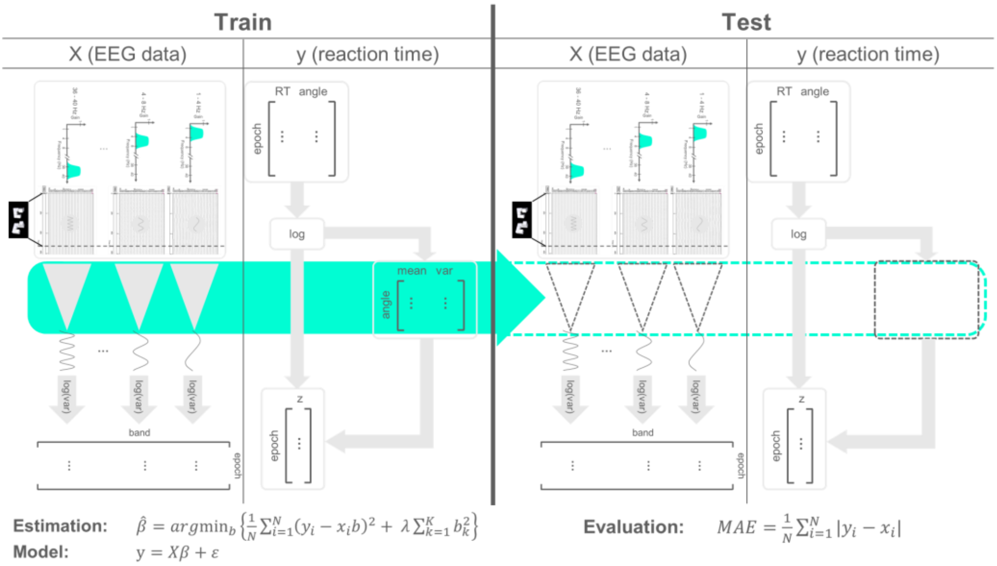

Figure 6. Feature extraction and model evaluation. For each participant, the first 75% of epochs were used as a train set and the remaining 25% as a hold-out set. In the train set, we first removed epochs which we classified as outliers (not visualized in the figure) and then extracted the EEG features by first bandpass and

then spatially filtering the EEG signal and the labels by standardizing the log-transformed reaction times. During training we estimated the coefficient (β) which minimizes for all epochs (N) the sum of squared errors between the reaction time labels (y) and the model predictions with EEG features (x) while penalizing the sum of squared coefficients (b) with the optimized penalty term λ. For the evaluation, we applied the same spatial and frequency filters and label standardization procedure to the hold-out set to extract new features and used the trained model to generate new predictions whose error we finally measured with the recorded reaction times in the hold-out set (see filled arrow in Figure 6).

To extract the EEG features predicting the log-transformed and standardized reaction times, we applied spatial filters and calculated the energy for each bandpass filtered EEG signal per epoch. By optimizing spatial filters via SPoC separately for each frequency band, the spatial filters adapted to the band-specific characteristics aiming to maximize the comodulation between the spatially filtered EEG time series and the reaction time labels. To be specific, we applied the SPoC_λ algorithm (Dähne et al., 2014) as implemented in the MNE framework (version 0.23.0) which maximizes the covariance between the two variables of interest. Given the relatively small number of epochs available for training, we only kept the component with the highest eigenvalue for each band-pass filtered multivariate EEG signal. Similar to the reaction times, we applied the same spatial filters which we extracted from the training set to spatially filter the hold-out set in order to avoid data leakage. Applying the spatial filters on each frequency band's multi-channel signal yielded a univariate time series. We then performed a log-variance transformation to extract the final EEG feature value approximating the power per frequency band and epoch.

3.2.4.4 Final model evaluation and interpretation

With the hyperparameter lambda minimizing the MAE in our hyperparameter tuning routine, we finally trained the model with the total training set (i.e., initial 75% of all epochs available) and evaluated its performance with the remaining hold-out epochs which have not been used yet (see Figure 6). To estimate the ridge regression coefficients, we trained our models with the extracted features from the training set (see section 3.2.4.3). Then, we predicted (log-transformed and standardized) reaction times using the trained model with the hold-out set’s samples. To evaluate the model, we finally calculated the MAE between the predicted reaction times and the actual reaction times. For model interpretation we estimated SHAP values for each frequency band per epoch in the final hold-out set.

To evaluate the intra-individual prediction performance of the EEG model, we measured for each participant the MAE for (a) the “EEG model” which predicted reaction times based on the EEG features in the participant’s hold-out set and (b) the “RT model” which predicted the average, standardized reaction time per angular disparity (i.e., 0). To evaluate the inter-individual prediction performance of the EEG model, we measured for each participant the MAE of the participant’s EEG model using (a) the same participant’s hold-out set and (b) the hold-out sets of all other participants (whose MAE we then averaged). For both the intra- and inter-individual evaluation, we finally performed paired t-tests using bootstrapping with 9999 iterations to take the skewed distribution into account and to evaluate the differences between models (a) and (b) based on the measures from all 40 participants.

3.3 Results

Our goal was to develop individually-tailored models predicting reaction times for correct answers in a mental rotation task based on EEG features. To make generalizable predictions, we applied a machine learning approach wherein we trained person-specific linear ridge regressions. After pre-processing the EEG data and removing outliers from the training set, an average of 110 epochs (min = 76, max = 138 epochs) remained for training and an average of 40 epochs (min = 26, max = 46 epochs) for the hold-out set. For the training, we individually optimized the hyperparameter lambda through a sliding-window cross-validation procedure minimizing the prediction error (i.e., the MAE) in the validation sets. Next, we estimated the regression coefficients of the EEG features from the training set (i.e., the EEG model) to predict reaction times (see Figure 7). For the testing, we predicted reaction times using the trained model with new EEG features from the hold-out set and calculated the MAE.

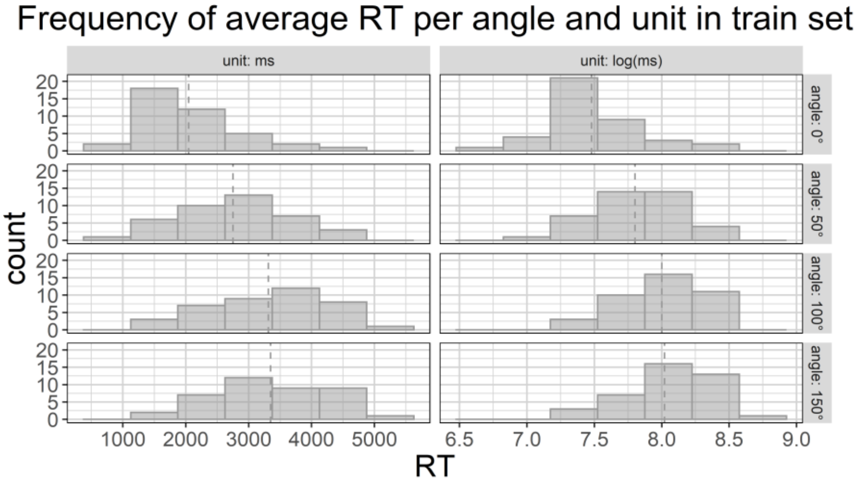

Figure 7. Histograms visualizing the distribution of participant-level reaction time (RT) averages per angular rotation (i.e., 0°, 50°, 100°, 150°) and unit (i.e., ms, log(ms)) included as labels in the train set. The dotted lines indicate the average RT per angular rotation and unit.

3.3.1 Intra-individual model evaluation

First, we evaluated the predictive performance of individually trained ridge regression models to predict reaction times for the hold-out set belonging to the same person. To extract the labels from the first 75% of epochs for both the EEG and the RT model, we log-transformed and standardized reaction times per angular disparity and, for the EEG model, we additionally applied spatial filters on the band-pass filtered EEG data via SPoC analysis. We then trained the EEG model with the cross-validated value for lambda. For performance evaluation, we predicted reaction time labels based on the samples of the hold-out set. For the EEG model, we extracted the features from the last 25% of epochs using the same reaction time parameters (i.e., means and standard deviations per angular disparity) for standardization of reaction times and the same spatial filters for feature extraction from EEG data. Next, we predicted (a) reaction times with the trained model and the new data from the hold-out set (EEG model) and (b) average reaction times per angular disparity (RT model). The model comparisons regarding their predictive performance revealed that the EEG model making predictions based on EEG features with a mean (M) MAE of 0.89 and a standard deviation (SD) of 0.16 performed significantly better (p < .001) than the RT model predicting the average reaction times (M=0.91, SD=0.16) (see Figure 8). When transforming the standardized and log-transformed reaction time labels back to their original scale (i.e., milliseconds; ms), the EEG model predicted the true reaction time labels with a mean MAE of 748 ms and the RT model with a mean MAE of 772 ms.

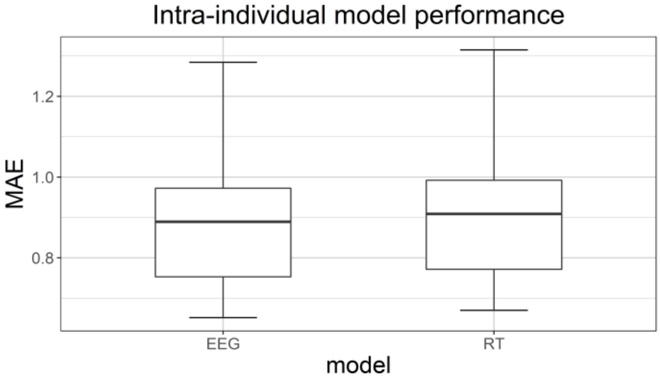

Figure 8. Boxplots of mean absolute error (MAE) in predicting standardized and log-transformed reaction times (RTs) using either a model trained on the same person's EEG features (EEG model) or a baseline model predicting the average RT (RT model).

Given the inverse relationship between stimulus difficulty (i.e., angular disparity) and accuracy in the mental rotation task (Ganis & Kievit, 2015), the number of samples to train and test our models varied across rotational angles as we excluded samples with incorrect responses. For training, we had averaged across participants most epochs for stimuli with 0° rotation (M=41), followed by 50° (M=39), 100° (M=37) and 150° rotation (M=33). To evaluate whether the predictive performance varied as a function of angular disparity, we performed a repeated measure ANOVA including participant as a random effect and angle as a fixed effect nested within participant. The ANOVA revealed that there was no significant difference in the MAE between the different angles (F(3, 117)=0.22, p = .88).

3.3.2 Inter-individual model evaluation

Next, we evaluated the predictive performance of individually trained EEG models to predict reaction times with the last 25% of epochs from other participants (i.e., the hold-out sets). Similar to the intra-individual model evaluation, we extracted for each participant (‘train participant’) features using reaction time parameters and spatial filters from their train set. After individually training the EEG model with the cross-validated value for lambda, we evaluated for every other participant (‘test participant’) the inter-individual prediction performance (i.e., MAE) based on the samples from the test participant’s hold-out set (Porter et al., 2023). Finally, we averaged for each train participant the MAE measured in the hold-out sets from the remaining 39 test participants. Comparing the intra-individually tested EEG model (M=0.89, SD=0.16) with the inter-individually tested EEG model (M=1.59, SD=0.67) revealed that the intra-individually tested EEG model performed significantly better ($p < .001$). Due to inter-individual variations in reaction times and informative oscillatory sources, it is unclear how much the drop in inter-individual prediction performance can be attributed to either the ridge regression model or to an unsuitable feature extraction.

To inspect this, we additionally evaluated the impact of individualized pre-processors (i.e., person-specific reaction time label aggregates for standardization, and spatial filters belonging to the same frequency band) on model performance. In contrast to the previous inter-individual model evaluation where we applied the train participant’s pre-processors (i.e., reaction time parameters and spatial filters) to each test participant’s data, we used the test participant’s pre-processors for feature extraction. In both cases, we applied the train participant’s ridge regression parameters for the prediction with the test participant’s features. For final comparison, we again averaged the test participants’ MAEs for each train participant. The comparison revealed that the EEG model with the test participants’ pre-processors (M=0.93, SD=0.03) predicted the test participants’ reaction times significantly better than the EEG model with the train participants’ pre-processors ($p < .001$). We then compared the outperforming inter-individually evaluated EEG model to the intra-individually evaluated EEG model (see section 3.3.1). The intra-individually evaluated EEG model slightly outperformed the inter-individually evaluated EEG model applying the test participants’ pre-processors ($p = .1$).

3.3.3 Feature importance

To assess person-specific feature importance scores of the trained ridge regression model, we relied on SHAP values. In contrast to permutation feature importance evaluating the decrease in model performance, SHAP values partition the contribution of each EEG feature to the predicted, log-transformed and (per angle) standardized reaction time. To measure the global importance, we calculated for each participant and EEG feature the mean absolute SHAP value. In Figure 9a, we display the SHAP feature importance of a representative participant with the EEG features sorted in ascending order of frequency band. To inspect the relationship between feature values and SHAP values, we display the participant’s Beeswarm plot in Figure 9b. These show that, for this participant, lower frequencies contributed more to the prediction than higher frequencies with a peak at the alpha frequency and that an increase in alpha activity was associated with a decrease in reaction time.

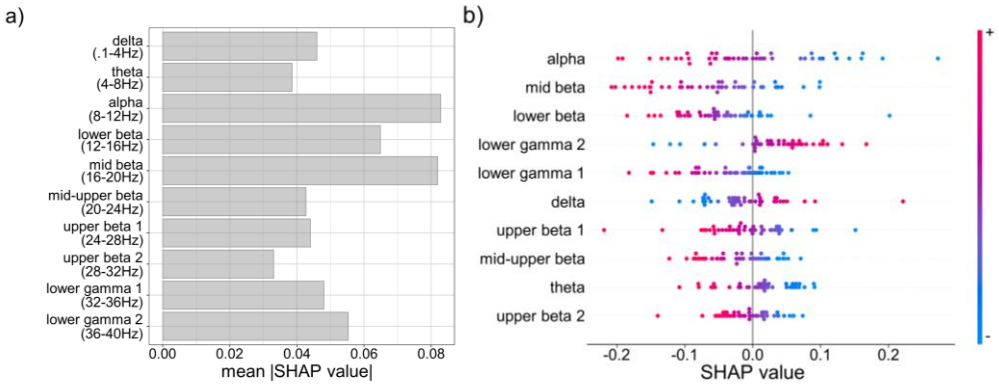

Figure 9. Feature importance scores based on log-variance features for a representative participant. a) Barplot of absolute SHAP values averaged per EEG feature displaying that lower frequency bands contributed more to the final prediction than higher frequencies with the alpha frequency being the most important feature. b) Beeswarm plot of SHAP values inspecting the direction of the association between EEG feature and predicted values. For this participant, the association between alpha and predicted reaction time was negative, hence, the more power in the alpha frequency band increased the more the predicted reaction time decreased.

Next, we aggregated the individual measures of feature importance across all participants to visualize patterns at the group level. In Figure 10a, we display the median of absolute SHAP values per EEG feature. These show an inverted-U shape relationship between the frequency bands and the median SHAP feature importance and, furthermore, substantial inter-individual differences in the importance of each EEG feature. Overall, frequency bands in the beta range contributed the most to the prediction of reaction times. We additionally calculated the difference in mean absolute SHAP value between all EEG features and visualized it in a heat map (see Figure 10b). The pattern revealed that frequency bands closer to another differed less in their mean absolute SHAP value than more distant frequency bands.

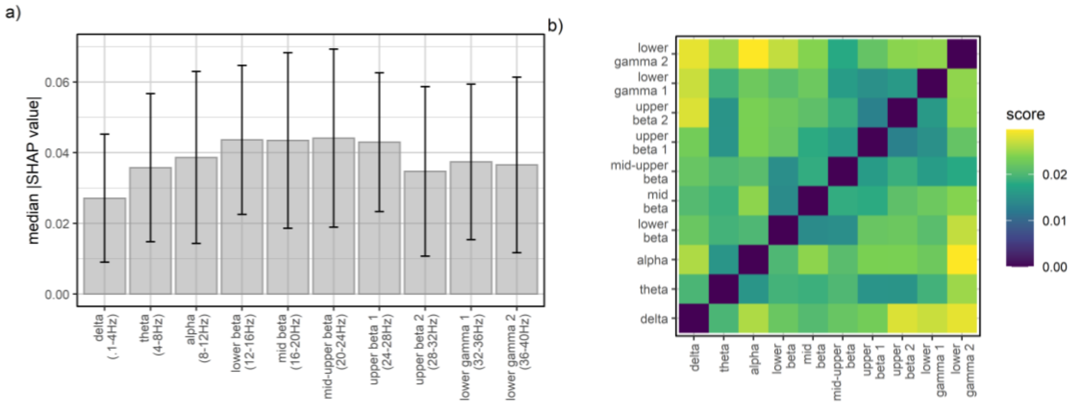

Figure 10. Feature importance scores of all participants. a) Barplot of the median absolute SHAP values per EEG feature with higher values for the beta frequency range indicating that these features contributed more to the final prediction than other features. Error bars denote the median absolute deviation (MAD). b) Heat map of the averaged difference in absolute SHAP value between EEG features indicates that more distant frequency bands differed more in their contribution to the prediction than frequency bands which were closer to one another.

To inspect the neural source of the SPoC components, we estimated the forward model and averaged the resulting patterns across all participants (see Figure 11). Mostly, we observed an increased activity in the left frontal cortex and the right posterior parieto-occipital regions. However, the frequency bands differed in their topographic pattern of their SPoC components correlating the band’s power time course with the time course of reaction time labels. In the alpha and mid beta range activity relating to mental rotation mainly peaked in left frontal and right posterior parieto-occipital regions. In the upper beta band and lower gamma ranges the activity increased predominantly in the right occipital region. Despite the ICA routine reducing neural activity unrelated to mental rotation, we observed source activity in the frontal and lateral temporal regions of faster frequency bands typically associated with physiological artifacts.

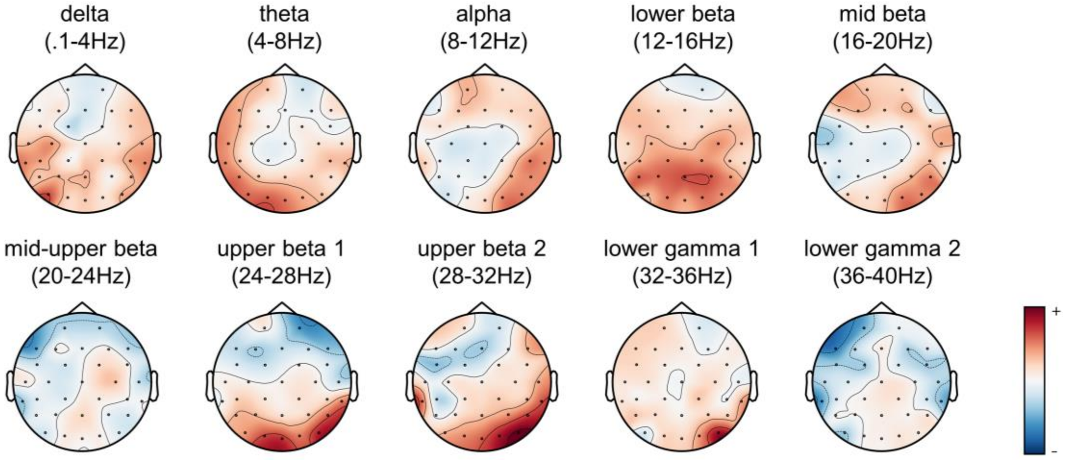

Figure 11. Topographic patterns of average Source Power Comodulation (SPoC) components per frequency band. After estimating the topographic patterns using the forward model for each participant, we averaged the activation pattern across all participants per frequency band.

3.4 Discussion

The present paper designed and evaluated a person-specific machine learning approach to extract neural correlates of mental rotation. Therefore, we recorded the response, reaction time and the EEG activity in 192 trials in which participants decided whether or not two 3D objects were rotationally invariant (Ganis & Kievit, 2015). Due to the low error rate in this task (Ganis & Kievit, 2015) and the respective disproportionate class distributions for classification models, we trained a ridge regression model predicting the reaction time in trials with correct responses. Using established methods for modelling mental processes based on neural activity, in combination with the widely used mental rotation task capturing visuospatial performance, we successfully created person-specific models which accurately predicted reaction times based on that person’s EEG activity and to a lesser degree based on another person’s EEG activity. Additionally, we gave insights into the contribution of the various EEG features to the final prediction.

For the design of our pre-processing routine, we took stimulus-specific and neurophysiological aspects into account. Since the task's difficulty level influenced the reaction time, we based the extraction of the reaction time labels on its angular disparity. Thereby, we could successfully express the reaction time relative to its stimulus characteristics with equal mean and variance for all rotational angles. This ensured that lower values in the prediction were not based on stimulus-specific characteristics but rather on faster mental processing. Furthermore, we have considered neurophysiological properties to extract meaningful EEG features. We processed the EEG signals to reduce activity unrelated to the mental rotation (e.g., ocular movements, cardiac activity, motor preparation) and bandpass-filtered the EEG activity into well-established frequency bands. To reduce the dimensionality and increase the association with the labels (i.e., reaction time), we applied spatial filters which we estimated with the SPoC algorithm. When testing the trained models, we used the same pre-processing routine for the hold-out set with the identical reaction time aggregates and spatial filters to avoid data leakage. Notably, our approach estimates the person-specific contribution of frequency bands and topographic patterns to the prediction and, thereby, provides an individually-tailored model of neural activity involved in mental rotation.

First, we demonstrated that models using person-specific EEG features (i.e., EEG models) predicted the reaction times of the same person significantly more accurately than models relying on the average reaction time (i.e., RT models) for prediction. Although this difference was small, the observed MAE for the EEG model is in line with previous research and represent the lower bound of what can be achieved, especially when considering the slower reaction times compared to previous studies (Binias et al., 2020; Rahman et al., 2022). Since we excluded the reaction time of trials in which participants responded incorrectly and given the inverse relationship between angular disparity and accuracy, the number of available samples decreased with angular rotation. However, we did not find changes in predictive performance as a function of angular disparity indicating that this imbalance did not affect model performance or interpretability. These results suggest that EEG features contributed more to the prediction of reaction times than the average reaction time. Furthermore, the similarity of predictive performance across levels of rotational angles in the mental rotation stimuli suggests that the model learned from all difficulty levels (i.e., rotational angles) during training. We also found that person-specific EEG features predicted the same person's reaction times significantly more accurately than the reaction times from another person. When taking the other person's reaction time aggregates and EEG topography patterns into account, we could increase the generalizability of a person-specific EEG model. However, the person-specific EEG model continued to predict reaction times of the same person more accurately indicating that associations between EEG activity and mental rotation are partly specific to a person. Finally, we found that across all participants alpha and beta band related activity contributed most to the mental rotation process.

This finding is well in line with previous research which found alpha and beta ERDs when performing a mental rotation task (Boiten et al., 1992; Ozga et al., 2019). Further, we also measured increased activity in left frontal and right parieto-occipital regions during mental rotation typically observed in mental rotation of non-bodily stimuli (Veldema et al., 2021; Zacks, 2008). It is noteworthy that these studies focused on the association between frequency band activity and mental rotation task performance in the general population and did not investigate the predictive performance on unseen data. Hence, our results extend the aforementioned findings by demonstrating similar frequency bands minimizing the prediction error in a machine learning approach. Furthermore, we gave insight into inter-individual variations of the associations between frequency bands and mental rotation performance. Taking individual topographical patterns into account was of major importance in generalizing one person's model to the data from another person. This is in line with individually trained classifiers to detect task states based on neural activity which performed well above chance for the same person and (to a lesser degree) for others (Porter et al., 2023).

Overall, our results indicate that a more individualized approach towards modelling neural activity and behavioral variables may be promising for neuropsychological research and clinical applications, particularly when combined with machine learning. This may enable person-specific adjustments of interventions targeting neural activity to individually maximize the effect on behavioral outcomes. Our findings also suggest that individual variations in behavior and topographical activity patterns have a large effect on the generalizability of a model trained on one person's data. To understand which neural activity pattern the brain relies on when processing visuospatial information, we proposed the use of SHAP values to estimate the contribution of neural activity patterns to behavioral responses. Although this should be seen as early evidence, the discovered pattern of SHAP values across participants – that is, alpha and beta band related activity contributed the most to the final prediction – replicates previous findings (Boiten et al., 1992; Ozga et al., 2019). Furthermore, we discovered great inter-individual variability in the importance of neural activity patterns for processing visuospatial information suggesting that the reliance on specific frequency bands in brain networks may be partly person-specific. Notably, these results are based on a small sample size (i.e., between 105 and 184 samples per person) indicating that our estimates represent a lower bound of what can be achieved.

Despite our promising results and their potential implications, it is important to point out some of the major limitations. For data collection we administered a mental rotation task in which the duration of each trial was determined either by the participant's response or a time-out after 7.5 seconds. While this procedure enabled us to capture neural activity related to mental rotation (in contrast to other implementations in which the presentation duration of the 3D objects is fixed in advance), the SPoC algorithm required epochs of equal size as input. Therefore, we only included the initial 500 ms of neural activity per trial. Although our model performed similarly in the prediction of reaction times across varying degrees of angular rotation indicating that the final epochs contained information of multiple stages of mental rotation, meaningful information may have been lost when cutting the varying epoch sizes into a standard size. The relatively small number of epochs used to train person-specific regression models predicting reaction time labels with EEG features risks yielding non-robust regression parameters (e.g., rank switches in feature importance estimates). To estimate more robust spatial filters, a regularized SPoC algorithm represents a promising approach for future studies (Meinel et al., 2019). For model training, we used the data collected during the mental rotation task from each person. Taking the time-order of the samples into account, we could train models to predict person-specific behavioral responses at a later point in time. Nonetheless, we would like to point out that these data were collected in a single session and that we did neither assess the congruent validity of our models with other tasks measuring visuo-spatial ability nor the discriminant validity regarding processes unrelated to mental rotation. For model interpretation, we estimated the contribution of each EEG feature to the final prediction using SHAP values. Since we collected observational data of neural activity patterns and behavioral responses, the models should be interpreted with caution and do not imply causality.

Further research is required to overcome these limitations and to extend our knowledge about the relationship between neural activity and behavioral variables. Our results indicate that an individualized machine learning approach towards modelling behavior with neural activity could be promising for neuropsychological research. This may be particularly powerful for changing behavior based on modulations of neural activity. It is, however, important to point out that we investigated the association between behavior and neural activity with observational data which does not imply causation. To test for causality, one approach would be to experimentally manipulate EEG features contributing the most to the prediction and to measure the target behavior before and after the manipulation (e.g., with neurofeedback, transcranial magnetic stimulation, or transcranial direct current stimulation). Future research should also investigate the reliability and validity of these individualized models. Therefore, longitudinal studies measuring mental rotation performance and neural activity over multiple sessions and, further, which include other tasks designed to assess visuospatial processing as well as unrelated processing would make substantial contributions to this domain by assessing both the reliability and validity of the developed models. Finally, the design of an appropriate task and methodology to capture meaningful neural activity during mental rotation requires further attention. We artificially constrained the duration of recorded neural activity preceding the behavioral response to apply the SPoC algorithm for further processing. One interesting approach would be to investigate how additional time for mental rotation would improve modelling the association with neural activity by pre-specifying the presentation duration of the 3D objects during a mental rotation task in incremental steps. As artificially delaying a response may invoke processes unrelated to the decision (Schall, 2003), novel algorithms processing EEG signals which deal with varying epoch sizes may be as beneficial.

To conclude, we present an individually-tailored machine learning approach to model mental rotation as a function of neural activity. Therefore, we trained ridge regression models to predict reaction times in trials of a mental rotation task where participants responded correctly using EEG features which take individual topographical activity patterns into account. To this end, we showed that individualized models generate more precise predictions than when relying on a model from another person. Furthermore, neural activity preceding the response in the mental rotation task predicted the time of the response significantly more accurately than predictions relying on the average reaction time of that person. Finally, we demonstrated that taking individual variations in response patterns and topographical activity patterns into consideration significantly improves the generalizability of a model trained on one person's data to data from another person. Given the observational nature of the data used, further research is required to establish the causal effect of specific frequency bands on the mental rotation performance. Nonetheless, our research represents an early step towards individualized neurocognitive models and, finally, towards highly specified treatment options.

3.5 References

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CHAPTER 4

Personalized neurofeedback

Having demonstrated that individually trained regression models using EEG features outperform baseline models relying on average RT in predicting the time of future, correct responses, we now investigate the efficacy of person-specifically targeted EEG features in mediating changes to mental rotation performance in the context of a neurofeedback intervention. Therefore, we applied a similar study design as reported in chapter 2 with the first intervention arm receiving sham feedback and the second arm receiving personalized neurofeedback. This third and last manuscript of this thesis will be presented in form of a research poster at the 31st annual conference of the International Society for Neuroregulation and Research in Dallas (Texas, USA) and is currently in preparation for submission to the BioMed Central's journal of Neuroscience.

Abstract

To enhance spatial cognition, most studies designed the neurofeedback training to alter alpha waves in the electrocortical activity. Recently, identifying person-specific brain networks expanded our understanding of how our brains perform complex cognitive processes. In a randomized, double-blind, sham-controlled study, we investigated the efficacy of personalized neurofeedback in mediating changes to mental rotation performance. For the personalization, we applied a machine learning approach and individually trained ridge regression models to predict the performance in a mental rotation task based on task-related, electrocortical activity. While the experimental group did not reduce their reaction time in trials with correct responses significantly more than the sham group ($z = 1.28$, $p = .90$), they decreased their error rate significantly more than the sham group ($z = -1.67$, $p < .05$). Our results suggest that data-driven, individually tailored target specification for EEG neurofeedback increases mental rotation task performance more than sham feedback in healthy adults. Furthermore, the training effect was specific to spatial cognition involved in mental rotation and did not transfer to changes in cognitive flexibility measured with the Trail Making Test (TMT). One limitation of our study is that we cannot clearly distinguish between accuracy and reaction time due to the trial-based time constraint in our implementation of the mental rotation task. Future studies should investigate if such personalized neurofeedback designs outperform classical approaches where all participants share the same target feature.

4.1 Introduction

During neurofeedback training users are continuously provided with feedback on a feature of their brain activity. The feedback reinforces the generation of the targeted activity and thereby induces changes to brain activity, ultimately to mediate effects on cognitive-behavioral outcomes (Collura, 2014). Hence, it is common to specify the targeted neural feature for neurofeedback interventions based on the cognitive-behavioral function it is thought to be associated with. In electroencephalography (EEG) based neurofeedback, neural features have mostly differed in their spectral and topographical activity pattern (Gruzelier, 2014). While some of the spectral and spatial parameters have been validated in brain stimulation studies, the efficacy of neurofeedback in inducing electrocortical alterations and changes to behavioral-cognitive outcomes varies across studies and participants (Alkoby et al., 2018). More consistent findings have supported the application of some EEG spectral neurofeedback protocols including the sensory-motor rhythm (12-15 Hz) for stimulating attentional networks, the alpha rhythm (8-12 Hz) for modulating states of wakefulness, and the theta rhythm (4-7 Hz) for stimulating memory networks (Gruzelier, 2014). Although neurofeedback has further been used in clinical populations such as for the treatment of attentional-deficit/hyperactivity disorder (ADHD) (Garcia Pimenta et al., 2021), for the rehabilitation after stroke (Wang et al., 2018), and the treatment of depression (Thibault et al., 2018), its efficacy in regulating the targeted neural features has varied substantially across studies and its transfer effect to behavioral domains remains limited. Similarly, the heterogeneity in study designs and in the efficacy of neurofeedback interventions have also been reported in healthy populations (Alkoby et al., 2018; Gruzelier, 2014).

This has inspired some researchers to investigate factors influencing the efficacy of neurofeedback training. There is evidence that neurophysiological activity patterns such as the activity level of the targeted neural feature in resting-state (Wan et al., 2014) and at the beginning of the training (Weber et al., 2011), as well as measures of resting-state brain connectivity (Scheinost et al., 2014) have a significant impact on training success. Furthermore, psychological factors such as motivation (e.g., related to positive feedback received when successfully modulating the brain activity) (Han et al., 2016; Pérez-Elvira et al., 2021) and mental strategies for successful regulations of brain activity (Kober et al., 2013; Nan et al., 2012) significantly contributed to the prediction of training success. Self-agency is yet another relevant factor in brain-computer interfaces (Gaume et al., 2016; Jeunet et al., 2018): control over training pace has improved higher cognitive functions more than externally-paced training after a single session of individual upper alpha neurofeedback (Uslu & Vögele, 2023). As a complementary perspective on neurofeedback efficacy, some researchers have suggested to model changes in cognitive-behavioral variables separately from induced alterations in the targeted neural feature (Weber et al., 2020). Although this approach has received less attention, alpha activity at baseline and after neurofeedback targeting slow cortical potentials explained a significant part of the variance observed in the change of ADHD symptom severity (Gevensleben et al., 2009). Varying definitions of neurofeedback success further complicate synthesizing findings across studies with some focusing more on proximate effects of neurofeedback interventions on induced neural activity and others more on distant effects on cognitive-behavioral variables (Alkoby et al., 2018).

For both effects of neurofeedback, on neural activity and cognitive-behavioral outcomes, several methodological approaches have been proposed to evaluate success in neurofeedback interventions (Alkoby et al., 2018; Tursic et al., 2020; Weber et al., 2020). These methods mostly fall either into classification or into regression approaches. With regards to classification, some researchers have labeled participants as responders or non-responders based on their learning rate (which in itself has several conceptualizations) during neurofeedback and separated their analyses for these two classes (Autenrieth et al., 2020; Eschmann et al., 2022; Hsueh et al., 2016). Regarding the regression approach, other researchers have investigated the effect of learning rate on cognitive-behavioral and neurophysiological outcome measures in a continuous manner (Naas et al., 2019; Nan et al., 2012; Navarro Gil et al., 2018). Given the continuous nature of the data, arbitrary thresholds in neural activity to classify the responsiveness of users to neurofeedback interventions seem inappropriate. While most studies have assessed cross-person factors of neurofeedback success, findings of more recent studies suggest that meaningful, person-specific brain-behavior mappings may explain part of the inter-individual variations regarding the efficacy of neurofeedback (Porter et al., 2023; Uslu et al., 2023). Although personalization and the use of machine learning algorithms to individually tailor neurofeedback protocols have recently received increasing attention as one approach to overcome some of the limitations in neurofeedback literature, only a few studies have been undertaken to validate this claim (Han et al., 2016; Uslu et al., 2023).

Machine learning algorithms outperform traditional statistical methods in predictions and can further be trained to perform well on unseen data using regularization techniques, much needed for the discovery of individual-level patterns, the identification of clinical subgroups, and for estimating neural correlates of cognitive and affective processes (Chen et al., 2022). Recently, researchers have identified person-specific fMRI features for the classification of task states and have further demonstrated that the individually trained classifiers performed significantly above chance when classifying task states using data from the person the model was trained with and to a lesser degree when using fMRI recordings from another person (Porter et al., 2023). This finding indicates that person-specific neural correlates contain both person-specific and more general information which are common across people.

For EEG data, supervised filtering methods including Common Spatial Patterns (CSP) and Source POwer Comodulation (Dähne et al., 2014) have been designed to increase the signal-to-noise ratio and to foster the bridging of neural activity and cognitive-behavioral outcomes. In brain-computer interface research, it is common to pre-process multi-channel EEG data first by band-pass and then by spatial filtering (Ang et al., 2008). For classification problems, Filter Bank CSP (FBCSP) of EEG signals have significantly differentiated between left- and right-hand motor imagery tasks (Ang et al., 2008; Blanco-Diaz et al., 2022). For regression problems, Filter Bank SPoC (FBSPoC) has provided insights into inferring mental workload based on EEG activity, particularly when combined with regularized regression models such as ridge regression with an optimized shrinkage penalty to deal with the curse of dimensionality (Planke et al., 2021). These processing pipelines have proven effective in extracting features for machine learning applications and in decoding neural activity.

In this study we validated a novel neurofeedback paradigm targeting the modulation of person-specific neural features related to mental rotation performance.

Prior to neurofeedback we estimated the contribution of several neural features to the prediction of mental rotation performance using a machine learning approach. The feature contributing the most to the prediction determined the neural feature which was then modulated in a single neurofeedback session. Before and after the neurofeedback intervention we administered a mental rotation task and the trail making test. To assess the efficacy of this personalized neurofeedback paradigm, we applied a double-blind, sham-controlled design and we expected that participants receiving real neurofeedback would improve their mental rotation performance more than participants undergoing sham feedback.

4.2 Materials and methods

For our double-blind, randomized, sham-controlled study, we collected the data of participants in a 2-hour lab assessment at the University of Luxembourg. The 40 healthy young adults (25 females, mean age: 24.97 years, age range: 19-35 years) participating in the study had normal or corrected-to-normal vision and underwent the same procedure except for the type of neurofeedback: real or sham neurofeedback. To ensure that the experimenter was blinded, a randomized allocation sequence was implemented in advance and masked from the experimenter and evaluator. After giving their informed written consent, the participants first answered a socio-demographic questionnaire. They then performed versions A and B of the Trail Making Test (TMT) on paper (Bowie & Harvey, 2006) and 192 trials of a mental rotation task on a computer (Ganis & Kievit, 2015). After the experimenter had extracted the target EEG feature based on the participant’s mental rotation performance, they continued with the single neurofeedback session lasting 30 minutes. Finally, the participants performed 96 trials of the mental rotation task and both versions of the TMT. For reimbursement, they received vouchers worth 10€ per hour dedicated to the study. This study was approved by the Ethics Review Panel of the University of Luxembourg (ERP 20-068).

4.2.1 Mental rotation task

We sampled stimuli without replacement from a validated set of 384 stimuli each of which displayed two 3D objects (Ganis & Kievit, 2015). The stimuli were parameterized by rotational invariance (i.e., either invariant or not) and angular disparity (i.e., 0°, 50°, 100°, 150°). Each trial started with a fixation cross appearing for a random duration between 1 and 3 seconds followed by the stimulus which appeared for a maximum duration of 7.5 seconds or until a response was recorded. For stimulus sampling, we constrained our sampling procedure to ensure that the stimuli were balanced in their rotational invariance and angular disparity. In each trial we recorded stimulus parameters, the given response (if any) and the latency of the response in relation to stimulus onset.

4.2.2 Neurofeedback

Throughout the study, we applied the same neurofeedback methodology to all participants. First, we performed a calibration measure to extract filters reducing EEG activity related to artifacts. Next, we extracted the target feature for neurofeedback based on a personalized machine learning approach estimating the contribution of EEG features to the prediction of mental rotation performance. Finally, participants underwent a single session of neurofeedback with half of them receiving the same sham feedback based on another participant’s pre-recorded feedback.

In a 1-minute, eyes-open calibration measure performed prior to neurofeedback, we recorded the participants’ EEG activity when instructed to remain calm but to move their eyes horizontally and vertically. We then applied an independent component analysis to decompose the EEG signal into independent components using the ICA.fit method from the MNE package (Gramfort et al., 2013). Based on the visual inspection of each component’s signal in the time and frequency domain and its topographical activity pattern, we removed those components which represented artifacts (e.g., eye movements, cardiac activity) by zeroing out the corresponding columns in the mixing matrix. To apply the filtering procedure during neurofeedback, we finally extracted and stored the values used for whitening, centering the EEG signal as well as the transformed mixing matrix.

To specify the target feature for the single neurofeedback session, we applied a personalized machine-learning approach to predict the response time of correct responses in the mental rotation task using EEG features in a ridge regression (Uslu et al., 2023). First, we denoised the continuous EEG activity recorded during the mental rotation task by applying the procedure extracted from the calibration measure. We then applied a FBSPoC methodology (Ang et al., 2008; Dähne et al., 2014; Planke et al., 2021) to obtain optimal spectral and spatial filters for linking EEG activity to behavioral response time. After bandpass-filtering the recorded EEG activity with ten filter banks the frequency bounds of which ranged from [0.1, 4] to [36, 40] Hz, we epoched the continuous signal into 192 equally sized epochs with an interval of [0, 500] ms from stimulus onset. From these epochs we first removed epochs in which the given response was incorrect and second removed outliers based on response time and EEG spectral energy. Next, we split the remaining epochs into a training containing the first 75% of epochs and a test set the former of which we used in a sliding-window cross-validation routine to tune the regularization parameter lambda. We then trained the ridge regression with the whole training set and the optimized lambda and evaluated the performance based on the unseen test set. Finally, we estimated SHapley Additive exPlanations (SHAP) values (Lundberg & Lee, 2017) to estimate the importance of each EEG feature. For neurofeedback, the spectral and spatial filters contributing the most to the prediction of response times determined the target feature.

Before and after neurofeedback we measured EEG resting-state activity in a 1-minute eyes-open recording. For participants in the experimental condition, we applied the extracted spectral and spatial filters best predicting mental rotation performance to calculate the feedback value on a 1 s Hanning window with an overlap of 75%. During neurofeedback, we standardized the online calculated feedback value using the average and standard deviation estimated from the resting-state activity prior to neurofeedback (i.e., the baseline value). Participants in the sham condition received the feedback with the same update rate of 4 Hz as for participants in the experimental condition. The feedback was realized by a moving bar plot whose height corresponded to the calculated target value. We instructed participants to increase the height of the bar using their brain and to keep the bar above a horizontal line presented at two-thirds of the monitor’s height which corresponded to the baseline value. To ensure that the experimenter remained blinded throughout the session, he did not see the feedback provided to the participants and prepared the target feature as if all participants belonged to the experimental condition as the allocation to a condition was automatized in the background.

4.2.3 EEG recording and analysis

For recording EEG activity during the mental rotation task, resting-states and neurofeedback, we used a BrainAmp system (Brain Products, Gilching, Germany). To synchronize the signals from the keyboard, the stimulus presentations and the EEG amplifier, we sampled the digitized signals via the lab streaming layer protocol at a rate of 1 kHz. For the EEG, we mounted 32 Ag/AgCl electrodes according to the 10/20-system and referenced them to FCz. Prior to the first resting-state recording, we applied conductive gel underneath the electrodes to keep their impedance below 5 kΩ throughout the experiment.

4.2.4 Statistical analyses

We statistically analyzed our data in R version 4.1.3 (R Core Team, 2022) and used the lme4 package version 1.1.28 (Bates et al., 2015) to estimate our linear mixed models (LMMs). For modeling binary responses, we estimated generalized linear mixed models (GLMMs) with a logit link function instead. To evaluate the difference between the two groups in their mental performance change from before to after neurofeedback, we estimated marginal means and calculated contrasts using the emmeans package version 1.7.3 (Lenth, 2022). We further tested interactions with angular rotation and corrected for multiple testing using the multivariate t distribution (Genz & Bretz, 2009). To achieve more reliable estimates for highly unbalanced data, we expanded our analyses with a Bayesian approach and weakly informative priors on the fixed effects. All our models included the time (i.e., pre, and post neurofeedback) and condition (i.e., personalized neurofeedback, and sham feedback) as fixed factors and the participant as a random intercept.

4.3 Results

In this section we first report the effect of personalized neurofeedback on mental rotation which we measured with the error rate and the reaction time of correct responses. Next, we estimated the effects on the performance in the TMT and, finally, we analyzed changes in the targeted frequency band from before to after and during neurofeedback training. The results of the machine learning algorithm evaluated with the data from this experiment have been published elsewhere (Uslu et al., 2023).

4.3.1 Mental rotation task performance

4.3.1.1 Reaction time

From the trials presented to each participant before (n=192) and after (n=96) neurofeedback we first removed those during which no or an incorrect response was given. As expected, we observed more missing and incorrect responses with increasing angular disparity due to the inverse relationship between trial difficulty (i.e., rotational angle) and both reaction time and accuracy (Ganis & Kievit, 2015). We then log-transformed the reaction times to approximate a Gaussian distribution for further processing. To estimate the effect the effect of personalized neurofeedback on the decrease in reaction time from before to after neurofeedback, we applied a linear mixed modelling approach with time-point (i.e., pre/post neurofeedback), condition (i.e., personalized/sham neurofeedback), and angular disparity (i.e., 0°, 50°, 100°, 150°) as fixed factors and the participant as a random intercept. We compared models including the factor of interest to baseline models which contained all but the factor of interest. The likelihood-ratio tests revealed that neither the interaction between condition and time-point (χ^2 (1) = 1.63, p = 0.2) nor the three-way interaction between condition, time-point and angular disparity (χ^2 (3) = 2.07, p = 0.56) was significant.

4.3.1.2 Error rate

We estimated a series of generalized linear mixed models with a logit link function to investigate the effect of personalized neurofeedback on the reduction of error from before to after neurofeedback training. First, we excluded on average 3 trials (min = 0, max = 25 trials) with missing responses per participant (see Figure 12). We then compared a model including the interaction between time-point and condition to a baseline model without that interaction. The likelihood ratio test revealed that the two-way model fitted error rates better than the baseline model although the difference failed to reach significance (χ^2 (1) = 2.77, p = 0.1). Further post-hoc comparisons showed that personalized neurofeedback reduced the error rate from pre to post neurofeedback training significantly more than sham neurofeedback (z = -1.67 $p < .05$). While participants receiving personalized neurofeedback reduced their probability to commit an error from 11.75% to 8.13%, participants in the sham condition reduced theirs from 12.47% to 10.48%. Although the largest difference appeared for most difficult stimuli (see Figure 13), including the three-way interaction term between time point, condition and angular disparity, did not further improve model performance (χ^2 (3) = 0.14, p = 0.99).

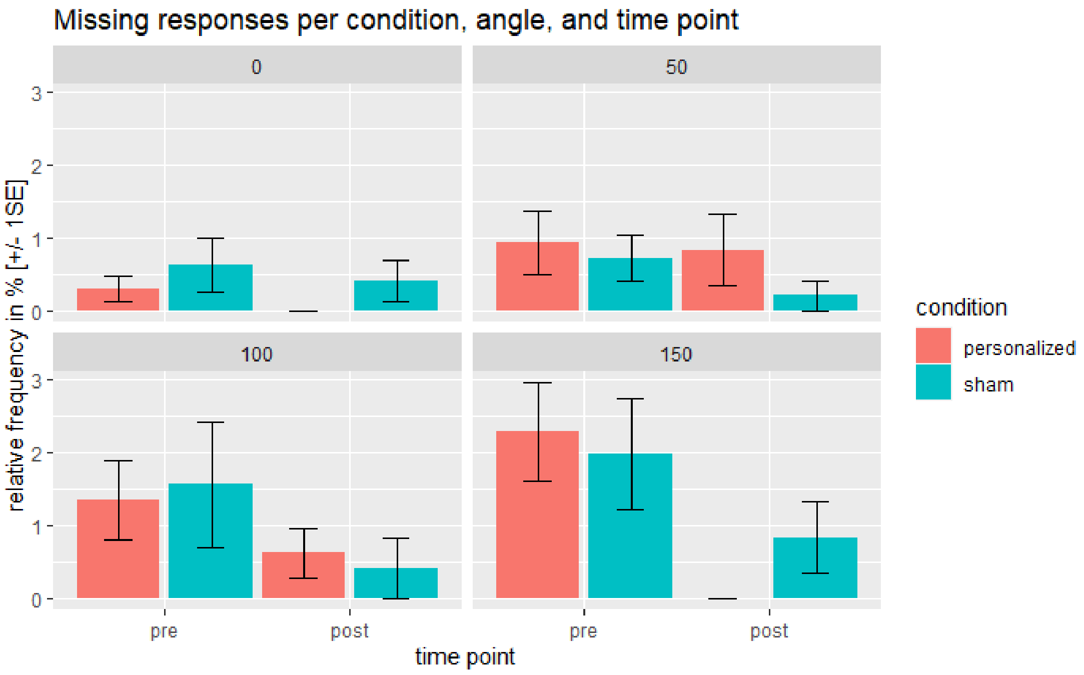

Figure 12. Barplots visualizing the relative frequencies of missing responses per condition (i.e., personalized/sham neurofeedback), angular disparity (i.e., 0°, 50°, 100°, 150°), and time point (i.e., pre/post neurofeedback).

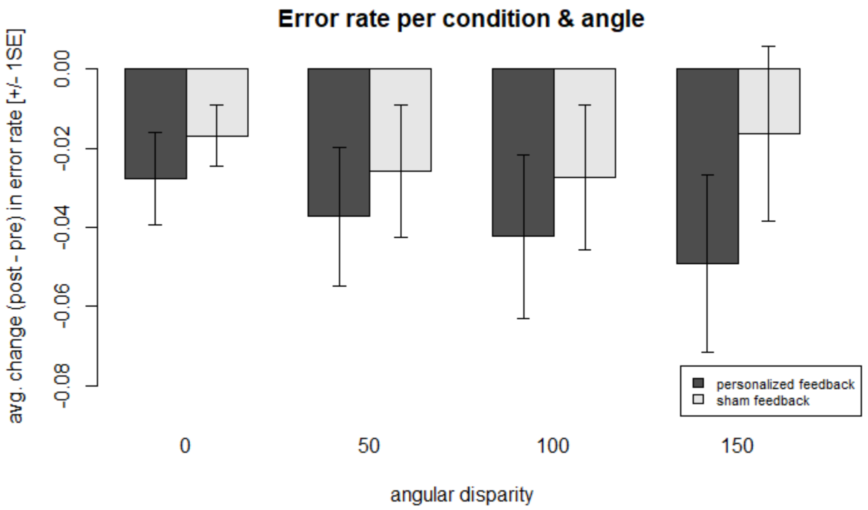

Figure 13. Barplots representing the change (post-pre neurofeedback) in error rate per condition and angular disparity.

4.3.1.3 Missing responses

Since a reduction in reaction time may lead to less missing responses, we additionally investigated whether personalized neurofeedback reduced the number of missing responses more than sham neurofeedback. Therefore, we coded missing responses as binary scores (response missing as 1; response given as 0) and performed a generalized linear mixed model approach with a logit-link function. As participants receiving personalized neurofeedback did not miss any response for stimuli rotated by 150° (see Figure 12), we adopted a Bayesian approach with a weakly informative prior on the fixed effects (i.e., $\Sigma=9I$) to overcome the issue of having large standard errors due to complete separation when applying maximum likelihood estimation. Our two-way interaction model comparison revealed that the logit of not responding decreased similarly after personalized and sham neurofeedback ($b=0.06$, 95% HPDI: -0.62, 0.85). However, our three-way interaction model indicated a significant interaction between time-point, condition and angular disparity. Only in stimuli with an angular rotation of 150°, participants receiving personalized neurofeedback reduced their logit of missing a response significantly more than participants in the sham neurofeedback group ($b=-2.78$, 95% HPDI: -4.19, -1.05).

4.3.2 Trail Making Test

To investigate whether the effect of personalized neurofeedback was specific to mental rotation, we next estimated mediated changes to the TMT performance. First, we log-transformed the completion times for part A and B to reduce the skewness of the distribution. We then fitted a constrained linear mixed model per part only including the fixed effects for time point, condition, and a random intercept for participant. After estimating full models including the two-way interaction term between time point and condition, we performed likelihood-ratio tests to evaluate the significance of the interaction terms. Our results indicate that participants receiving personalized neurofeedback and participants in the sham feedback group reduced their completion time similarly in part A (χ^2 (1) = 0.095, p = 0.28) and B (χ^2 (1) = 0.005, p = 0.84).

4.3.3 Neurofeedback performance

In this section we restrict our analyses to participants who received personalized neurofeedback to evaluate, first, whether participants significantly modulated their targeted EEG feature during the training and second, whether this modulation transferred to changes in resting-state activity. As participants varied in (a) their spectral filters, (b) their spatial filters, and (c) the direction of regulation (i.e., down- and up-regulation), we individually applied the filters and extracted the log-variance of the univariate signal approximating the band power for resting-state segments and for each 5-minute segment during neurofeedback. To take the difference in regulation direction into account, we then multiplied for each segment the change in log-variance from baseline with the targeted regulation direction (i.e., 1 for up- or -1 for down-regulation) and added the baseline value. Hence, an increase in the log-variance indicated that the value of the EEG feature changed in the targeted direction.

4.3.3.1 Training activity

To estimate the magnitude of change during the five consecutive training runs, we compared a model including run as a fixed effect to an intercept-only baseline model. The likelihood ratio test revealed that the fixed effect (b = 0.06, SE = 0.03) significantly improved the model fit compared to the baseline model (χ^2 (1) = 5.29, p < .05). Across runs, participants receiving personalized neurofeedback significantly regulated their EEG feature towards the targeted direction (see Figure 14). To evaluate whether the magnitude of regulation across runs significantly varied between participants, we estimated two additional models: (1) a baseline model only including a random intercept for participant and a random slope for run and (2) a hypothesis model additionally including a fixed effect for run. The likelihood ratio test revealed a small but non-significant difference in model fit (χ^2 (1) = 2.05, p < .15).

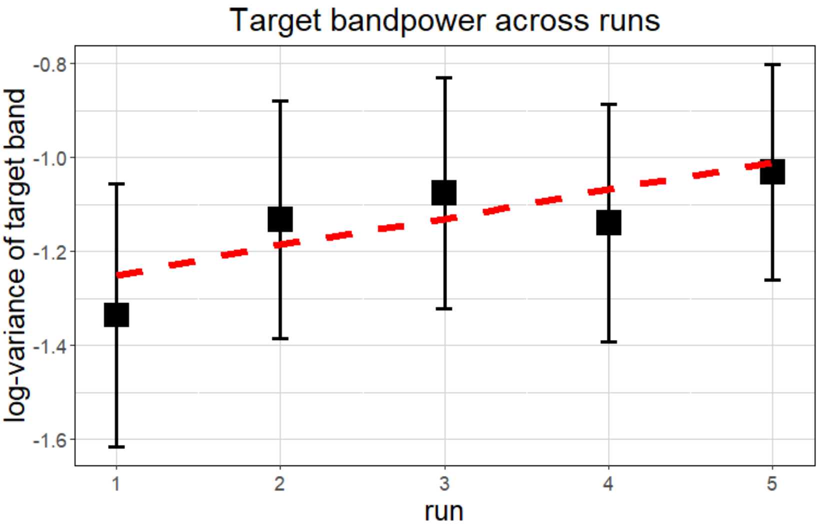

Figure 14. Average (± 1 SE) log-variance of targeted narrow-band activity per run (i.e., 5-minute segment) during neurofeedback training with the dotted red line representing the fitted values of a linear mixed model.

4.3.3.2 Resting-state activity

Finally, we evaluated whether the observed change in brain activity during training transferred to alterations of electrocortical activity in resting state. Therefore, we extracted the log-variance of the spectrally and spatially filtered EEG signal measured in an eyes-open one-minute resting-state recording before and after neurofeedback. We then performed a paired t-test to evaluate whether the activity in the targeted EEG feature significantly changed. As we corrected for varying regulation directions, we expected an increase of the targeted band power. On average, however, participants decreased the log-variance of their targeted narrow-band activity in resting-state from before (M = -0.53, SD = 0.80) to after neurofeedback (M = -0.55, SD = 1.09). A paired t-test revealed that this difference was not significant (t(19) = -0.11, p=.91). The changes in targeted band power across training runs was weakly positively correlated with the difference in activity measured in resting-state (r(18) = .14, p = .57).

4.4 Discussion

In this study we investigated the efficacy of personalized neurofeedback to enhance visuo-spatial performance as measured with the mental rotation task. Therefore, we randomly allocated a total of 40 healthy participants either to personalized neurofeedback or sham feedback. All participants performed (a) the mental rotation task on 192 trials before and 96 trials after neurofeedback and (b) the TMT on two versions before and after neurofeedback. For personalization, we defined spectral and spatial filters most contributing to the prediction of reaction times (when responding correctly) in a mental rotation task on a person-specific level (Uslu et al., 2023). Further, we individually defined the targeted regulation direction (i.e., up- or down-regulation) by inspecting the linear association between the extracted EEG features and behavioral responses. For each participant, the overall procedure of the experiment including the training of our machine learning model took approximately two hours.

We first estimated a linear mixed model to assess whether our neurofeedback intervention induced changes to electrocortical activity during training and in resting-state measured immediately after training. A significant fixed effect of training runs on the targeted EEG feature indicated that participants receiving personalized neurofeedback successfully regulated their EEG feature during training. When further evaluating the effect on resting-state activity, we did not observe significant changes suggesting that regulation of EEG activity during training did not induce functional plasticity in resting-state. This is in line with other studies investigating the effects of a single session of neurofeedback where effects on training-related EEG activity are larger compared to effects on resting-state EEG activity. While systematic alterations in brain activity seem to be trainable within the course of a single neurofeedback session, more training may be required to induce changes in resting-state activity. Furthermore, some have suggested that the trainability of EEG activity may depend on the targeted frequency band with some frequencies easier to modulate than others. However, our findings do not support this notion as our linear mixed model predicting activity in the targeted frequency band did not explain significantly more variance when adding individual learning rates in the form of a random slope to the model. To summarize, our findings support the notion that the applied neurofeedback protocol induced changes to the targeted neural feature during training which, however, did not transfer to changes in resting-state.

By tailoring the targeted neural feature to person-specific mappings between EEG signals and mental rotation performance, we demonstrated that the modulation of the targeted neural feature mediated changes to response suggesting a causal role for personalized spatial and spectral EEG features in mental rotation. An inspection of spatial and spectral components across participants revealed (a) that during mental rotation most activity originated from left frontal and right parieto-occipital areas, and (b) that oscillatory activity in the alpha and beta bands contributed most to the prediction of response time (Uslu et al., 2023). These findings are in line with previous research suggesting that some neural features are commonly involved in mental rotation across people (Boiten et al., 1992; Ozga et al., 2019; Veldema et al., 2021; Zacks, 2008). Although previous neurofeedback studies have targeted the regulation of those features, the magnitude of the mediated effect on mental rotation varied substantially with some studies not observing a significant performance increase compared to control conditions (Alkoby et al., 2018). Our findings suggest that part of this variation in effect sizes may be due to inter-individual differences in brain-behavior mappings of mental rotation. However, we expected our neurofeedback intervention to rather reduce the latency to respond correctly than the probability of responding correctly as we trained the person-specific ridge regression models to predict response times.

After the single neurofeedback session, participants who received feedback based on their own neural feature responded significantly more accurately than participants who received sham feedback but both groups similarly decreased their response latency. One potential explanation for this unexpected finding is that the per-trial time limit of 7500 ms masked too late responses. This notion is supported by the finding that real neurofeedback not only led to significantly lower error rates but also to significantly less responses missed in difficult trials compared to sham feedback. Observing participants after real neurofeedback to respond (a) in difficult trials significantly more often and (b) overall more accurately than participants after sham neurofeedback suggests that alterations of the targeted neural features decreased the processing time for more complex mental rotation operations. Notably, the cognitive-behavioral effect of our personalized neurofeedback protocol was specific to mental rotation and did not influence executive control processes involved in set-switching operations as measured with the TMT. To conclude, neurofeedback-induced alterations in electrocortical activity which is associated with performing mental rotations significantly increased mental rotation task performance more than sham feedback.

Despite our promising results, it is important to point out some of the main limitations of our study. Although we observed an effect of neurofeedback on mental rotation performance, our analysis of resting-state EEG activity did not disclose any significant, neurofeedback-induced alterations. Therefore, the increased mental rotation performance may rather be explained by task-related electrocortical activity than by EEG activity in resting-state. On the other hand, more training time may be required for inducing changes in neural activity patterns when measured in resting-state. Furthermore, we did not assess how our personalized target feature specification for neurofeedback compares to other types of neurofeedback not taking inter-individual variations into account. Future research is required to investigate whether such individual adaptations are beneficial over more conventional neurofeedback protocols relying on features common across people. Finally, our implementation of the mental rotation task has masked some of the responses as we had introduced a time limit. Other implementations which do not impose a time limit on responses may be required to reveal more clearly the effect of neurofeedback interventions on processing times for mental rotation operations.

To conclude, we have presented the effect of a novel personalized neurofeedback protocol on both neurophysiological and cognitive-behavioral outcome measures. For the neurofeedback intervention, we extracted for each participant spatial and spectral EEG features contributing most to the prediction of their mental rotation task performance. Our results indicate that participants receiving a single session of neurofeedback training significantly altered their targeted neural feature.

Furthermore, our developed neurofeedback intervention increased the performance in a mental rotation task from before to after training significantly more than sham feedback. These findings suggest the causal role of the targeted neural features for mental rotation and, further, demonstrate the trainability of those features to improve cognitive functions related to mental rotation.

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CHAPTER 5

General Discussion

Due to the heterogenous pattern of success rates inherent to neurofeedback protocols ranging from some users being highly susceptible to the procedure to others not inducing changes to their brain activity at all, we carried out a series of studies investigating the effect of specific neurofeedback parameters, namely control over training pace and estimation procedure of the feedback feature, on both neurophysiological and cognitive-behavioral outcome measures. We conducted two experimental studies applying a neurofeedback training protocol and one methodological study determining the validity of a machine learning approach designed to estimate person-specific neural correlates of mental rotation processing. Both experimental studies were designed with the same control condition (i.e., sham feedback) to investigate the efficacy of the applied neurofeedback procedure and, further, to reduce the impact of non-specific factors (e.g., motivation) on study outcomes. For the methodological study, we compared person-specific regression models relying on EEG activity to baseline models relying on past mental rotation performance to generate predictions about future mental rotation performance. In all three studies, we analyzed EEG activity recorded from healthy young adults and assessed performance measures in a mental rotation task and the TMT.

In this final chapter of the thesis, we first provide a summary of each study's findings and we, further, address the relevance of our results in the wider context of neurofeedback related literature. We then proceed with a review of the evidence for the efficacy of personalization procedures applied to neurofeedback parameters (mainly relying on the findings reported in chapters 2 and 4) followed by a discussion of potential benefits and pitfalls when applying machine learning approaches to generate individually-tailored predictions and interventions (mainly relying on the findings reported in chapter 3).

5.1 Summary of findings

In the following, each of the completed studies is summarized in the order they were presented throughout this thesis. In our first study, we investigated the effect of pacing and learning rate in neurofeedback on neurophysiological and cognitive-behavioral outcome measures. Next, we validated a machine learning approach estimating person-specific neural correlates of mental rotation. We, finally, investigated in our third study the efficacy of person-specific neural features targeted in a neurofeedback training to increase visuospatial working memory involved in mental imagery.

5.1.1 The effect of pacing and learning rate in neurofeedback on neural and cognitive functions

To investigate the efficacy of self-pacing in neurofeedback, we designed a double blind, sham-controlled RCT, the gold standard in intervention-based studies. In self-paced training, participants distributed 30 minutes of training and four minutes of resting time freely on their own, whereas the distribution of training and resting time was pre-determined for externally-paced training. To assess induced alterations in brain activity and cognitive-behavioral patterns, we measured the brain activity and the performance in cognitively demanding tasks before and after the neurofeedback intervention.

As indicated by a significant time and brain activity interaction in the linear mixed model estimates, participants receiving real neurofeedback successfully modulated their targeted neural feature during training. This only transferred to alterations of EEG oscillatory activity in resting-state when taking individual variations in learning rate into account. Such changes in resting-state may be considered as an indicator of neural plasticity (Ros et al., 2014). Notably, we similarly observed systematic alterations of the same neural feature (i.e., IUA activity) in the group receiving sham feedback indicating that non-specific factors inherent to the training context may induce similar electrocortical changes. However, the magnitude of these induced changes was smaller compared to real neurofeedback and may rather be a result of relaxation when viewing a moving bar on a screen than the specific result of reinforcing successful regulations of the targeted neural feature. Regarding the effect of pacing, participants self-pacing their neurofeedback training increased the regulatory success of the targeted neural feature similar to participants who underwent externally-paced training indicating that the control of training pace did not influence learning progress during training.

When assessing the extent to which cognitive-behavioral changes were mediated by the neurofeedback intervention, participants receiving real neurofeedback increased their performance measures by a similar magnitude as participants who received sham feedback. However, participants who controlled the pacing of their training improved some of their cognitive-behavioral performance measures more than participants undergoing externally-paced training. This effect was task-specific and may be explained by the degree to which self-pacing is involved in the administered task. We did not observe an additional synergistic effect of real neurofeedback and self-paced training on cognitive-behavioral outcome measures suggesting that the effect of pacing did not differ between real and sham neurofeedback. When accounting for inter-individual differences in learning progress during neurofeedback training, we finally demonstrated that the more successful participants were in regulating their neural feature during training, the larger their cognitive-behavioral performance gains were.

5.1.2 Person-specific neural correlates of mental rotation

In our second study, we investigated a machine learning approach for estimating person-specific neural correlates of cognitive-behavioral functions. For the validation of the developed machine learning approach, we used part of the data collected within our third study where participants responded to 192 trials of a mental rotation task prior to the neurofeedback intervention. We trained ridge regressions using neural features based on the EEG activity preceding correct responses to predict the response time, measured their performance using a hold-out set and compared them to other baseline models.

When comparing person-specific regression models using spectrally and spatially filtered EEG signals for the prediction of response times in a mental rotation task (i.e., EEG models) to models only predicting the average response time (i.e., RT model), we demonstrated that EEG models significantly outperform RT models. Furthermore, our results indicate that EEG models contain person-specific information as the predictive performance of EEG models decreased when using model parameters estimated using EEG signals from one person to predict response times with the EEG signals from another person. Taking another person's topographic activity pattern informing spatial filters of their EEG signal into account significantly increased the generalizability of person-specific EEG models indicating that inter-individual variations in the localization of electrocortical oscillatory activity partly explain varying strengths of associations in brain-behavior mappings. However, person-specific EEG models continued to outperform EEG models from another person even when taking variations in topographic activity into account suggesting a synergistic effect of both spectral and spatial person-specific characteristics on the mapping of EEG signals onto cognitive-behavioral functions. We, finally, inspected (a) the importance of features and (b) the spatial filters in person-specific EEG models and observed that (a) alpha and beta oscillations in EEG signals preceding a response contributed most to the prediction of the RT in a mental rotation task and (b) activity in the left frontal lobe and the right posterior parieto-occipital regions increased during mental rotation.

These findings are consistent with the evidence from other studies indicating that some functional associations between neural activity and mental rotation are common across people and others are person-specific. Previous neurostimulation studies have demonstrated that, across participants, alpha and beta band related EEG activity is involved in performing mental rotation (Kasten & Herrmann, 2017; Ozga et al., 2019; Schmidt et al., 2019). Albeit our person-specific modelling approach, we similarly observed larger effects of those frequency bands on mental rotation performance than other frequency bands after aggregating the effects across participants. Furthermore, our findings on involved brain regions are also in line with previous research replicating the key role of left frontal and right parieto-occipital areas for visuo-spatial working memory processes suggesting that the estimated neural features contain meaningful information and not only noise (Ptak et al., 2017; Zacks, 2008). Our findings extend previous studies by taking person-specific characteristics into account and thereby reveal novel features of brain-behavior mappings otherwise masked in population averages.

5.1.3 Personalized neurofeedback

In our third study, we investigated the efficacy of personalized neurofeedback on mental rotation task performance in a double blind, sham-controlled RCT. All 40 participants underwent the same procedure including the administration of the TMT and a mental rotation task before and after 30 minutes of neurofeedback training. For personalization, we applied the person-specific machine learning strategy validated in our second study to estimate spectral and spatial filters most relevant in predicting RT when responding correctly in a mental rotation task. Twenty participants randomly assigned to the sham control condition received pre-recorded feedback instead of feedback based on their own EEG activity.

Regarding induced neural activity, our results show that while participants receiving personalized neurofeedback significantly improved the regulation of their targeted EEG feature during training, this did not transfer to changes in resting-state measured immediately after training suggesting that no neural plasticity was induced.

In contrast to our first study, we did not observe an effect of learning rate during training on electrocortical changes in resting-state.

To inspect whether induced changes in neural activity during training influenced cognitive-behavioral outcomes, we finally assessed changes in behavioral performance measures. As our machine learning approach estimated the contribution of EEG features on RT in a mental rotation task, we expected for the personalized feedback group a larger decrease in RT of correct responses from before to after training compared to participants receiving sham feedback. However, we only found a significant main effect of time suggesting that both groups reduced their RT similarly. Since the RT was limited in our mental rotation paradigm, we next analyzed changes in error rate which revealed that personalized neurofeedback decreased error rates significantly more than sham feedback with the largest effect in trials with a high difficulty level. Further analyses revealed that participants after personalized neurofeedback responded more frequently to very difficult trials (independent of the accuracy of the response) compared to after sham feedback indicating that the administered mental rotation task may have masked mental rotation processes taking longer than the pre-defined maximum duration.

5.2 Synthesis

After having summarized the results from our three conducted studies, we now discuss to what extent our findings converge. More specifically, we discuss the efficacy of self-agency, personalization, and machine learning in optimizing neurofeedback interventions. Since rehabilitation in clinical populations is one application domain of neurofeedback interventions, we lastly discuss the impact of our findings on clinical applications.

5.2.1 Self-agency in neurofeedback

In our first study, we varied the degree of agency to which participants had control over the distribution of their training time during a single session of neurofeedback and observed that a higher degree of self-agency was associated with a more pronounced effect on cognitive performance. To specify, self-pacing the training time during neurofeedback reduced the completion time in a TMT more than externally-paced training. While self-pacing reduced the completion time in both parts of the TMT, the difference only reached significance for part B which rather involves higher-level cognitive functions such mental flexibility than visual search and motor speed components (as in part A). Albeit our limited sample size, we observed a significant effect of pacing on higher-level cognitive functions supporting the notion that self-agency influences changes in cognitive-behavioral outcomes after neurofeedback.

While self-agency is not only involved in the pacing of training time but also in controlling the feedback representation, we additionally inspected how the degree in control over feedback influenced outcome measures (Ninaus et al., 2013). Therefore, we estimated person-specific linear learning trends indicating the magnitude of change in the targeted neural feature per time unit during neurofeedback training (i.e., the learning rate). In both our first and third study, our results indicate that participants receiving real neurofeedback performed with a significantly positive learning rate. For IUA neurofeedback in our first study, we further demonstrated that the learning rate was significantly higher for real compared to sham neurofeedback since an increase in alpha activity may not only be the consequence of neurofeedback but also of prolonged states of relaxation. Due to the heterogenous spectral and spatial filters in our third study, we focused on induced electrocortical activity within the group receiving personalized neurofeedback instead of comparisons to a sham control group. Furthermore, some of our results differed between studies one and three. While our results from study one support the notion that learning rate influences not only changes to resting-state activity but also to cognitive-behavioral outcomes, we did not observe those mediated effects in our third study. One potential explanation is that the highly heterogeneous neural features derived from personalized spatial and spectral filters in study three may be more difficult to train than the IUA frequency band targeted in our first study (Rogala et al., 2016).

There are mixed findings regarding the effect of self-agency on neurophysiological and cognitive-behavioral outcomes in the neurofeedback and broader BCI literature. While some researchers promote the relevance of self-agency for successful neurofeedback interventions (Gaume et al., 2016), others highlight variations in the efficacy of mental strategies applied to regulate neural features depending on the targeted frequency band (Autenrieth et al., 2020; Kober et al., 2013). Our findings suggest that control over training time neither de- nor increase regulatory control over neural activity. However, self-paced training had a positive effect on higher cognitive functions measured with part B of the TMT suggesting that self-regulating the time of the training may involve similar cognitive functions as relevant for the TMT. Others have highlighted that the conscious experience of self-agency via cognitive strategies used to induce alterations in neural activity may impair training success (Autenrieth et al., 2020; Kober et al., 2013). As the mechanism behind neurofeedback still is under current debate, particularly regarding the role of consciousness for gaining control over neural activity (Gaume et al., 2016), more research is required to investigate how users may learn to regulate their own brain activity.

5.2.2 Personalization

We have investigated the effect of personalization on cognitive-behavioral and neurophysiological outcomes by varying some of the neurofeedback parameters such as training time and neural feature.

By allowing some users to self-pace their training in study 1, we not only expected to alter the degree of perceived self-agency but also to promote an efficient exploration of mental strategies and their efficacy in successfully regulating the targeted neural feature. Prior research has highlighted that mental strategies may facilitate the learning process (Autenrieth et al., 2020; Kober et al., 2013). Neurofeedback protocols applying a block design for training (e.g., five six-minute blocks of training interleaved by four one-minute blocks of resting) may force users to spend some of their training time for reflecting on the efficacy of the mental strategy used and, hence, leave them less time for regulating their brain activity. In self-paced training designs, users can briefly interrupt their training to process information (e.g., thinking of a new mental strategy) which do not require an immediate feedback signal. As we did not observe an interaction effect between pacing (i.e., self- and externally-paced training) and neurofeedback (i.e., real and sham neurofeedback), our finding does not support this notion.

Our findings from study 2 suggest that personalized estimation of neural correlates and their contribution in predicting cognitive-behavioral performance measures outperform between-person approaches. We have estimated parameters of ridge regressions modelling the time of correct responses in a mental rotation task as a function of preceding EEG features. We have chosen to estimate ridge regression models due to their high interpretability and their predictive performance for sparse datasets while reducing the risk of overfitting (Hoerl & Kennard, 1970). Previous studies have further highlighted the efficacy of ridge regression to infer mental workload (Planke et al., 2021) and fatigue-induced delays in reaction time (Binias et al., 2020). When inspecting feature importance scores of trained regression models, we have identified similar spectral (i.e., key role of alpha and beta band related activity for mental rotation) and spatial patterns (i.e., increased activity in left frontal and right parieto-occipital regions during mental rotation) to reports from previous studies applying cross-person analyses (Kasten & Herrmann, 2017; Ozga et al., 2019; Ptak et al., 2017; Schmidt et al., 2019; Zacks, 2008). This series of findings suggests that between-person variation in neural underpinnings of mental rotation contain meaningful information (i.e., is not merely noise), particularly useful for making more accurate predictions of cognitive-behavioral outcomes on an individual level.

In study 3, we further validated the efficacy of personalized determination of neural correlates for neurofeedback in mediating changes to mental rotation performance. Our findings indicate that participants receiving real neurofeedback respond more accurately after the training than participants receiving sham feedback. Notably, we did not find such an effect of neurofeedback condition in study 1 for which we had applied an IUA neurofeedback procedure indicating that an adjustment of the upper alpha frequency band to the individual alpha peak was insufficient to yield changes in mental rotation performance. Given the mixed findings of previous work on IUA neurofeedback, it remains unclear whether such an arbitrary choice of a frequency band has a mediating effect on cognitive-behavioral outcome measures (Alkoby et al., 2018; Escolano et al., 2014; Gruzelier, 2014a). To conclude, individually informed specifications of target neural features for neurofeedback provide a fruitful approach to overcome some of the limitations regarding training inefficacy, particularly when combined with machine learning.

Despite the varying approaches for personalization in neurofeedback, most of our findings support the notion that the individual tailoring of brain-behavior mappings and neurofeedback training parameters outperform group-based approaches in predicting and mediating changes in cognitive-behavioral processes.

5.2.3 Clinical implications

Although we did neither investigate the effect of training-pace and user-informed neural feature specifications on neurofeedback outcomes nor the accuracy of person-specific neural correlates for brain-behavior mappings in clinical populations, some of our findings may inspire future research and applications in clinical settings.

In study 1 we have demonstrated the impact of self-agency in neurofeedback interventions on higher cognitive functions within a healthy population. It remains unclear if the positive effect of self-pacing training time in neurofeedback on cognitive functions transfers to clinical populations where self-agency may be impaired (Baptista et al., 2021; Giuliani et al., 2021; Roth et al., 2023). Most patients undergoing post-stroke rehabilitation have reported at least one comorbid complication including motor impairments suggesting the need for different user-interfaces other than a physical keyboard to gain control over the distribution of training time in neurofeedback interventions. Future studies are required to assess the feasibility of different user interface designs and to investigate whether impaired self-agency interferes with self-pacing.

Relating intra-individual differences in cognitive-behavioral functions to neural activity represents an alternative approach to z-score neurofeedback which relies on normative databases to regulate neural activity towards the reference activity in healthy populations (Collura, 2014, 2016; Thatcher & Lubar, 2014). Specifically, when combined with machine learning, we have demonstrated that modulating person-specific neural correlates had a causal effect on associated cognitive-behavioral functions. One important limitation in clinical populations is, however, the under-investigated ecological validity of neurocognitive assessments (Pinto et al., 2023). Therefore, it remains unclear to what degree changes in neurocognitive functions via neurofeedback-induced alterations of person-specific, validated neural correlates transfer to restoration of functionality in daily living.

Altogether, our findings suggest that personalized approaches of estimating neural correlates of neurocognitive functions and delivering neurofeedback interventions are effective in healthy populations and represent a promising way to improve treatment options in clinical populations.

5.3 Limitations and future directions

To further contextualize our findings and to highlight potential directions for future research, it is worth examining some of the main limitations of our studies. In all our studies we used EEG to assess neural activity. While this provided a comparatively high temporal resolution for capturing electrocortical dynamics during short epochs of mental rotations, the spatial resolution is much lower compared to other brain imaging techniques such as fMRI and MEG (Murakami & Okada, 2006; Thibault et al., 2016, 2018). Therefore, the observed topographic patterns of EEG signals should be interpreted with caution and require further investigation. Given that we observed similar cross-person brain regions associated with mental rotation as previous studies, it is unlikely that all our findings are merely a result of noise. However, imaging techniques with higher spatial resolution are required to validate our findings.

In both of our neurofeedback studies (i.e., studies one and three), we applied a RCT protocol to investigate the causal effect of neurofeedback parameters on outcome measures. Some reviews have pointed out that the specificity of neurofeedback interventions to only induce changes to the pre-determined neural target feature remains questionable and requires offline analyses to assess potential changes to other neural features. While such analyses may be feasible in some scenarios, they are much more complicated in other scenarios even requiring arbitrary choice of control conditions as it is the case for spatial filters. In EEG based neurofeedback, one approach to estimate the specificity of the intervention is measuring the magnitude of change in the targeted frequency band relative to changes in neighboring frequency bands (Gruzelier, 2014a, 2014b).

While we adapted the cutoff values for the IUA band in study 1, we selected the optimal frequency band out of the same fixed set of frequency bands in study 3. Hence, it remains unclear how different cutoff values for frequency bands may perform as neural correlates. One approach to overcome this limitation would be to specify the cutoff values of frequency bands in a data-driven fashion. Recently, the clustering of squared correlations across spatial filters which maximally separate narrowband filtered EEG signals from broadband data has been proposed to identify frequency boundaries when looping over a range of frequencies (Cohen, 2021). Although this method takes similarity between narrow frequency bands into account and adapts to individual differences regarding broadband EEG activity, it is not informed by cognitive-behavioral variables for specifying boundaries in the spectral domain as it is the case for SPoC in the spatial domain (Dähne et al., 2014). Future studies are required to investigate the efficacy of person-specific frequency boundaries in modelling behavioral processes with EEG activity and their potential benefit in neurofeedback interventions.

Despite our promising results from study 2 and 3 indicating not only that neural correlates of mental rotation vary across people but also that these estimated EEG features play a causal role in mediating changes to behavioral response patterns, the predictive performance of our regression models represents the lower bound of what may be achieved. First, we recorded brain activity only with EEG and not with other imaging techniques such as fNIRS. While EEG allowed us to capture temporal dynamics related to mental rotation processes with a higher resolution, fNIRS offers a higher spatial resolution and is more robust to movement artifacts (Waldert et al., 2012). Multimodal recordings may, hence, enhance the SNR and potentially improve the performance of machine learning algorithms in predicting cognitive-behavioral outcomes based on brain activity (Li et al., 2022). Secondly, we arbitrarily specified a standard time window to extract the trial-based EEG features from as the SPoC algorithm requires standard input to estimate spatial filters. The classification of mental states during mental rotation is one approach to estimate time windows in a data-driven approach (Kong et al., 2018). Due to our limited sample size to train a machine learning model, we thirdly have restricted the modelling approach to ridge regression models. Another interesting approach would be to design a machine learning system to learn from real-time streamed EEG data as it has been applied for the classification of emotional states (Nandi et al., 2021). Such a system would further overcome the necessity to specify the sample size for training in advance. Lastly, we followed a semi-automated procedure involving the manual inspection of components resulting from ICA decomposition to reduce the impact of artifacts (e.g., eye blinks, muscle activity, and cardiac signals). Besides the offline training of the ridge regression, this signal cleaning step requires a considerable amount of time limiting its feasibility for applications in real-world clinical settings. Trained classifiers to detect artifactual ICA components for automatic cleaning of EEG signals represent a promising tool to overcome this limitation (Winkler et al., 2011).

Despite our rigorously controlled experiments, we discussed several limitations some of which may lead to new research questions for future studies. As we found significant effects given a small sample size to investigate the efficacy of neurofeedback protocols and to train the machine learning models, larger studies are likely to observe similar effects.

5.4 Conclusion

This thesis aimed to investigate the mediating effect of adapting neurofeedback parameters to contextual variables and user characteristics on neural activity and cognitive-behavioral outcomes. We reviewed existing literature and explained our motivation to adapt a personalized approach in chapter 1, specifically addressing the potential of interdisciplinary efforts to overcome some of the limitations in current neurofeedback research and to increase the efficacy of neurofeedback interventions in mediating changes to neurophysiological and cognitive-behavioral functions.

Our results indicate that (a) control over training-pace had a positive effect on higher cognitive functions, (b) using person-specific EEG features to predict mental rotation performance increased the predictive accuracy, and that (c) neurofeedback-induced changes to person-specific EEG features mediated mental rotation performance suggesting a causal relationship. Overall, our findings support the notion that inter-individual variability represents rather a source of meaningful information to consider for neurofeedback interventions than a mere consequence of random noise. We discussed explanations for these findings in terms of parameters specific to the applied neurofeedback protocol and the inter-disciplinary framework of this thesis.

Although we provided some directions for the validation and optimization of neurofeedback interventions, our efforts should be interpreted as an early step towards the optimization of neurofeedback, specifically for the integration of machine learning methods. As highlighted in section 5.4, future studies are required to replicate and extend our findings. For example, it would be useful to design computerized cognitive-behavioral tasks for other domains than mental rotation which enable the recording of task-related neural activity. Since some measures rely on paper-pencil tasks, the feasibility to synchronize EEG signals with behavioral activity is limited. Moreover, future studies could investigate the efficacy of the investigated parameter adjustments in clinical populations with impaired behavioral and cognitive functions.

Overall, our findings indicate that person-specific characteristics should be treated as relevant information for transitioning from standardized training protocols towards adaptive neurofeedback systems which are finally optimized for both inducing changes to neural activity and altering cognitive-behavioral functions.

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