Investigating the Use of Neurofeedback to Promote Self-Regulation of Cortical Motor Activities as a Potential Rehabilitation Tool Post-Stroke

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Abstract

Stroke-induced damage often leads to a more bilateral motor activation pattern, with under-activation of affected ipsilesional motor areas and over-activation in undamaged contralesional (i.e., ipsilateral) motor areas during movement of the stroke-impaired limb. This change in the functional organization of the brain, affecting cortical laterality can significantly impact individuals' ability to perform activities of daily living. Therefore, a potential rehabilitative strategy for post-stroke motor recovery is promoting self-regulation of cortical motor activity to rebalance this abnormal brain activation pattern.

This thesis explored the use of two different neuroimaging modalities as the mode of neurofeedback to promote self-modulation of cortical motor brain activities. fMRI offers a higher spatial resolution of activation over other neurofeedback technologies. On the other hand, EEG offers higher temporal resolution, lower cost and increased portability over other neurofeedback techniques, making it more amenable for widespread clinical use. By examining multiple neuroimaging modalities, this thesis hopes to explore the potential of various neurofeedback setups for motor rehabilitation after stroke.

The first experiment examined the effect of one fMRI neurofeedback training session on increasing the laterality of cortical motor activity during the movement execution in stroke patients using the “gold standard” of clinical trials. Using a double-blind, sham-controlled, between-subject design, 24 stroke patients underwent a single session of real or sham real-time fMRI neurofeedback training. Results suggest that in the presence of real neurofeedback, lateralisation was higher during the movement of the affected hand in stroke participants

The second experiment investigated the potential of using a low-cost, mobile, wireless EEG system for neurofeedback training. Using a within-subject, sham-controlled design, fourteen healthy volunteers underwent four EEG neurofeedback training sessions to modulate event-related desynchronization(ERD) activity using a simple motor execution task. Functional MRI before and after the training were also collected to assess training effects and possible individual differences more comprehensively. Results suggest that neurofeedback training with a low-density EEG setup can be effective for increasing lateralised ERD. BOLD activity in the non-dominant hemisphere was shown to be a predictor for an individual’s ability to control neurofeedback self-regulated ERD activities using motor execution.

Taken together, this thesis provides a preliminary investigation of using fMRI and low-density EEG as modes of neurofeedback in the context of motor rehabilitation for stroke. Nevertheless, more studies are needed before translation to clinical practice can be achieved.

This thesis is approximately 28 000 words

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Abbreviations

9HPT	9 Hole Peg Tests
ANCOVA	Analysis of covariance
ANOVA	Analysis of Variance
ARAT	Action Research Arm Test
BBR	Boundary Based Registration
BCI	Brain-Computer Interface
BET	Brain Extraction Tool
BOLD	Blood-Oxygenation-Level-Dependent
CSP	Common Spatial Pattern
EEG	Electroencephalogram
EMG	Electromyography
ERD	Event-Related Desynchronization
ERSP	Event-Related Spectral Perturbation
FB	Feedback
FC	Functional Connectivity
FEAT	FMRIB's Expert Analysis Tool
FLIRT	FMRIB's Linear Image Registration Tool
fMRI	Real-Time Functional Magnetic Resonance Imaging
FNIRT	FMRIB's Non-Linear Image Registration Tool
FWHM	Full-Width Half-Maximum
HRF	Haemodynamic Response Function
ICA	Independent Component Analysis
LDA	Linear Discriminant Analysis
LS	Laterality Scores
M1	Primary Motor Cortex
MI	Motor Imagery
ML	Machine Learning
MRI	Magnetic Resonance Imaging
NFB	Neurofeedback
PE	Parameter Estimates
PFC	Prefrontal Cortex
PMv	Ventral Premotor Cortex
PSC	Percent Signal Change
RM-ANOVA	Repeated-Measures Analysis of Variance
RMS	Root-mean-squares
ROI	Region-of-Interest
SE	Standard Error
SICI	Short-interval Intracortical Inhibition

TBV	Turbo-BrainVoyager

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Chapter 1

General Introduction

Stroke is the leading cause of long-term disability worldwide (Ward, 2004). Approximately half of stroke survivors require assistance in activities of daily living (ADLs) (Belda-Lois et al., 2011; Schaechter, 2004) and up to 30 percent of them experience very limited motor recovery even after months of standard therapy (Kwakkel, Kollen, & Lindeman, 2004; Members et al., 2008). As these patients often show atypical motor-related brain activities, it is posited that one possible rehabilitative approach is to reduce these abnormal brain activities with neurofeedback (Birbaumer, Murguialday, & Cohen, 2008; Daly & Wolpaw, 2008; Dimyan & Cohen, 2011).

Stroke, Functional Reorganization and Recovery

A stroke, also known as a cerebrovascular accident (CVA), is a medical emergency that occurs when there is a sudden interruption of blood flow to the brain. This interruption can be caused by a blockage in the blood vessels supplying the brain (ischemic stroke) or by the rupture of a blood vessel in the brain (hemorrhagic stroke). When the blood supply to part of the brain is interrupted or reduced, this can lead to neurological damage and various physical and cognitive impairments, depending on the site and extent of the brain damage.

Following a stroke, the brain's adaptive capacity is particularly evident as it seeks to reorganize and compensate for the loss of function. Neuroplasticity involving mechanism such as synaptic changes, dendritic branching, and even neurogenesis, can contribute to the recovery of cognitive and motor functions (Dancause, 2006). Post-stroke motor recovery is typically categorized into two phases: early and late recovery. Early recovery, often occurring within the first few weeks after a stroke, involves spontaneous improvements and recovery of viable cells from a state of shock. Late recovery, extending over several months or even years, is more influenced by rehabilitation efforts and neuroplasticity (Ballester et al., 2019).

Functional Reorganisation in the Cortical Motor System after Stroke

One of most common deficits after stroke is hemiparesis of the contralateral upper limb, with more than 80% of stroke patients experiencing this condition acutely and more than 40% chronically (Cramer et al., 1997; Hatem et al., 2016; Langhorne, Coupar & Pollock, 2009; Rathore et al., 2002; Tsao et al., 2022). Brain lateralization, the functional specialization of the left and right hemispheres, plays a significant role in healthy motor functioning. For instance, in normal healthy brains, the primary motor cortex (M1) exhibits contralateral

organization, wherein the left hemisphere predominantly controls movements on the right side of the body, and vice versa (Bear, Connors, & Paradiso, 2016). This lateralized control is particularly evident in fine motor skills, where the left hemisphere is often dominant and more competent than the right hemisphere, especially in right-handed individuals (Serrien, Ivry, & Swinnen, 2006). The preferred hand provides an enhanced performance as compared to the non-preferred hand (Sainburg 2002) and is also less disturbed by perturbations such as visual illusions (Gonzalez et al. 2006). In addition, the left hemisphere is strongly linked with right hand and bimanual movements, whereas, the right hemisphere is mostly associated with left hand movements (Serrien 2009). It has also been observed that several motion-related factors such as complexity and praxis are primarily represented in the left hemisphere (Frey 2008; Haaland et al., 2004). Stroke-induced damage can lead to changes in the functional organization of the brain, affecting cortical laterality, leading to the loss of lateralized motor control, and significantly impacting individuals' ability to perform activities of daily living.

Studies using neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), have demonstrated alterations in activation patterns within the motor cortex following a stroke (Cramer et al., 1997; Gerloff et al., 2006;

Johansen-Berg, 2007; Ward & Cohen, 2004). Previous studies have identified three distinct patterns of brain activation after stroke recovery, each likely representing different mechanisms of neural reorganisation. The first pattern is increased activation in the primary motor cortex of the damaged hemisphere (Stinear et al., 2015; Sharma & Cohen, 2012). The second pattern is compensatory enhanced activation and recruitment of the secondary areas connected to the lesioned areas and is generally observed in the lesioned hemisphere (Jaillard et al., 2005; Zhang et al., 2014). The secondary areas usually include the secondary motor cortices such as the supplementary motor area, premotor cortex, somatosensory cortex or cingulate areas. The third pattern reported is the recruitment of the sensorimotor cortex, supplementary motor area, premotor cortex and the cingulate and intraparietal sulcus in the undamaged hemisphere ipsilateral to the moving limbs (Fridman et al., 2004; Caramia et al., 2000; Cao et al., 1998; Seitz et al., 1998; Johansen-Berg et al., 2002; Ward, Brown, Thompson, & Frackowiak, 2003a).

Despite the identification of distinct patterns of brain reorganization, considerable heterogeneity still exists. Several factors were found to contribute to this heterogeneity. The first being the lesion location (Shih et al., 2023; Chen et al., 2021; Lewis & Perreault, 2007; Luft et al., 2004). For example, Luft et al.,

2004 explored how lesion locations affect brain activation pattern during paretic movements and found lower whole brain activation for patients with cortical stroke relative to healthy controls. However, the reverse is found for patients with subcortical stroke i.e., greater whole brain activation than healthy controls. More specifically, ipsilesional motor cortex, contralesional cerebellum, bilateral mesial (cingulate, SMA), and perisylvian regions were active in subcortical stroke, but cortical patients recruited only contralesional postcentral mesial hemisphere regions, and areas at the rim of the stroke cavity. Similarly, strokes in the left or right hemisphere also led to distinctive brain structural changes. Patients with right hemispheric stroke were found to have gray matter expansion in the ipsilesional medial superior and orbitofrontal cortex (Chen et al., 2012) whereas this is absent in patients with left hemispheric stroke. Stroke severity also contributed greatly to the heterogeneity observed (Ward et al., 2006; Ward et al., 2003). Ward et al., (2006) found that patients with more extensive damage to the corticospinal tract also show enhanced bilateral activation in the primary motor cortex, premotor cortex, SMA and also prefrontal cortex. Other additional factors include time after injury (Serrien et al., 2004; Newton et al., 2002), stroke stages i.e., acute or chronic (Ward et al., 2003) and also the degree of spontaneous recovery (Ward et al., 2023; Zemke et al., 2003; Feydy et al., 2002). Regardless of the heterogeneity, one common

conclusion made from most, if not all, of these stroke studies is that they all demonstrate greater recruitment or activation in secondary motor cortex with increased stroke severity and this is independent of all aforementioned factors.

Furthermore, the role of the ipsilateral or undamaged contralesional hemisphere in controlling movement of the more affected hand remains unclear and contentious. On one hand, increased ipsilateral or contralesional activation is considered suggestive of reduced interhemispheric inhibition from ipsilesional to contralesional hemisphere, thereby hindering patient's recovery and is considered detrimental (Murase et al., 2004; Schimizu et al., 2002; Boroojerdi et al., 1996). Indeed, increased activity of the contralesional hemisphere is generally observed in patients with more severe impairments and is hence associated with poorer recovery and adverse treatment efficacy (Birbaumer et al., 2008; Ward, Brown, Thompson, & Frackowiak, 2003b). Recently, Wilkins et al (2020) combined MRI, high-density EEG and robotics to measure cortical activity of 17 patients with severe stroke and contrasted their neural activity with age-matched controls. Both patients and controls performed hand opening tasks either supported on a table or when lifting against a shoulder abduction load. Greater recruitment was found in ipsilateral/contralesional secondary motor cortex relative to controls. However, critically, this increased recruitment

is correlated with decreased hand opening ability thereby suggesting a compensatory role of ipsilateral secondary motor cortex after stroke that has no functional relevance.

On the other hand, many earlier studies examining brain reorganisation in patients with congenital paralysis illnesses often found corticospinal projections within the ipsilateral/contralesional hemisphere that appears to control the more affected limb (e.g., Benecke et al., 1991; Staudt et al., 2002). Such ipsilateral activation was initially associated with mirror movements (Weiller et al., 1992; Weiller et al., 1993) and later suggested to reflect compensatory mechanisms pivotal for recovery (Cramer et al., 1997). Indeed, when compared to the unaffected healthy limbs or with age-matched healthy subjects or controls, studies have found a more bilateral motor activity, with over-activation in undamaged contralesional (i.e., ipsilateral) motor areas during movement of the stroke-impaired limb (Johansen-Berg et al., 2002; Ward, Brown, Thompson, & Frackowiak, 2003a; Lotze et al., 2006) to compensate for lost functions (Cramer, 2008; Cramer et al., 1997) and seem to promote recovery. Lotze et al., (2009) used fMRI-navigated repetitive transcranial magnetic stimulation (rTMS) to induce functional lesions over the primary motor cortex, dorsal premotor cortex and the superior parietal lobe of the contralesional hemisphere in four

patients with congenital hemiparesis while they performed a sequential finger-tapping task. Both rTMS-induced functional lesions of the dorsal premotor cortex and primary motor cortex led to less temporally precise taps thereby providing evidence for potential functional importance of the contralesional hemisphere after stroke. Similarly, in a study by Tscherpel et al. (2020), TMS interferences on the contralesional dorsal premotor cortex also induced deterioration of motor performance of the paretic hand in patients who were more than three months post-stroke. However, such deterioration following TMS interference on contralesional dorsal premotor cortex was not observed in the first week after stroke. Taken together, studies from congenital hemiparesis and stroke patients suggest that the contralesional hemisphere can play a supportive role in functional reorganisation following brain damage.

In order to reconcile contradicting findings on the role of contralesional areas in motor recovery, the concept of structural reserve characteristics has been proposed (Di Pino et al., 2014; Murphy & Corbett, 2009). Structural reserve considers how changes in contralesional networks are influenced by the state of ipsilesional networks, i.e.,whether the contralesional hemisphere's influence is compensatory or maladaptive may depend on the extent of unaffected structures within the ipsilesional hemisphere and the remaining functionality of

ipsilesional motor areas and the corticospinal tract (CST) (Bertolucci, Chisari & Fregni , 2018; Cramer 2008; Di Pino et al., 2014). For patients with a high structural reserve, competitive inhibition from the contralesional hemisphere is believed to be more prominent. Conversely, patients with fewer remaining resources in the ipsilesional hemisphere might rely more on the compensatory recruitment of contralesional areas (Brancaccio, Tabarelli & Belardinelli, 2022; Di Pino et al., 2014).

Nevertheless, longitudinal studies have also shown that for some patients with better recovery and outcomes, this initial over-activation tends to decrease with time, paralleling their recovery process (Calautti, Leroy, Guincestre, & Baron, 2001; Marshall et al., 2000; Ward et al., 2003a). Hence, increasing hemispheric laterality when moving the stroke-impaired limb, by downregulation of activity from the contralesional hemisphere and/or upregulation of the stroke-affected ipsilesional hemispheric activity, shows promise as a rehabilitation strategy to promote motor recovery for at least a subset of stroke patients (Soekadar, Birbaumer, & Cohen, 2011).

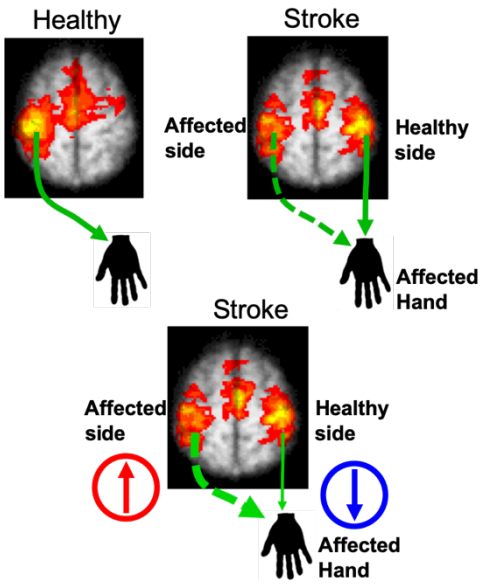

Figure 2.1 Changes in motor activation pattern following a stroke incident. Poor motor recovery after stroke is associated with a more bilateral pattern of brain activity when moving the stroke-affected limb (top right). Rebalancing cortical motor activity may be beneficial to stroke rehabilitation (bottom).

Promoting Cortical Laterality for Stroke Rehabilitation

Promoting recovery after stroke involves harnessing the brain's capacity for neuroplasticity. Rehabilitation strategies aim to optimize cortical laterality by encouraging the adaptive reorganization of neural circuits. For instance, non-invasive brain stimulation (NIBS) techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have shown promise in promoting cortical laterality after stroke. These techniques modulate neural activity and can be applied to either inhibit the contralesional

hemisphere or stimulate the affected hemisphere, depending on the rehabilitation goals (Hsu et al., 2012). As these techniques allow to experimentally manipulate brain activity and study its consequences for perception, cognition, and eventually, behaviour, causal inferences can be made potentially (Bergmann & Hartwigsen 2021). In fact, a meta-analysis of 112 studies conducted by McDonnell and Stinear (2017) aims to compare measures of corticomotor excitability, intracortical function, and interhemispheric inhibition, between the ipsilesional and contralesional hemispheres of people with stroke, and measures made in healthy adults. They established that ipsilesional M1 excitability is lower than contralesional and healthy control M1 excitability in both the early and chronic phases of stroke. Second, ipsilesional hemisphere short-interval intracortical inhibition (SICI) is lower than contralesional and healthy control SICI in the early phase of stroke, with no difference in the chronic phase of stroke. Lastly, there are essentially no differences between the contralesional hemisphere and healthy controls in either the early or chronic phases of stroke. Together, these findings indicate that the effects of stroke on motor cortex excitability and intracortical function are primarily localised to the Ipsilesional hemisphere. Ipsilesional hemisphere SICI may be initially reduced after stroke, perhaps as a mechanism supporting cortical reorganisation and recovery (Murphy & Corbett, 2009). Measures of

excitability and intracortical function in the contralesional hemisphere seem to be similar to healthy controls, and stable over time. Hence, they concluded that facilitating lesioned M1 excitability directly may be beneficial for promoting post-stroke recovery.

Using Neurofeedback to promote Functional Reorganisation

Neurofeedback, a form of biofeedback that involves monitoring and providing real-time feedback on brain activity, has shown promise as a complementary approach in stroke rehabilitation (Marzbani, Marateb & Mansourian, 2016). In neurofeedback, users are given visual or auditory feedback of their brain states in real-time with a brain-computer interface (BCI). Real-time feedback allows individuals to consciously influence brain activity patterns associated with motor function, potentially fostering improved motor control and coordination (Birbaumer, et al., 2009). At its core, neurofeedback operates on principles akin to reinforcement learning. Individuals receive immediate feedback when their brain produces desired patterns associated with motor function (Sitaram, et al., 2017). This is generally thought to be a form of operant conditioning, where the feedback also indicates users' success in controlling their brain signals, thereby providing the reward for correct modification (Soekadar et al., 2011). With

sufficient training, brain activities can be reconditioned and retrained to attain the recommended beneficial activation pattern and reduce atypical activities (Hammond, 2011).

Research has already shown that self-regulations of brain activity can be achieved with neurofeedback training (Birbaumer et al., 2008; Daly & Wolpaw, 2008; deCharms et al., 2005; Sitaram et al., 2007; Weiskopf et al., 2007). In effect, neurofeedback has been applied to the treatment of various neurological and psychiatric disorders such as ADHD (Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Strehl et al., 2006), epilepsy (Kotchoubey et al., 2001), chronic pain syndrome (Lotze et al., 1999) and stroke (Pfurtscheller, Guger, Muller, Krausz, & Neuper, 2000).

Modes of Neurofeedback

Functional magnetic resonance imaging (fMRI)

Functional Magnetic Resonance Imaging (fMRI) is a non-invasive imaging technique that measures and maps brain activity. It is based on the principle

that neural activity is accompanied by changes in blood flow, oxygenation, and volume. fMRI relies on the Blood Oxygenation Level Dependent (BOLD) contrast. When a particular brain region becomes active, there is an increase in blood flow to that area. This increased blood flow leads to a change in the magnetic properties of blood, which can be detected by an MRI scanner. The BOLD (Blood Oxygen Level Dependent) contrast is then used as a proxy for neuronal activity (Ogawa et al., 1990).

Previous research in healthy participants has shown that participants were able to modulate the activation in motor cortex when receiving neurofeedback from real-time functional magnetic resonance imaging (rtFMRI) while performing both physical actions and motor imagery (e.g., Chiew et al., 2012). Studies with stroke patients have also been increasing in the recent years. For example, Giulia et al. (2021) ran a study with five chronic stroke patients with multi-session fMRI neurofeedback training over a period of five weeks. They applied the Dynamic Causal Modelling and Parametric Empirical Bayes frameworks for the estimation of effective connectivity changes in a motor network including both ipsilesional and contralesional premotor, supplementary and primary motor areas. Visual feedback was provided in the form of a ball moving along a one-dimensional bar and was based on the normalised average of the EEG ERD in 8-30Hz band and

fMRI percent signal change in SMA and M1. Their study shows inter-hemispheric effective connectivity between premotor and primary motor regions decreased, and ipsilesional self-inhibitory connections (i.e.,negative coupling rates) were reduced in strength, suggesting greater brain activity in the leisoned hemisphere. In addition, in a separate pilot study with 4 patients using a similar neurofeedback protocol and diffusion tensor model to assess corticospinal tract integrity, only the two patients with a preserved CST and subcortical lesions succeeded in upregulating the ipsilesional primary motor cortex and exhibited a functional improvement of upper limb motricity. This highlights the importance of taking into account the variability of the stroke patients' population and enabled to identify inclusion criteria for the design of future clinical studies. (Giulia et al., 2020). However, these studies share number of features that were identified as weaknesses in a systemic review on the effectiveness of real-time fMRI neurofeedback training in modulating motor and cognitive processes performed by Wang, Mantini & Gillebert (2017). In this review which examined 33 rt-fMRI neurofeedback studies, including 651 healthy individuals and 15 stroke patients in, it was concluded that real-time fMRI neurofeedback training can lead to a learned modulation of brain signals, with associated changes at both the neural and the behavioural level. However most neurofeedback studies with stroke patients have the following caveats: 1) small/limited sample size, 2)

did not include a sham/control group, 3) potential biases in participant allocation in single-blinded studies and 4) lack of long-term follow- up studies. As such, any evidence of clinical improvement should be interpreted cautiously. Hence, more research is needed to establish how its use can be optimized in the context of stroke rehabilitation.

Electroencephalogram (EEG)

Electroencephalography (EEG) is a non-invasive neuroimaging technique that measures the electrical activity of the brain. This method involves placing electrodes on the scalp to detect and record the electrical signals generated by neurons in the brain (Niedermeyer & da Silva, 2004). The recorded signals, known colloquially as brain waves, reflect the synchronized activity of groups of neurons and can be categorized into different frequency bands, including delta, theta, alpha, beta, and gamma. Decrease in the power of neural oscillations in specific frequency bands, typically in the alpha and beta ranges, in response to a stimulus or during the execution of a motor task is known as Event-Related Desynchronization (ERD) (Pfurtscheller & Neuper, 1997). In the motor domain, the desynchronization of mu rhythms (neural oscillatory activity observed in the mu frequency band of approximately 8-13 Hz over the sensorimotor cortex) is

often associated with voluntary movement preparation and execution (Neuper, Wörtz, & Pfurtscheller, 2006; Pfurtscheller & Lopes da Silva, 1999).

To date, EEG neurofeedback training has been extensively studied in healthy adults to improve sport performance, attention and cognitive functioning (Goon et al., 2021). In the clinical field, there is also a growing interest in using it as a rehabilitation tool in for disorders such as ADHD (McGough, 2022; Pimenta et al., 2021), PTSD (Steingrimsson et al., 2020) and stroke (Ang et al., 2015; Wada et al., 2019). For instance, Kober et al. (2015) studied the specific effects of EEG based neurofeedback training on memory functions in post-stroke victims. In total, 11 stroke patients received sensorimotor(12-15Hz) neurofeedback training (SMR-NFB), 6 stroke patients received upper alpha (10-12Hz) neurofeedback training (UA-NFB) and 7 stroke patients received the conventional rehabilitation. In addition, 40 healthy particitpants also performed NFB training, either SMR protocol or UA protocol. Each group participated in 10 sessions spread over 4 weeks, receiving audio-visual feedback that reflects the absolute power of the trained EEG frequency. After NFB, the SMR patient group and the SMR control group showed significant improvements in verbal short- and long-term memory and in visual-spatial memory (CVLT—California Verbal Learning Test; and VVM2 tests—Visual and Verbal Memory Test). The UA group

improved the verbal memory (CVLT test) and the working memory significantly (CBTT backward task, Corsi Block Tapping Test). Overall, both stroke patients and healthy control showed general improvement in verbal short- and long-term memory performance after NF training. Unfortunately, no between group differences were tested.

In another study, Mottaz et al. (2018) studied modulation of functional connectivity (FC) with EEG neurofeedback in 10 patients with chronic stroke and moderate to severe upper limb motor impairment using a controlled cross-over design. In this study, researchers manipulated the sum of FC (quantified using the absolute imaginary part of coherency in the alpha band of the EEG signal) between the ipsilesional primary motor area and the rest of the brain with visual neurofeedback. Patients were alternatively assigned to start with either the motor cortex FC training or the control region FC training. Each arm of training was composed of eight sessions, two per week, distributed over one month. A wash-out period of one month was implemented to avoid carry-over effect. It was shown that patients were able to increase FC and motor function (measured with Fugl-Meyer assessment) when receiving real neurofeedback and the improvement in motor function was proportional to the degree of FC enhancement.

Lastly, in a preliminary clinical trial by Rayegani et al. (2014), 30 patients with stroke were allocated to three intervention cohorts: (1) occupational therapy (OT), (2) OT plus EMG-biofeedback therapy, and (3) OT plus neurofeedback therapy. Each cohort received 10 sessions of their assigned therapy over a 2-week period. EMG-biofeedback therapy was performed to strengthen the abductor pollicis brevis (APB) muscle. Neurofeedback training was aimed at enhancing sensorimotor rhythm after mental motor imagery. It was observed that hand function (assessed with Jebsen Taylor Hand Function Test) improved significantly in all three groups but there was no difference among groups. Maximum and mean contraction values of electrical activities of the APB muscle during voluntary contraction increased significantly after EMG-biofeedback training. The spectral power density of the sensorimotor rhythm band in the neurofeedback group increased after mental motor imagery. However, as there was no sham control administered and no difference among groups was observed, drawing conclusions regarding the effect and efficacy of neurofeedback is less straightforward.

In addition, most advances in the motor domain have been largely focusing on using real-time EEG data to drive brain-computer interfaces such as exoskeleton

and robotic gloves (Ang et al., 2015, Cheng et al., 2020; Wada et al., 2019), functional electrical stimulation (Jang et al., 2016; Kim et al., 2016) and some other forms of orthosis (Nishimoto et al., 2018). Thus far, studies on EEG neurofeedback, its potential effect on cortical reorganisation and functional changes have been very limited (Yoo, 2019).

Comparing fMRI and EEG modalities

Functional Magnetic Resonance Imaging (fMRI) and Electroencephalography (EEG) are pivotal neuroimaging techniques that enable researchers to investigate and understand brain function. While both methods contribute valuable insights, they differ significantly in their underlying principles, temporal and spatial resolutions, and practical applications (Table 1.1).

	fMRI	EEG
Signal	BOLD	Electro-physiological
Spatial Resolution	Sub-millimetre	centimetre
Temporal Resolution	1-3Hz	>1000Hz
Depth of Measurement	Whole head	Cortex
Portability	None	Yes
Cost	High	Low
Contraindications	Many	Very rare

Table 1.2 Comparing fMRI and EEG signals

Principles of Measurement (signal)

Functional Magnetic Resonance Imaging relies on the blood-oxygen-level-dependent (BOLD) contrast to detect changes in blood flow and oxygenation levels associated with neural activity (Ogawa et al., 1990). In contrast, Electroencephalography directly measures the electrical activity of neurons by recording voltage fluctuations resulting from ionic current flows within the brain (Niedermeyer & da Silva, 2004).

Spatial resolution

Spatial resolution pertains to the ability to localize brain activity in terms of anatomical structures. fMRI provides high spatial resolution, offering detailed information about the location of brain activity at sub-millimetre range (Moerel

et al., 2020). On the other hand, EEG has lower spatial resolution compared to fMRI (centimetre range). As the measured signal is the sum of the electrical activity from neurons beneath the electrodes and scalp, this makes it challenging to pinpoint the exact source of neural activity (Michel et al., 2004).

Temporal resolution

Temporal resolution refers to the ability to capture changes in brain activity over time. fMRI exhibits relatively poor temporal resolution, capturing changes in brain activity on the order of seconds as it is relies on the change in sluggish and delayed haemodynamic response that unfolds over the course of seconds (Huettel, Song, & McCarthy, 2004). In contrast, EEG boasts exceptional temporal resolution, capturing changes in neural processes with millisecond precision (Luck, 2014).

Depth of Measurement

The depth of measurement refers to the ability to capture neural activity in both cortical and subcortical structures. fMRI can measure brain activity in both deep structures and cortical regions (Kwong et al., 1992), while EEG primarily reflects cortical activity and is less sensitive to deep brain structures (Nunez & Srinivasan, 2006).

Portability

The practical aspects of implementing these techniques, including portability and setup considerations, are crucial for their applicability in various settings and particularly relevant for clinical applications. fMRI requires a dedicated and expensive scanner, and participants need to lie still inside the scanner (Huettel et al., 2004). In contrast, EEG is more portable and flexible, allowing for a wider range of experimental setups, including mobile and real-world scenarios (Luck, 2014).

Cost

The cost associated with acquiring and maintaining these neuroimaging techniques is a significant factor. fMRI is known for its high acquisition and maintenance costs (Ogawa et al., 1990), but EEG systems are generally more cost-effective than fMRI setups (Niedermeyer & da Silva, 2004), making it an ideal tool for long-term rehabilitation.

Contraindications

As magnetic fields in MRI scanners can cause dangerous interactions in patients with metallic foreign bodies, e.g., projectile effect, twisting, burning, artifacts, and device malfunction, there are many contraindications associated with MRI

scanning (e.g most metallic implants and cardiac pacemakers) (Ghadimi & Sapra, 2023). However, EEG is relatively contraindications-free, allowing it to be accessible to most people.

Usage & Efficacy

Based on current literature, it appears that EEG neurofeedback has been more established, has more widespread applications and has been used to treat a greater range of both neurological and psychological disorders. In effect, in a literature search performed by Thibault et al. (2015) on Web of Science for neurofeedback/biofeedback based on different imaging modalities, it has been estimated that the first application to neurofeedback for EEG was in the year 1958, and it has since been used by more than 1000 practitioners and over 50 research laboratories. For other modalities, fMRI, MEG and fNIRS, application to neurofeedback appeared after the year 2000, are not used by practitioners yet and are studied by less than 10 research laboratories.

In terms of efficacies, the difference between fMRI and EEG might be dependent on the underlying condition and pathologies of the brain. For instance, for conditions like ADHD and anxiety, EEG neurofeedback has shown high efficacy for promoting self-regulations of brain oscillations related to the condition and

faster real-time feedback capabilities. For conditions requiring precise brain region targeting, such as post-stroke motor rehabilitation, fMRI neurofeedback may be more effective (Bezmaternykh, 2021, Ciccarelli, 2023). However, more studies are still needed to established whether clinical improvements can be attributed to neurofeedback per se or to factors such as placebo effects. Few neurofeedback studies (e.g., Ramos-Murguialday et al., 2013) utilised a double-blind paradigm and this is potentially a confound as it is close to impossible to dissociate between the effects of the neurofeedback or other factors. In addition, EEG neurofeedback studies typically include much longer and/or more sessions than fMRI neurofeedback due to the lower cost and being more accessible, making comparison between these modalities even harder.

In conclusion, fMRI offers higher spatial resolution of activation over other neurofeedback technologies. It therefore allows for a greater spatial specificity for the heterogenous patient population and provides an important proof of principle regarding the feasibility of using neurofeedback for motor rehabilitation after stroke. On the other hand, even though EEG has lower spatial resolution than fMRI, it offers higher temporal resolution, lower cost and increased portability over other neurofeedback techniques, making it more amenable for widespread clinical use. Thus, examining multiple neuroimaging

modalities can enhance the overall understanding of the effect of neurofeedback for motor rehabilitation after stroke

Challenges in Using Neurofeedback in Rehabilitation

Even though neurofeedback holds potential for enhancing motor recovery post-stroke, several challenges remain to hinder its clinical transfer to stroke rehabilitation programs. For instance, while there is a growing body of literature on neurofeedback in stroke rehabilitation, some studies still lack methodological rigor. Issues such as small sample sizes, lack of appropriate control groups, and limited follow-up periods can compromise the validity and generalizability of findings (Bowman et al., 2021, Liu et al., 2023). Placebo effects and participant expectancy can also play a significant role in the perceived benefits of neurofeedback (Lee & Suhr 2020). Stroke survivors' belief in the effectiveness of the intervention may lead to improvements in functioning, irrespective of the specific neurofeedback mechanisms. A robust sham-controlled design is crucial to discern the true effects of neurofeedback from placebo responses (Fede et al., 2020; Sanders et al., 2022). Therefore, well-designed randomized controlled trials with larger sample sizes and longer follow-up durations are essential to

establish the efficacy of neurofeedback in stroke rehabilitation conclusively (Bowman et al., 2021).

In addition, stroke is a heterogeneous condition, and individuals exhibit diverse motor and cognitive deficits. The challenge arises in predicting and understanding how different stroke survivors will respond to specific neurofeedback protocols. Factors such as lesion location, severity, and the individual's baseline cognitive and motor function contribute to significant variability in treatment outcomes (Franc et al., 2022; Li, Uehara, & Hanakawa, 2015; Wang et al., 2018).

Lastly, the implementation of neurofeedback in stroke rehabilitation can be resource-intensive. Specialized equipment, trained professionals, and the need for multiple sessions can contribute to the overall cost (Franc et al., 2022). This raises concerns about the accessibility of neurofeedback, particularly for stroke survivors in regions with limited healthcare resources. Furthermore, longitudinal studies and treatments with extended follow-up periods are essential to elucidate the enduring impact of neurofeedback on stroke recovery (Mane, Chouhan & Guan 2020). Overcoming financial and infrastructural

barriers is crucial for the widespread adoption of neurofeedback in stroke rehabilitation.

Aims of this thesis

The current thesis aims to extend this work by examining the effects of neurofeedback with different brain imaging modalities on stroke patients and healthy adults. The first study examined the effect of using fMRI neurofeedback with chronic stroke patients using the "gold standard" of clinical trials, i.e a double-blind, sham/placebo-controlled design. With the high spatial resolution inherent in fMRI signals, this study hopes to provide an important proof of principle in using neurofeedback for motor rehabilitation to rebalance cortical laterality after stroke. The second study used a portable wireless EEG device to provide neurofeedback to healthy adults across multiple training sessions with the objective of increasing cortical laterality during motor execution. To study the effectiveness of the portable EEG neurofeedback setup, an fMRI scan was carried out before and after the training sessions to further examine possible changes in cortical laterality. The objective of this study is to assess the feasibility of using such a small portable EEG neurofeedback device to increase

cortical lateralisation during motor execution, for it to be adopted for widespread clinical uses.

Chapter 2

Methods

This thesis makes use of two non-invasive methods for monitoring the human brain and providing real-time feedback based on brain activity signals: magnetic resonance imaging (MRI) and electroencephalography (EEG). The previous chapter outlined the advantages and disadvantages of these methods in the context of neurofeedback. The current chapter summarises the nature of the recorded signals in each case, and standard methods for data acquisition and analysis.

Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) is a non-invasive medical imaging technique that provides detailed visualization of internal structures in the human body based on the principles of nuclear magnetic resonance (NMR). MRI relies on the interaction of hydrogen nuclei, abundant in the human body due to the prevalence of water molecules. When placed in a strong magnetic field, these hydrogen nuclei align themselves with the magnetic field. Upon exposure to a radiofrequency (RF) pulse, the hydrogen nuclei absorb energy and transition to a higher energy state. As the nuclei return to their equilibrium state, they emit RF signals, which are detected by specialized coils in the MRI machine (Huettel, Song, & McCarthy, 2009; Nishimura, 2010).

The contrast in MRI images is determined by the relaxation times of tissues—specifically, the longitudinal relaxation time (T1) and the transverse relaxation time (T2). T1 relaxation influences the recovery of longitudinal magnetization, affecting the brightness of tissues in the images, while T2 relaxation influences the decay of transverse magnetization, influencing tissue contrast. Different tissues exhibit varying T1 and T2 relaxation times, resulting in the distinct contrast seen in MRI images (Huettel et al., 2009; Nishimura, 2010).

MRI excels at providing high-resolution anatomical images, allowing clinicians to visualize soft tissues with excellent detail. The technique is particularly valuable for imaging the brain, spinal cord, joints, and organs (Huettel et al., 2009; Nishimura, 2010).

Functional Magnetic Resonance Imaging (fMRI)

Functional Magnetic Resonance Imaging (fMRI) is a powerful neuroimaging technique that provides insights into the functioning of the human brain. This imaging technique is grounded in the principles of MRI but is specifically tailored to capture changes in blood flow associated with neuronal activity, enabling the mapping of brain regions involved in various tasks and functions (Bandettini & Wong 1997).

The principles of fMRI lies in the Blood Oxygenation Level Dependent (BOLD) contrast, which reflects the variations in blood flow and oxygenation that occur when neurons are active (Ogawa et al., 1992). When a specific brain region becomes active, there is an increased demand for oxygen and nutrients. In response, blood flow to that region increases to meet these metabolic needs. The oxygen-rich blood causes a change in the magnetic properties of haemoglobin, specifically its susceptibility to the magnetic field generated by the MRI machine. This change is detected by the MRI scanner, and the resulting signal forms the basis for fMRI data (Logothetis, 2008). The acquired fMRI data consists of a series of images or volumes captured over time. Each volume represents a specific period during the experiment, allowing researchers to observe dynamic changes in brain activity.

Haemodynamic Response

The hemodynamic response refers to the physiological changes in blood flow, volume, and oxygenation that occur in response to neural activity. In the context of functional magnetic resonance imaging (fMRI), the hemodynamic response is a key phenomenon used to infer brain activity. Understanding the temporal dynamics of the HRF is crucial for experiment planning and fMRI data analysis.

The time course of the hemodynamic response function (HRF) refers to the temporal pattern of changes in blood flow, volume, and oxygenation that occur in response to neural activity. The HRF begins with a brief initial dip, representing a transient decrease in blood oxygenation immediately following neural activation. This initial dip is thought to be related to an initial surge in oxygen consumption by activated neurons (Bandettini et al., 1992). Following the initial dip, there is a rapid increase in blood flow and oxygenation, leading to an overshoot of the hemodynamic response. This overshoot is a consequence of the neurovascular coupling mechanism, where increased neural activity leads to a local increase in blood flow (Ogawa et al., 1990). Following the overshoot, there is a period of undershoot where blood flow and oxygenation level fall below baseline due to local metabolic demands (Malonek & Grinvald, 1996). The complete time course typically takes place over several seconds (Boynton, 1996).

Given the basis of the BOLD fMRI response, it is important to consider whether disruptions to the neurovascular system, as might be expected in disorders such as stroke, might influence the recorded signal. The current thesis explores the use of fMRI in stroke patients, as a basis for neurofeedback (Chapter 3) and as a read-out of brain activity signals (Chapters 3 and 4). Use of fMRI here relies on

the assumption that BOLD signals reliably reflect neuronal activity even in the presence of neurovascular disease. While this assumption is shared by most studies using FMRI in stroke patients, it has previously been reported that stroke can disrupt the usual neurovascular coupling relationships and hence alter behaviour of the fMRI BOLD signal (Veldsman, Cumming & Brodtmann, 2015).

Task-based fMRI & Block Design

Task-based fMRI is a type of experimental design that involves scanning participants while they perform specific cognitive or motor tasks. Changes in BOLD signal during these tasks reveal brain regions activated in response to the stimulus. Tasks can be presented in a block design paradigm, where different experimental conditions or tasks are presented to the participants as distinct, consecutive blocks of time. These blocks can be randomised or counterbalanced, with a baseline/resting block in between them. Each block is usually around 15-20s to capture the haemodynamic response.

Analyses of fMRI data

Preprocessing

Preprocessing steps are important for enhancing data quality, correcting for artifacts, and preparing the data for subsequent statistical analyses. All fMRI processing within this thesis was performed using tools from the FMRIB Software Library (www.fmrib.ox.ac.uk/fsl). This includes motion correction using MCFLIRT, which corrects for motion artifacts by aligning each volume to a reference volume (Jenkinson et al., 2002). This step is essential to prevent motion-related distortions that could confound subsequent analyses. Then B0 Unwarping using Boundary Based Registration (BBR) is used to reduce fieldmap distortion (Greve and Fischl, 2009). Next Brain Extraction Tool (BET) is applied to remove non-brain tissue and enhance the signal-to-noise ratio (Jenkinson, Pechaud and Smith, 2005). This step is particularly important for focusing analyses on relevant brain regions and minimizing computational load. In addition, spatial smoothing and temporal filtering are also used during preprocessing to enhance signal-to-noise ratio by removing irrelevant data. Lastly, functional data is registered to a structural MRI image using FMRIB's Linear Registration Tool (FLIRT) (Jenkinson and Smith, 2001; Jenkinson et al., 2002) and then to standard space (e.g.,such as MNI152) using FMRIB's Non-

Linear Registration Tool (FNIRT) (Andersson, Jenkinson and Smith, 2007). These steps are completed so activation across participants can be compared for group analyses later.

Statistical Analyses

Once the data is preprocessed, statistical analyses are employed to identify brain regions that exhibit significant changes in activity during specific tasks or experimental conditions. The General Linear Model (GLM) is a commonly used statistical framework for analysing fMRI data, allowing researchers to assess the relationship between neural activity and experimental manipulations (Worsley et al., 1996). Activation maps are then generated, highlighting regions of the brain where the BOLD signal deviates from the baseline or control group, indicating increased or decreased activity (Logothetis, 2008).

In FSL, a first-level analysis is used to analyse an individual session's data. It combines the preprocessing steps mentioned above and statistical steps to model the task design used for the experiment at single subject level. Higher Level FEAT analyses combine outputs from multiple First-Level FEAT analyses to

assess group-level results, either across several sessions or across multiple subjects.

Electroencephalography

Electroencephalography (EEG) is a non-invasive neuroimaging technique that plays a pivotal role in studying the electrical activity of the brain. EEG operates on the principle that the synchronized electrical activity of neurons produces detectable voltage fluctuations on the scalp. More specifically, EEG measures the sum of postsynaptic potentials of cortical pyramidal neurons, creating a macroscopic representation of neural activity. The synchronous firing of neurons contributes to detectable voltage fluctuations on the scalp. Electrodes are strategically placed across the scalp to capture these electrical signals, forming an EEG recording. The electrical potentials detected by the electrodes are typically in the microvolt range and represent the aggregate activity of thousands to millions of neurons firing in synchrony (Niedermeyer & da Silva, 2004).

Motor-related EEG Frequency Bands

EEG signals are characterized by a complex symphony of neural oscillations, with different frequency bands associating with specific cognitive and physiological states. Delta waves (0.5-4 Hz) are prominent in deep sleep, theta waves (4-8 Hz) are linked to drowsiness (Basar, 2012), alpha waves (8-13 Hz) signify relaxed wakefulness (Basar, 2012), beta waves (13-30 Hz) are associated with active concentration (Engel & Fries, 2010), and gamma waves (>30 Hz) are implicated in higher cognitive functions (Başar, 2012, Herrmann et al., 2013).

Out of these frequency bands, a subtype of the alpha rhythm (called Mu rhythms) and beta oscillations are thought to be associated with motor-related brain activities. These oscillations are observed mainly over the sensorimotor cortex and have been extensively studied in the context of motor planning and execution. Changes in these oscillations can serve as indicators of motor system dysfunction and may aid in the diagnosis and monitoring of neurological conditions (Pineda, 2005). They are also the targets in neurofeedback interventions, where individuals are trained to modulate these activities for intervention purposes.

Event-Related Desynchronization (ERD)

ERD refers to the reduction in power or synchronization of neural oscillations relative to a baseline or resting state (Pfurtscheller & da Silva, 1999) (Figure 2.1).

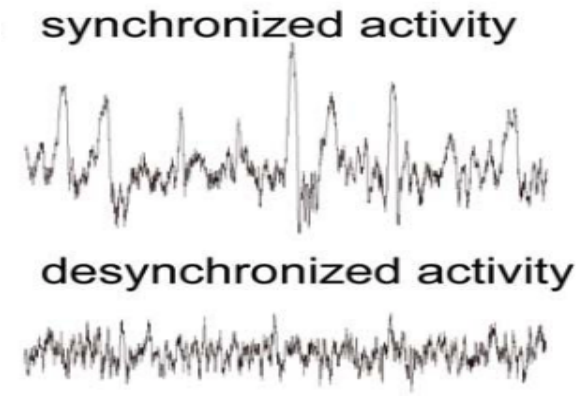

Figure 2.1 Representative EEG traces for synchronized and desynchronized states. Synchronized activity is characterized by high amplitude slow wave. Desynchronized state of EEG is characterized as smaller and rapid activity. From "Cortical Layer 1 and Layer 2/3 Astrocytes Exhibit Distinct Calcium Dynamics In Vivo" by Takata et al., 2008, PloS one. 3. e2525. 10.1371/journal.pone.0002525 CC By 4.0

More specifically for motor-related activities, mu and beta rhythms are typically prominent at the sensorimotor regions when an individual is at rest. However, during the preparation and execution of voluntary movements, there is a suppression of mu and beta activity (Pfurtscheller & da Silva, 1999). Increased cortical activation leads to the desynchronization of neural ensembles, resulting in a decrease in power in these frequency bands. ERD reflects the release of cortical resources to meet the increased processing demands. It is thought that

the brain exhibits a state of desynchronization when it is actively engaged, facilitating optimal information processing (Klimesch, 1999). Desynchronization in the mu and beta activity the is considered indicative of increased cortical activity related to motor planning and execution (Pfurtscheller & da Silva, 1999).

ERD can serve as a valuable neuroimaging marker. By quantifying the degree of desynchronization, ERD provides a continuous measure of cognitive or motor engagement. This principle has been used in brain-computer interface (BCI) and neurofeedback systems, where ERD is used as the feature for decoding user intent and motor-related activities in real-time applications (Pfurtscheller & Neuper, 2006).

ERD Analyses

In this thesis, EEG data are analysed EEGLAB B 10.2.2.4b (Delorme and Makeig, 2004) and MATLAB R2011b (Mathworks, Inc, Natick, MA). Raw EEG data are first preprocessed to isolate frequency bands of interest using bandpass filters. Artifacts such as eye blinks and muscle activities are then removed via Independent Component Analyses (ICA), artifact rejection algorithms and manual rejection. Next the data has to be segmented into epochs based on the

onset of task-related events or stimuli. EEG spectral power is derived by squaring the data.

Derivation of ERD then involves comparing the spectral power of EEG signals between task-related and baseline periods. The ERD magnitude is quantified by calculating the percentage change in power within the frequency band of interest. The ERD formula is commonly expressed (Pfurtscheller & da Silva, 1999):

- $\Delta ERD(\%) = \frac{Power_{baseline} - Power_{event}}{Power_{baseline}}$ x 100

Lastly, statistical tests, such as t-tests or ANOVA, may be employed to assess the significance of ERD differences across conditions or between groups

Chapter 3

Effect of fMRI Neurofeedback Training on Increasing Laterality of Cortical Motor Activity during Movement Execution in Stroke Patients

Abstract

A potential rehabilitative strategy for post-stroke motor recovery is self-regulation of cortical motor activity. This study aims to examine the effect of one fMRI neurofeedback training session on increasing the laterality of cortical motor activity during the movement execution in stroke patients using the "gold standard" of clinical trials. Using a double-blind, sham-controlled, between-subject design, 24 stroke patients underwent a single session of real or sham real-time fMRI neurofeedback training. Results suggest that in the presence of real neurofeedback, lateralisation was higher during the movement of the affected hand in stroke participants. Voxel-wise analyses suggest that activity was higher in the ipsilesional primary motor cortex. However, upon removal of neurofeedback, this change in lateralisation was not maintained.

Introduction

Poor motor recovery after stroke is associated with a bilateral pattern of brain activity, with an under-activation of the ipsilesional motor areas and over-activation of contralesional motor areas when moving the stroke-affected limb. In patients with better motor recovery, activity becomes increasingly lateralized, paralleling their recovery process (Bhadgat et al, 2020; EI Nahas et al, 2022; Fridman et al., 2004, Ward & Cohen, 2004). Hence, a potential rehabilitative strategy could be to promote lateralized motor activity. The current study aims to investigate the use of neurofeedback with real-time fMRI as a means for chronic stroke patients to regulate their cortical motor activity, leading to an increase in laterality during simple hand movements.

Blood-oxygenation-level-dependent (BOLD) signals measured with real-time functional magnetic resonance imaging (fMRI) will be used as feedback for self-regulation of brain activity. The high spatial resolution of fMRI allows examination of anatomically-specific brain regions, providing a means for addressing structural and functional heterogeneity in stroke patients (Weiskopf

et al., 2007; Sitaram et al, 2017). Previous research using neurofeedback in healthy subjects showed that self-regulation of region-specific BOLD signal could be learned, producing neural and behavioural modifications that were retained across weeks (Yoo et al., 2008, deCharms et al., 2005). For example, Sampaio-Baptista et al. (2021) explored the bidirectional effects of fMRI neurofeedback on both brain activity and white matter structure in the motor system of adult humans using DTI. It was shown that fMRI neurofeedback can be used to bidirectionally modulate (i.e.,either up or down regulate) sensorimotor activity which results in rapid corresponding changes in corpus callosum microstructure. More specifically, opposing changes in corpus callosum microstructure were observed, that depended on the direction of activity modulation of required by the experimental condition, such that changes indicative of improvement in white matter integrity were observed with activity increases and the opposite for activity decreases. This study shows that fMRI neurofeedback can be used to endogenously alter not only brain-activity patterns but also WM pathways connecting the targeted brain areas in a specific direction. In addition, Neyedli et al. (2018) performed two proof-of-concept studies, one in younger and one in older healthy volunteers to determine if participants could manipulate laterality of activity between the motor cortices using real-time fMRI neurofeedback while performing simple hand movements. In both studies

participants in a neurofeedback group were able to achieve more lateralized activity than those in a sham group when feedback was present. The results offer evidence supporting the utilization of neurofeedback in conjunction with executed movements to enhance lateralized brain activity in older adults. This suggests potential applications in the rehabilitation of older adults with motor impairments stemming from aging or disorders such as stroke.

Studies on using fMRI neurofeedback for stroke rehabilitation have also been increasing in the recent years. For instance, Liew et al. (2016) showed 3 out of 4 patients learned to voluntarily modulate cortico-subcortical connectivity following two days of fMRI feedback training with BOLD signal connectivity between left M1 and thalamus. Sitaram et al. (2012) trained two chronic subcortical stroke patients with residual movement and four young healthy controls for three days to regulate BOLD response in the ventral premotor cortex (PMv) which has extensive anatomic connections with the M1. After training, using paired-pulse TMS, it was shown that intracortical inhibition in the M1 decreased significantly with the volitional increase of the BOLD response in the PMv, indicating a beneficial effect of self-regulation training on motor cortical output. Lastly, Robineau et al. (2017) had six patients with hemineglect after right parietal stroke trained to up-regulate their right visual cortex activity

successfully and showed mild reduction in neglect severity. However, these studies are still preliminary in nature, with limited sample size, lacks of proper sham control and long-term follow ups (Wang, Mantini & Gillebert, 2017). Therefore, more research is still needed to establish how its use can be optimized in the context of stroke rehabilitation.

Objectives of this study

In conclusion, it is hypothesized that neurofeedback training for stroke patients would bring about functional reorganization in terms of normalisation of atypical brain activation. The objective of this study is to examine the effect of one fMRI neurofeedback training session on increasing laterality of cortical motor activity during the movement execution in stroke patients. More specifically, I hypothesised that by providing neurofeedback using real-time fMRI of motor cortical activity during movement of the affected hand, stroke patients would be able to use the feedback to volitionally increase brain activity in the ipsilesional motor cortex. However, this effect would not be observed in the group receiving the sham neurofeedback.

By adopting the “gold standard” of clinical trials, i.e., a sham-controlled, double-blinded experimental design that is lacking in the current literature, it is hope that the outcome for this study can be the preliminary step before embarking on more comprehensive multi-sessions clinical trials exploring the use of fMRI neurofeedback for stroke rehabilitation.

Methods

Participants

Twenty-four chronic patients were recruited for this study (10 females, mean age =58.16yo, mean years post stroke = 3.74). The inclusion criteria were: aged 18–85 years, only one prior symptomatic stroke with ongoing effects on upper limb movements on one side of the body and some residual movement in the stroke-affected hand. Exclusion criteria included MRI scanning contraindications, previous history of neurological or psychiatric illness and limited communication or inadequate understanding of instructions. Sample size was based on previous neurofeedback studies using similar study design on healthy participants (Neyedli et al. (2018); Sampaio-Baptista et al.,2021). All participants provided informed consent in accordance with the Declaration of Helsinki and the National Research Ethics Service (NRES) committee approved the protocol (14/LO/0020).

All participants completed the Edinburgh Handedness Inventory to assess their handedness prior to their stroke incident and underwent the Action Research Arm Test (ARAT) and Nine-Hole Peg Test (9HPT) before scanning to assess for their remaining upper extremity and finger dexterity levels (Table 3.1 & 3.2). Items comprising the ARAT are categorized into four subscales (grasp, grip, pinch and gross movement) and arranged in order of decreasing difficulty, with the most difficult task examined first, followed by the least difficult task (Yozbatiran et al 2008). This hierarchical ordering should improve efficiency of testing, as normal movement on the most difficult items would be indicative of successful performance on proceeding items. Task performance is rated on a 4-point scale, ranging from 0 (no movement) to 3 (movement performed normally). On the other hand 9HPT is used to measure finger dexterity in patients with various neurological diagnoses, including stroke (Mathiowetz et al, 1985). Patients are instructed to take the pegs from a container, one by one, and place them upright into a board with nine holes, as quickly as possible, using only the hand being evaluated. They then remove the pegs from the holes, one by one, and replace them back into the container. Performance is evaluated by the total time taken to complete the task for each hand.

Participant	Sex	Age	Handedness	Hand affected	Time since stroke (months)	ARAT	9HPT	
							Affected(s)	Healthy(s)
R1	M	67.93	R	R	30	57	43.95	20.58
R2	F	55.41	R	L	15	0	0	19.04
R3	M	55.06	R	L	57	9	0	20.19
R4	M	48.48	R	R	18	0	0	15.74
R5	F	45.78	R	L	48	54	0	17.65
R6	M	56.32	R	R	42	20	0	19.86
R7	M	48.16	L	R	48	57	23.51	24.37
R8	M	61.29	R	R	84	57	78.21	21.12
R9	M	74.37	R	L	36	1	0	28.44
R10	F	69.08	R	L	48	57	24.51	22.41
R11	F	39.71	R	L	48	57	23.68	18.29
R12	F	59.4	R	R	42	57	16.28	15.63
Mean		56.75			43	35.5	NA	19.81

Table 3.1 Demographics of Participants in the Real NFB conditions

Participant	Sex	Age	Handedness	Hand affected	Time since stroke (months)	ARAT	9HPT	
							Affected(s)	Healthy(s)
S1	F	55.55	R	L	15	57	17.02	15.35
S2	M	60.31	R	L	24	39	0	20.47
S3	M	65.45	R	R	48	57	17.12	20.35
S4	F	47.4	R	R	21	4	0	16.57
S5	M	57.91	R	R	17	57	89.87	29.11
S6	M	60.98	R	L	42	57	25.66	31.24
S7	F	76.13	R	R	60	57	20.84	23.89
S8	F	69.89	R	L	86	31	0	21.36
S9	M	58.49	R	R	67	10	0	21.66
S10	F	53.67	R	L	81	18	0	18.33
S11	M	56.64	R	L	91	3	0	24.25
S12	M	52.55	R	R	10	57	22.23	16.43
Mean		59.58			46.83	37.25	NA	16.43

Table 3.2 Demographics of Participants in the Sham NFB condition

Following a double-blind between-subject design, the participants were randomly assigned to either the Neurofeedback Group (Real NFB, n=12, mean age = 56.75, 5 females) or the Sham Group (Sham NBF, n=12, mean age = 59.58,

5 females), with minimisation of variance in age and time since stroke using a open-source minimisation programme, MinimPy (Saghaei & Saghaei 2011, http://sourceforge.net/projects/minimpy). However, the first two participants were forced into the Real group as the feedback used for Sham condition is a playback of the feedback received by participants in the Real FB group . Participants were not aware of their group assignment and instructions to the participants were provided by an experimenter who was blinded to the group assignment.

Procedure

Participants underwent a pre-feedback (FB) scan, three runs of FB scans and a post-FB scan. A block-design paradigm was adopted for all the scans, with 30s of active hand movement blocks with their affected hand (squeezing an elastic ball at their own pace) interspersed with 30s of rest periods. The pre-FB scan which also served as a functional localizer, consisted of three active blocks for each hand. Based on the results from the pre-FB scan, an 18x18x10mm region-of-interest (ROI), centred over the peak activation in the primary motor cortex (M1) was chosen for each hemisphere. During FB scans, FB signals were derived

from BOLD percent signal change (PSC) from these ROIs and presented to the participants using two bar graphs, one for each ROI (see online analysis methods below). There were 3 FB scans and each scan consisted of six active blocks. Participants were instructed to increase the height of the bar that represents brain activity from their ipsilesional side and minimize the activity from their contralesional side during the active blocks. The squeezing was unpaced and participants were encouraged to try out different strategies that deemed to be helpful in controlling the FB bar. For participants in the Sham group, a replay of FB from another participant was used instead. Lastly, in the post-FB scan with 3 active blocks, participants moved their stroke-affected hand in the absence of FB to test whether any change in lateralized activity could be maintained following feedback removal (Figure 3.3).

Participants were briefed by researchers blinded to their group assignments and checked that they had understood the task before entering the scanner. In addition, EMG activities were monitored in real-time via 2 MRI safe surface electrodes (ConMed corporation, USA) from the flexor carpi radialis muscle on each arm to ensure participants were performing the task correctly. Lastly, a questionnaire was administered at the end of the experiment to investigate perceived control over the FB given and type of strategies they used to control

the FB (Figure 3.4).

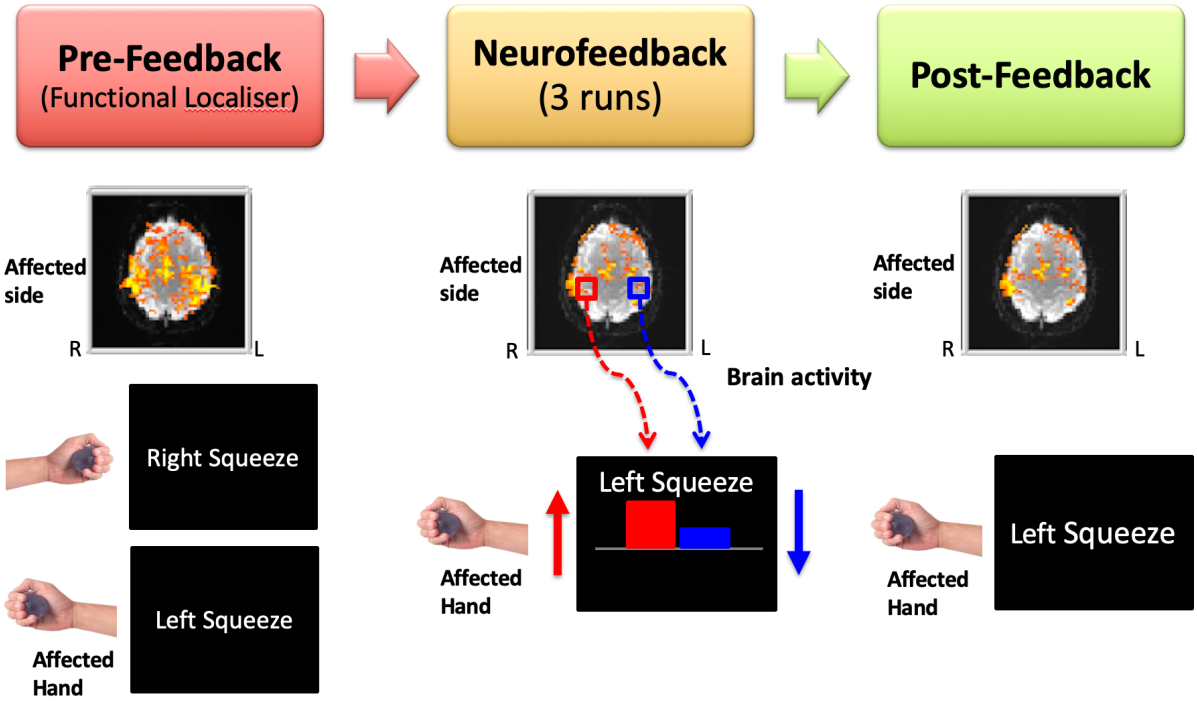

Figure 3.3. Scanning and Task Procedure. (Left hand is used as an example for the affected side here). Each experimental session started with a pre-feedback scan that served as a functional localiser to identify ROIs for FB values to be extracted. This was followed by 3 runs of neurofeedback scans when participants were required to increase their lateralised brain activities by moving their affected hand and using the FB provided. Lastly, a post-FB scan was carried out in the absence of FB for the stroke-affected hand. A block design with 30s on and 30s rest period was used in all the scans mentioned above.

Neurofeedback Questionnaire

How much control did you feel you had over the feedback
(1=not in control, 5 = fully in control)

On the scale of 1 to 5, how successful were the strategies below in controlling the feedback (1 =very unsuccessful, 5 = very successful):

Focus more on moving hand
Focus less on non-moving hand
Physically relaxing the non-moving hand
Increasing the rate of movement
Increasing the force of squeezing

Do you think it was real or sham?

Figure 3.4 Questions in the Neurofeedback Questionnaire

MRI acquisition

MRI data were acquired on a 3 T Siemens Magnetom Prisma MRI scanner (Siemens AG) using a 32-channel head coil. A whole brain anatomical T_1-weighted [magnetization prepared rapid gradient echo (MPRAGE), voxel-size = $1 \times 1 \times 1$ mm^3, TR = 1900 ms, 192 slices] image was collected. All task fMRI was acquired using multiband gradient echo-planar imaging (72 slices, whole brain coverage, voxel-size = $2 \times 2 \times 2$ mm^3, TR = 933 ms).

Online Analyses

Imaging was performed with a 3T scanner (Siemens, Erlangen, Germany), and Turbo-Brain Voyager software (TBV, Brain Innovation, Maastricht, The Netherlands) was used for online analysis of BOLD signals to generate neurofeedback. Raw data were first preprocessed with 3D motion correction algorithms to correct for head movements and a 3mm Gaussian spatial filter to improve signal-to-noise ratio before a whole-brain voxel-wise recursive general linear model (GLM) was applied to compute BOLD activity in real-time. Change in BOLD activity for each functional ROI was then calculated as percent signal change (PSC) from rest at each TR (2s) and fed back to the participant as the height of the bar graph. In short, the feedback signal was based on the averaged voxel time-course extracted from the localized motor ROIs and the feedback image was updated each TR (2s). Therefore, participants in the feedback condition were viewing a visual display containing two bar graphs whose heights altered every 2s in accordance with the calculated PSC values for contralateral and ipsilateral motor cortex ROIs. The maximum length the bar could move in either direction initially set at one percent PSC unit higher than what the participant achieved in the most active ROI during the Pre-FB scan. Participants in the sham group were viewing feedback from a participant in the FB group.

PSCs values generated for FB in each ROI were also extracted subsequently offline after the experiment to determine group differences statistically with IBM SPSS Statistics (version 25) using a two-way Mixed Analyses of Variance (ANOVA) with ROI and Feedback Group as factors.

Offline Analyses

Data were analysed in FMRIB Software Library (www.fmrib.ox.ac.uk/fsl), with standard preprocessing steps including motion correction, brain extraction, fieldmap-based EPI distortion correction using FUGUE, Gaussian spatial smoothing (FWHM of 5mm) and denoised with FIX and 100s high-pass temporal filtering). Results from FIX were checked independently by two researchers to ensure the automated signal and noise classification was correct and no signal was removed inappropriately. Co-registration was achieved by first using linear registration (FLIRT) to register the multiband functional data to a single volume, high-contrast (single-band) EPI image. Next, the high-contrast EPI image was linearly registered to the T1-weighted image using boundary-based registration (6 degrees of freedom). Lesion areas were identified and a mask was created for each participant to remove these areas from further analysis (for spread of lesion locations, see figure 3.5). The lesioned hemisphere was standardized to the right, i.e data from participants whose ipsilesional hemisphere was on the

left hemisphere was flipped. Data were then registered non-linearly to the standard MNI 2mm template brain to allow voxel-wise group comparison using FNIRT, with voxels in the lesioned area excluded using lesion masking. Intermediate fixed effects analyses were performed to average activity across the three runs where feedback was presented at the subject level. Group level analysis was carried out to compare difference between Real NFB and Sham NFB group (i.e.,Real minus Sham) using FMRIB's Local Analysis of Mixed Effects (FLAME) and LS from pre-FB scan was added as a covariate (as another separate explanatory variable (EV) in addition to the EVs for group difference) to account for baseline differences across groups. Group Z-statistic images were thresholded using clusters determined by $Z > 2.3$ and a family-wise corrected cluster significance threshold of $p < .05$ (Worsley 2001). No pre-threshold mask was used.

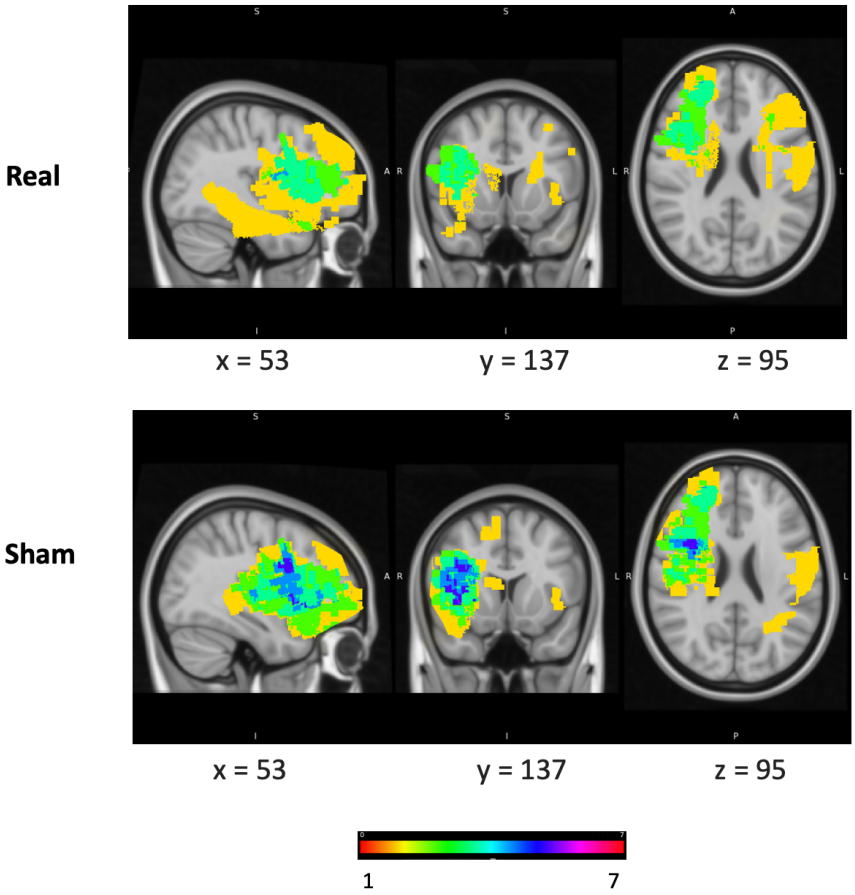

Figure 3.5. Location of lesions for Real and Sham group. Data were then registered non-linearly to the standard MNI 2mm template brain with FNIRT. Colour scale indicates number of participants with a lesion in that voxel.

In addition, to further examine the effect of FB training on laterality of cortical motor activity, parameter estimates (*PE*) from the general linear model were extracted from the ROIs used during neurofeedback and a laterality score was computed as follows:

- Laterality Score (LS) = Ipsilesional ROI_{PE} – Contralesional ROI_{PE}

To address for potential heterogeneity in laterality of cortical motor activity during stroke recovery, LS during the Pre-FB scan were used as a covariate in the subsequent statistical analyses. Analyses of covariance (ANCOVA) were subsequently performed with IBM SPSS Statistics (version 25) to look at the differences in LS between Real and Sham group during NFB scans. Subsequently, a two-way mixed ANOVA with ROI (Ipsi/Contralesional) and Group (Real/Sham) as factors was also carried out to further locate the change driving the differences in LS during these FB runs.

In addition, to study transfer effects, two-way mixed ANOVA with Group (Real vs Sham) and Scan (Pre vs Post FB scan) was conducted. To further localise the change in LS in the absence of neurofeedback, a three-way Group-by-Scan-by-ROI mixed ANOVA was performed.

Differences between Groups at Baseline

Group differences in age, time since stroke, ARAT scores and LS at baseline was compared with independent two-tailed t-tests to eliminate the possibility that factors other than NFB training might explain any differences in Real versus

Sham Groups.

Variances in FB success

To investigate factors that could possibly account for individual differences in the efficacy of NFB training, a "FB success" measure was derived using the average differences in LS between baseline and each FB scan for each participant. Correlation analyses were used to study whether 1) age, 2) time since stroke and 3) ARAT scores could account for any variances in FB-success between Real and Sham Group.

Motor Task and Electromyography (EMG) recording

Participants were given an elastic ball designed for hand grip strength training to squeeze inside the scanner, and their performance was monitored with EMG recording using Biopac and AcqKnowledge software (v4.2). Two MRI safe surface electrodes (ConMed corporation, USA) were used to record from the flexor carpi radialis muscle on each arm, with an additional electrode placed at the elbow olecranon on the unaffected arm as a ground electrode. However, for five out of 24 participants, their data were heavily corrupted by MRI-related artefacts and was therefore not usable. Another three participants did not have

their EMG recorded due to equipment failure. Remaining data were analysed in MATLAB R2011b (Mathworks, Inc, Natick, MA): denoised, fullwave-rectified, converted to root mean squares (RMS) and epoched according to conditions. RMS values were summed during the task active period (during motor execution) and averaged across trials and scans. Two-way mixed ANOVA with Scan (Pre, FB 1 to 3, Post) and NFB Group (Real vs Sham) was performed to study possible differences in motor output between these groups. Analyses were only performed for the affected hand, as the unaffected hand was not used in FB and Post-FB runs.

Analyses of Questionnaire Responses

Independent t-tests (two-tailed) were conducted to assess the differences between the Real and Sham NFB groups in their perceived levels of control over the FB given and success with the different types of strategies used.

Results

Differences between Groups at Baseline

Group differences at baseline were tested with independent t-test (two-tailed). Real and sham groups did not differ statistically in terms of age ($t_{(22)}$ = .78 , p = .45), time since stroke ($t_{(22)}$ = .39, p = .70), ARAT scores ($t_{(22)}$ = .17, p = .86), and LS ($t_{(22)}$ = 1.02, p = .33) .

	Real	Sham
Age (Years)	56.75 (3.11)	59.58 (2.38)
Time since Stroke (Months)	43.0 (5.45)	46.83(7.95)
ARAT	35.50 (8.01)	37.25 (6.91)
Laterality at baseline (pre-FB)	105.78 (23.56)	108.10 (23.05)

Table 3.6 Mean differences between groups at baseline (standard error stated in brackets).

Group Difference during Neurofeedback

Neurofeedback signals from Turbo-BrainVoyager

PSC values computed by Turbo-BrainVoyager (TBV) for real-time feedback were extracted and examined for group differences with a repeated-measures analysis of variance (RM-ANOVA). There was a significant Group-by-ROI interaction ($F_{(1,2.32)}$ = 6.16, p = .043), reflecting greater laterality in the Real NFB Group. The difference between the two ROIs was significant in the Real NFB Group ($F_{(1,\ 2.05)}$ = 4.86, p = .048) (Figure 3.7) but not in the Sham NFB Group ($F_{(1,\ .1.02)}$ = 0.86, p = .54).

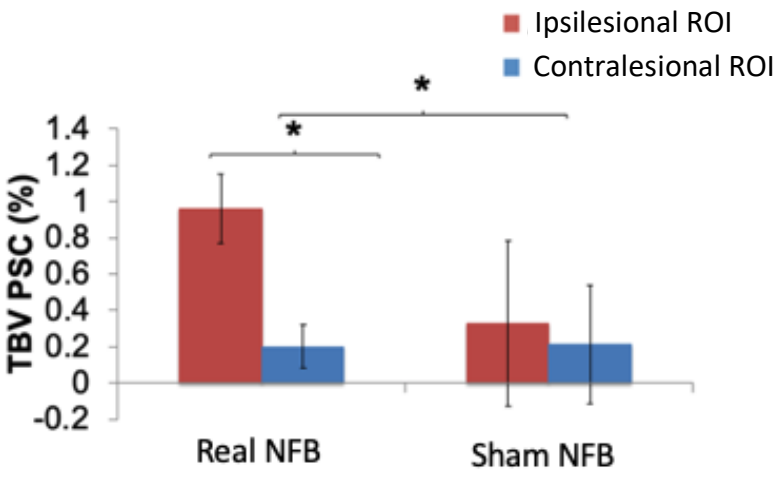

Figure 3.7 Neurofeedback signals from Turbo-BrainVoyager. For PSC values computed with TBV during the FB scans, a significant Group-by-ROI interaction ($F_{(1,2.32)}$ = 6.16, p = .043) was observed, The difference between the Ipsilesional and contralesional ROIs was only significant in the Real NFB Group $F_{(1,\ 2.05)}$ = 4.86, p = .048) (but not in the Sham NFB Group ($F_{(1,\ .1.02)}$ = 0.86, p = .44).

Laterality Scores (LS) differences during Neurofeedback Scans

LS derived from parameter estimates computed in FSL were statistically analysed. Analysis of covariance (ANCOVA) performed on LS during FB scans with LS from pre-FB scan as a covariate revealed that Real NFB Group had higher mean LS during FB scans than the Sham NFB Group ($F_{(1, 1.59)}$ = 6.50, p = .024) (Figure 3.8). Further analyses with *PE*s showed that ipsilesional side *PE* was greater than the contralesional side *PE* only in the Real NFB Group ($F_{(1, 6.54)}$ = 34.0, p < .001) but not in the Sham NFB Group ($F_{(1, 2.54)}$ = 2.55, p = .15) (Figure 3.9).

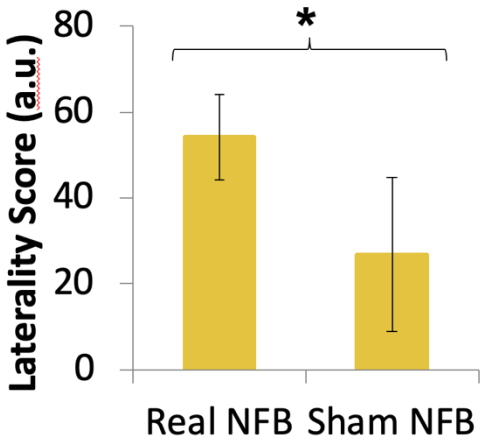

Figure 3.8 Laterality Scores (LS) differences during Neurofeedback Scans. Using LS from pre-FB scan as a covariate, ANCOVA revealed Real NFB Group had higher mean LS during FB scans than the Sham NFB Group ($F_{(1, 1.59)}$ = 6.50, p = .024). Raw LS values (without adjusting for covariate) are shown here.

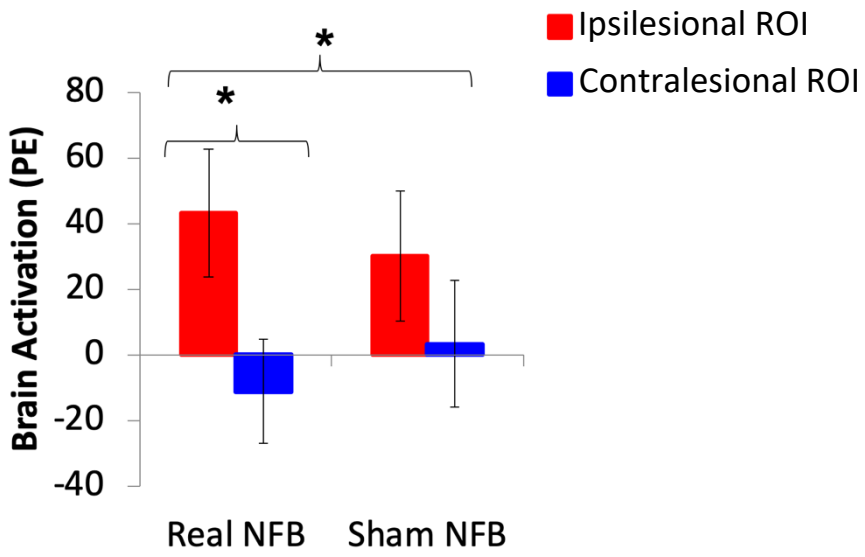

Figure 3.9 Differences in PEs at each ROI for Real and Sham NFB Group. PE from ipsilesional ROI was greater than that of the contralesional side only in the Real NFB Group ($F_{(1, 6.54)}$ = 34.0, p < .001) but not in the Sham NFB Group ($F_{(1, 2.54)}$ = 2.55, p = .15).

Voxel-wise group analyses

Voxel-wise analysis was conducted to test across the whole brain for differences between Real vs Sham group in movement-related activity during the NF scans after partialling out the difference in LS at Pre-FB scan. This analysis revealed greater activity for the Real NFB group than the Sham NFB group (i.e.,Real minus Sham contrast) in the primary motor cortex of the ipsilesional hemisphere after partialling out the difference in Laterality Score at Pre-FB scan (Figure 3.10).

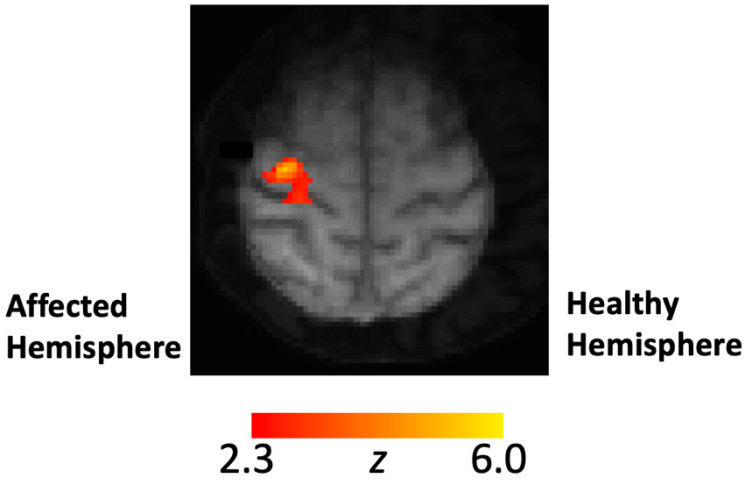

Figure 3.10 Voxel-wise group analyses. With LS at Pre-FB scan partialled out (included as another EV at FEAT), Real-minus-Sham contrast shows that brain activity was higher in M1 for the participants in the Real NFB group.

Post-FB vs. Pre-FB: transfer effects in the absence of Neurofeedback

In order to test whether NF related effects persisted in the absence of feedback, comparisons were made between the pre-FB and post-FB scans. RM ANOVA was performed for the LS from the pre-FB and post-FB scan for the ipsilesional hemisphere and revealed no significant Group-by-Scan interaction ($F_{(1,\ 1.22)}$ = 3.16, p = .083), but a significant main effect of scan ($F_{(1,\ 5.27)}$ = 5.64, p = .032). LS was lower in the Post-FB scan for both groups (Figure 3.11).

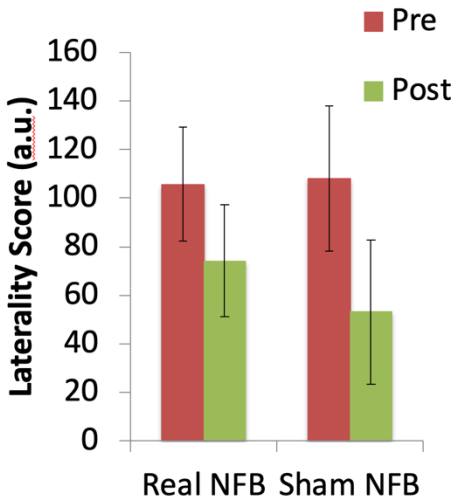

Figure 3.11. Transfer effects in the absence of Neurofeedback. Comparing the LS from pre-FB and post-FB scan revealed no significant Group-by-Scan interaction ($F_{(1, 1.22)}$ = 3.16, p = .083), but a significant main effect of scan ($F_{(1, 5.27)}$ = 5.64, p = .032). LS was lower in the Post-FB scan for both groups.

To further localise the change in the absence of neurofeedback, a three-way Group-by-Scan-by-ROI ANOVA was performed. The three-way interaction was not significant ($F_{(2, 3.26)}$ = 1.16, p = .153), but there was a significant Scan-by-ROI interaction ($F_{(1, 2.22)}$ = 4.76, p = .044). More specifically, there was a significant decrease in activity in the ipsilesional ROI from pre-FB scan to post-FB scan ($F_{(1, 3.27)}$ = 5.64, p = .032), but no change was observed in the contralesional ROI ($F_{(1, 1.27)}$ = 1.64, p = .192). In short, the reduction in LS at post-FB was due to mainly a reduction in ipsilesional activity (Figure 3.12)

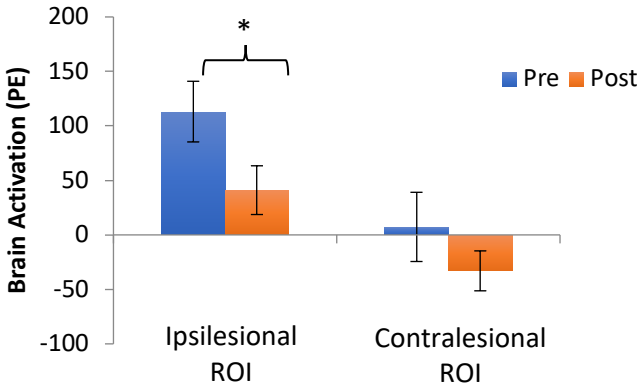

Figure 3.12. Comparing brain activation (pe) for ipsilesional and contralesional ROI for pre-FB and post-FB scan. Group-by-Scan-by-ROI was not significant ($F_{(2, 3.26)}$ = 1.16, p = .153), but there was a significant Scan-by-ROI interaction ($F_{(1, 2.22)}$ = 4.76, p = .044). Thus, figure above collapsed the data for both real and sham group. Decrease in activity in the ipsilesional ROI from pre-FB scan to post-FB scan was significant ($F_{(1, 3.27)}$ = 5.64, p = .032), but no change was observed in the contralesional ROI ($F_{(1, 1.27)}$ = 1.64, p = .192).

Analyses of LS across all the scans (i.e.pre, FB, post) revealed a significant linear decrease for both Real NFB Group ($F_{(1,26785)}$ = 5.07, p = .048) and Sham NFB Group ($F_{(1,56218)}$ = 13.28, p = .008), suggesting a possible effect of fatigue (Figure 3.13). However, the absence of any significant scan-by-group interaction provides no evidence for persistent effects of feedback when NF is removed.

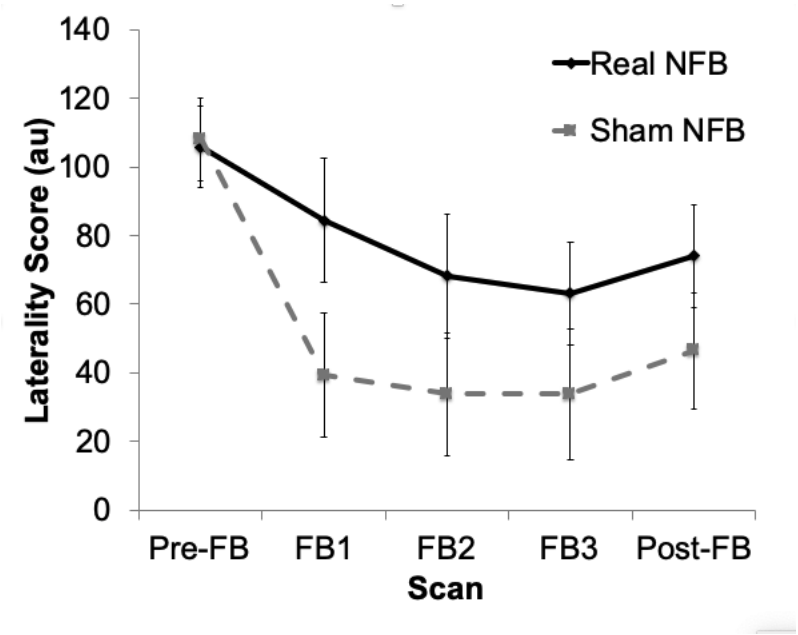

Figure 3.13 Changes in LS across all scans. Examining the change in LS across all scans for the ipsilesional hemisphere, there is a significant linear decrease for both Real NFB Group ($F_{(1,26785)}$ = 5.07, p = .048) and Sham NFB Group ($F_{(1,56218)}$ = 13.28, p = .008), suggesting a possible effect of fatigue

Explaining variances in FB-success

There were no factors at baseline that accounted for variances in FB-success in this study. For the Real group, correlation between FB-success and age was r = -.375 (p = .23), between FB-success and time since stroke was r = .412 (p = .18), and FB-success and ARAT scores was r = .138 (p = .67). For the Sham group, correlation between FB-success and age was r = .008 (p = .98), between FB-success and time since stroke was r = -118 (p = .712), and FB-success and ARAT scores was r = -.21 (p = .94). However, a number of participants scored full marks on the ARAT test (ceiling effect and range restriction), so it is not sensitive enough to explore upper

limb functioning differences in this group of participants. For visualisation purposes, scatter plots are shown in figure 3.14

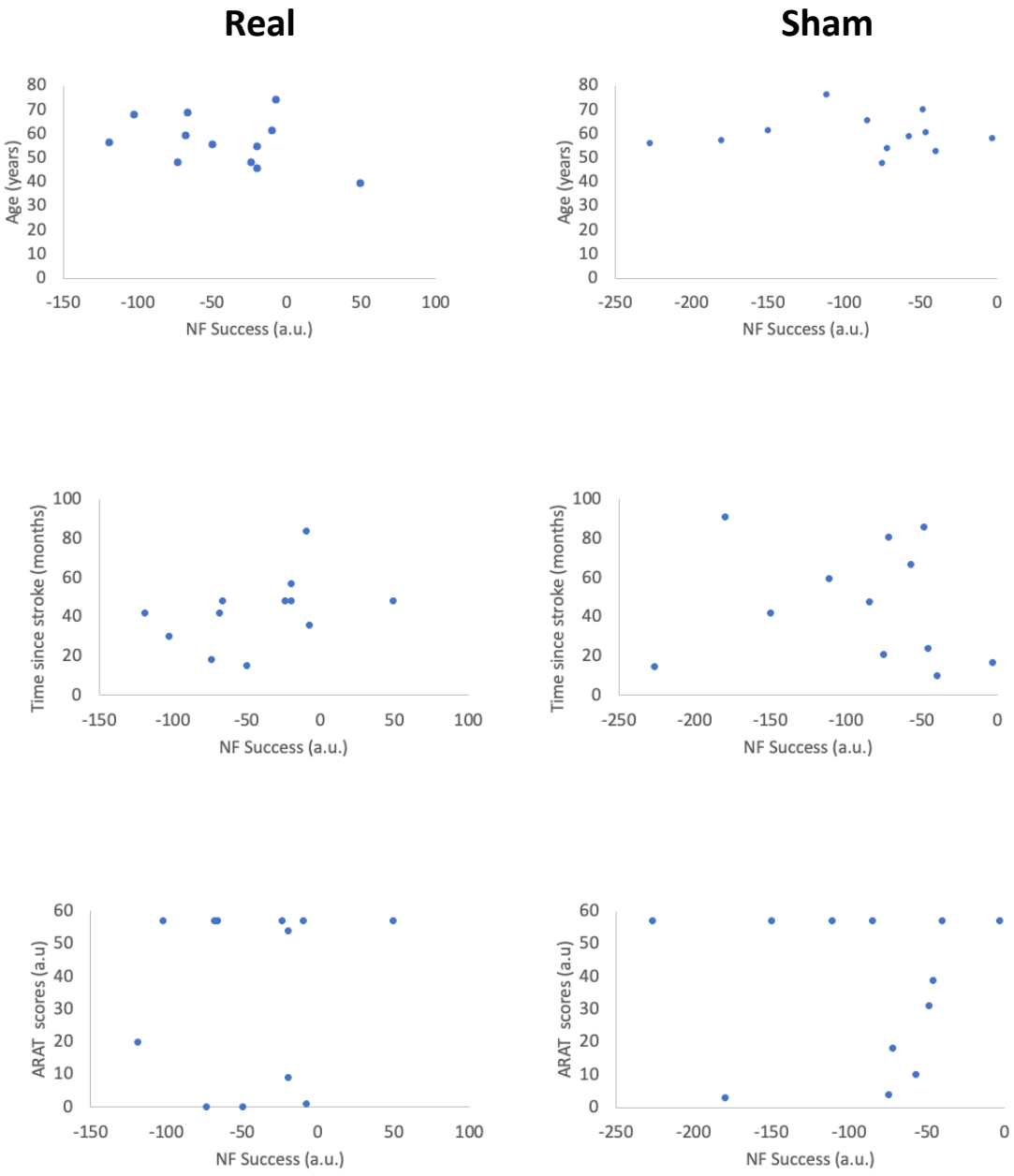

Figure 3.14. Scatter plots age, time since stroke and ARAT scores against “NF-success” for Real and Sham group.

EMG Results

No significant Scan-by-Group interaction ($F_{(1, 3785)}$ = .87, p = .78)and no significant main effect of scan ($F_{(1, 6785)}$ = 1.07, p = .46) and Group ($F_{(1, 5445)}$ =.97, p = .55)was found.

Questionnaire Responses

To test whether participants were effectively blinded to NF condition, a debriefing questionnaire was administered following the scan. For level of perceived control over the FB given, there was no difference between the Real NFB Group (M = 2.83, SE = 0.34) and Sham NFB Group (M = 2.75, SE = 0.28, t(22) = 0.188, p = 0.852, two-tailed) (Figure 3.15), suggesting that participants were effectively blinded to NF condition. Participants were also similar in their perceived success when employing different strategies to regulate feedback (Figure 3.16).

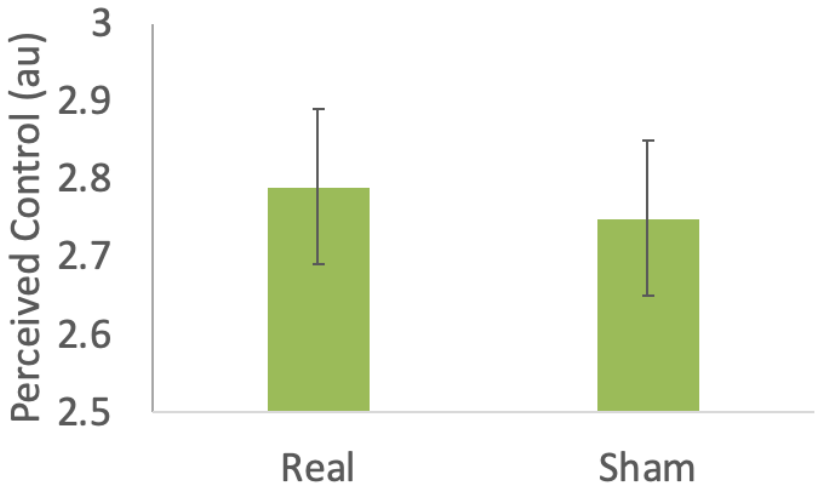

Figure 3.15 Perceived control over the FB. There is no difference between Real NFB Group and Sham NFB Group for the level of perceived control over the FB presented.

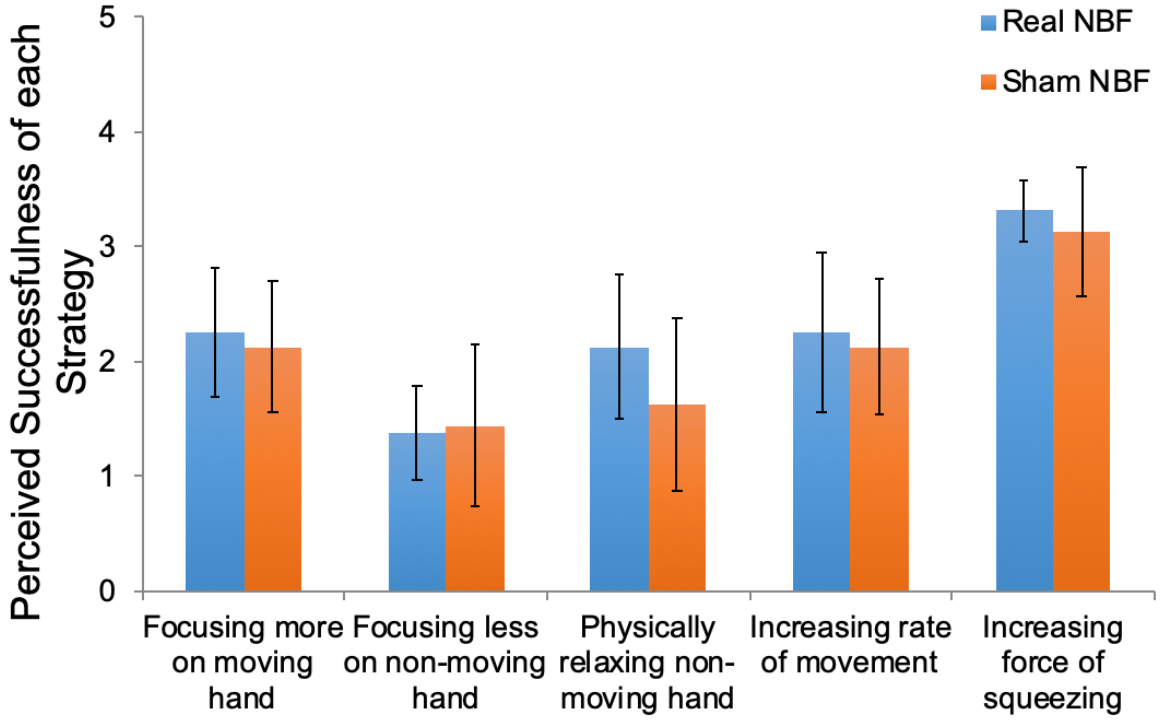

Figure 3.16. Perceived success when employing different strategies. No difference in perceived successful of each strategy

Discussion

Summary of Findings

The current study examines the effect of neurofeedback using real-time fMRI on increasing laterality of cortical motor activity during movement execution in chronic stroke patients using a sham-controlled double-blind design. Results suggest that in the presence of real neurofeedback, lateralisation was higher during the movement of the affected hand in stroke participants. However, such a difference was not observed in the group that was provided with sham feedback. In addition, voxel-wise group comparison suggests that difference in brain activities between the real and sham NFB group was localised in the ipsilesional primary motor cortex, i.e.,greater brain activity was observed in the ipsilesional hemisphere in the real NFB group. However, this study also did not find any significant factor (age, time since stroke, ARAT) that could explain variances in FB success.

A key consideration for clinical translation is whether NFB effects can be maintained in the absence of feedback. To test this, a post-NF scan was included,

with NF removed. When comparing laterality scores (LS) in Pre-FB and Post-FB scans for both groups, there was no statistical differences observed. In both groups, LS in the Post-FB scan was lower than the baseline Pre-FB scan, and the difference was mainly due to a decrease in activity in the ipsilesional hemisphere. Hence, following the removal of FB, increased laterality was not maintained.

Lastly, both Real and Sham NFB group perceived equal level of control over the FB presented. Further, 16 out of 24 participants (9 in Real NBF Group, 7 in Sham NBF Group) perceived themselves to be in the sham condition. Taken together, these results seem to imply that participants who underwent real NFB did not consciously experience any added congruity between their actions and the FB given when compared to participants in the sham condition and that participants were successfully blinded to their group assignment.

The potential of using FMRI neurofeedback for Stroke Rehabilitation

Research has shown that neurofeedback training can promote volitional regulation of brain activity in both healthy young adults and older adults (Neyedli et al., 2018; Sampaio-Baptista et al., 2021; Wang, Mantini, & Gillebert, 2017). This study expands on those findings by demonstrating that stroke

patients who undergo Real NFB training exhibit increased cortical motor laterality and a higher BOLD response in the ipsilesional M1. These changes could potentially aid in the recovery of their motor functions (Bhagat et al., 2020; EI Nahas et al., 2022; Fridman et al., 2004; Ward & Cohen, 2004). The current study also adds to the existing work by using a double-blind, sham-controlled design which is currently rare in the field. Results from this study shows that the effects of NFB training is specific to the group who received real NFB only and not found in participants who received sham FB. The advantages of such an experimental design are to rule out the possibility of placebo effect (Hróbjartsson & Gøtzsche, 2010), participants' and experimenters' biases (Schulz & Grimes, 2002), and non-specific or contextual confounds (Miller & Kaptchuk, 2004). As a result, the validity and robustness of causal inferences drawn from this study is enhanced (Hróbjartsson & Gøtzsche, 2010). In short, findings from this study further support that fMRI neurofeedback can be a potential rehabilitative tool for motor functioning post-stroke by promoting self-regulation of brain activity.

Transfer Effect in the absence of Neurofeedback

In this study, following the removal of FB, increased laterality was not maintained and no transfer effect was observed. In fact, this result is similar to

the study by Neyedli et al. (2018), where lateralised motor activity was also not maintained in older adults when feedback was removed, but it was maintained in younger adults after one day of training. It could be possible that older adults and brains with impairments require greater resources and more repetitions in order for the effects of neurofeedback to transfer to performance of other tasks in the absence of feedback (Langhorne, Bernhardt & Kwakkel, 2011). In addition, fatigue could also be a factor interfering with the successful retainment of volitional control over brain activity in the absence of feedback.

Limitations and Future Directions

Power of the study sample size

It should be noted that, although no statistically significant group-by-scan interaction was identified, a trend ($p<0.1$) in the predicted direction was detected, with the NFB group continuing to show greater laterality than the sham group in the post-NF scan. Sample size of the current study was based on previous studies on healthy participants that used similar neurofeedback methodology (Neyedli et al. (2018); Sampaio-Baptista et al.,2021). It is possible that our study was underpowered to detect a true significant effect in the heterogenous patient population. It is also possible that patients show

considerable variation in their response to NF, adding to the variance in results, and reducing the possibility of detecting group-level effects. Understanding what contributes to individual differences in NF response will be an important target for future work.

Heterogeneity in Stroke Patients

The current study focuses on using neurofeedback to promote cortical lateralization in stroke patients for rehabilitation. However, as discussed earlier, functional reorganization following a stroke is complex, and stroke patients are heterogeneous. Factors such as lesion location (Shih et al., 2023; Chen et al., 2021; Lewis & Perreault, 2007; Luft et al., 2004), the extent of preserved ipsilesional and contralesional areas (Di Pino et al., 2014; Murphy & Corbett, 2009, Ward et al., 2006; Ward et al., 2003), CST integrity (Bertolucci, Chisari & Fregni , 2018; Cramer 2008; Di Pino et al., 2014, Giulia et al. 2020), time after stroke (Serrien et al., 2004; Newton et al., 2002), and functioning levels can influence outcomes. For some patients, a bimanual pattern of activities may be more beneficial for promoting functional recovery than increasing cortical lateralization.

Additionally, these differences may explain individual variability in response to neurofeedback training. For instance, in a pilot study by Giulia et al. (2020) using bimodal EEG-fMRI NFB, only two out of four patients with preserved CST succeeded in upregulating the ipsilesional primary motor cortex and showed functional improvement in upper limb motricity. This highlights the importance of considering the variability within the stroke patient population to identify inclusion criteria for future clinical studies.

Unfortunately, the current study did not identify any factors explaining the variability in neurofeedback responders or success. It is possible that the study was underpowered. Moreover, the functional tests used (i.e., ARAT and 9HPT) were not sensitive enough to capture variations in functional levels within the sample, with many patients performing at ceiling or floor levels. This made statistical analyses looking at relationships between baseline functional levels and fMRI changes inconclusive. Future studies should consider other tests, such as the Jebsen-Taylor Hand Function Test (JTHFT) and the Fugl-Meyer Assessment (FMA) which might be more sensitive and robust.

In short, for neurofeedback training to be truly effective, it is crucial for future research to explore and understand how these factors influence the effectiveness of neurofeedback training and individual responses. This

understanding will allow for tailored treatment plans to achieve beneficial functional reorganization and motor recovery for each patient.

Perceived Control and Operant Learning

One potential limitation of the current study is that patients did not perceive to have more control even when they were given real feedback. This issue of perceived controls is a complex one as most studies (including the current one) aim to control for this though blinding, in order to control the real versus sham comparisons. On the one hand, the lack of group differences in perceived control adds confidence in the blinding procedure. On the other hand, it suggests that the changes in laterality detected for the real NFB group did not translate into any greater subjective feeling of perceived control, a factor which might be important for rehabilitation effects. For example, Ward (2017) highlights the importance of purposeful and repetitive activities in driving neuroplastic changes, especially in the chronic phase of stroke recovery. Moreover, the basis of neurofeedback lies in operant conditioning, where the feedback also indicates users' success in controlling their brain signals, thereby providing the reward for correct modification (Soekadar et al., 2011). In the present study, the sham control group received feedback from a real NFB participant, and therefore the amount of positive feedback should be matched

between groups. However, real feedback is directly related to participants, whereas the sham feedback is not. Despite this, participants receiving real feedback did not consciously perceive having more control. The lack of perceived control might lead to less reinforcement to strengthen the learned behaviour. Hence, future studies should explore different types of feedback presentation and factors that can improve participants' sense of control with the feedback presented.

Intensity and Duration of Neurofeedback training required

Lastly, intensity and duration of rehabilitation programs are crucial factors influencing functional brain reorganisation. Langhorne et al. (2011) conducted a systematic review that concluded that higher-intensity, structured and repetitive rehabilitation is associated with better motor outcomes after stroke. By adopting the "gold standard" clinical trials, this study provides the initial step and future studies should embark on more comprehensive multi-sessions clinical trials to fully exploring the effectiveness of fMRI neurofeedback for stroke rehabilitation. In effect, this study was subsequently followed with a randomized, double-blind, sham-controlled clinical trial (ClinicalTrials.gov:

NCT03775915) with 3 days of neurofeedback training using similar protocols to those first tested here. Findings from this study revealed that chronic stroke survivors are able to use functional MRI neurofeedback to self - modulate motor cortex activity in comparison to a Sham control, and that training is associated with improvements in gross hand motor performance and with white matter structural changes (Sanders, et al., 2022). Future studies should take this into consideration and investigate what is optimal duration of training and rest schedule to enhance both learning and retaining effects.

Chapter 4

Using a Low-Density, Portable EEG System for Neurofeedback Training to Increase Cortical Lateralisation during Motor Execution in Healthy Adults

Abstract

EEG neurofeedback training has been shown to be effective in modulating brain activity in various studies. However, studies have been largely focused on using motor imagery, which is less natural and more difficult to perform than motor execution. In addition, more studies are also needed to look at individual differences in the ability to control neurofeedback. The current study aims to investigate the potential of using a low-cost, mobile, wireless EEG system for neurofeedback training. Using a within-subject, sham-controlled design, fourteen healthy volunteers underwent 4 EEG neurofeedback training sessions to modulate ERD activity using a simple motor execution task. Functional MRI before and after the training were also collected to assess training effects and possible individual differences more comprehensively. Results suggest that neurofeedback training with a low-density EEG setup can be effective for increasing lateralised ERD. BOLD activity in the non-dominant hemisphere was shown to be a predictor for an individual's ability to control neurofeedback self-regulated ERD activities using motor execution. However, ceiling effects associated with the use of simple motor execution task in a healthy population might have influenced some of the findings in this study.

Introduction

Among various neuroimaging approaches, EEG neurofeedback is one of the more popular choices for rehabilitation purposes due to it being non-invasive, relatively cost-effective, with good temporal resolution and almost no contraindications (Dobkin, 2007; Hammond, 2011). This method involves placing electrodes on the scalp to record the brain waves generated by neurons in the brain (Niedermeyer & da Silva, 2004). In the motor domain, sensorimotor rhythms, which are oscillatory activities from fronto-central regions with peak frequencies around the 8-13Hz (mu rhythm) and 13-30Hz (beta) have been suggested for use in EEG neurofeedback (McFarland, Miner, Vaughan, & Wolpaw, 2000; Pineda, 2005). Event-related de-synchronization (ERD), i.e.,relative power decrease, in these frequency bands is observed during motor preparation, imagery, and execution. In addition, single-trial real-time classification and detection of ERD is possible, making it an ideal candidate for EEG brain-computer interface and neurofeedback in rehabilitation (Jeon, Nam, Kim, & Whang, 2011; Neuper, Scherer, Wriessnegger, & Pfurtscheller, 2009; Pfurtscheller, Brunner, Schlögl, & Lopes da Silva, 2006).

Over the past decade, studies have revealed the potential of brain–computer interfaces, including neurofeedback, to stimulate neural plasticity in motor areas of the brain and to promote functional improvement (Sreedharan et al., 2013). Increasingly, this technology has been studied for motor post-stroke rehabilitation, demonstrating results in inducing positive changes in brain function, reducing maladaptive plasticity, enhancing ipsilateral primary motor cortex activity, and facilitating clinical recovery based on various clinical scales. (Franc et al., 2022). For instance, in a scoping review by Yoo (2021), 14 studies were identified and reported significant improvements with EEG neurofeedback training when combined with some forms of occupational therapy. Improvements were observed in EEG activities, such as relative beta activity (Cho et al., 2016) and spectral power (Rayegani et al., 2014) and also in functional assessments such as the Fugl-Meyer test (Ang et al., 2015, Cheng et al., 2020, Kim et at., 2016) and Jebsen Taylor hand function test (Rayegani et al., 2014).

Motor Imagery vs Motor Execution

However, EEG neurofeedback research in stroke or patients with hemiplegia has also been focusing on motor imagery (MI) instead of motor execution or motor

attempt. It has been shown that MI activates brain structures that are largely similar to neural networks used in motor execution, including pre-motor, supplementary motor, cingulate, parietal cortical, basal ganglia, and cerebellum areas (Decety, 1996; Kilintari, 2016). Nonetheless, it is known that there are individual differences in ability to perform MI and participants' capability to do so after the stroke might also be affected. It has been shown that the ability to feel and visualize the imagined movement has been strongly correlated to offline BCI performances for the classification of left versus right-hand MI (Vuckovic and Osuagwu, 2013). Hence, individual differences in the ability to perform MI can interfere with the efficacy of EEG neurofeedback performance. Moreover, performing MI requires some form of active inhibition of motor neural activation not present in actual movement (Grospretre, Ruffino & Lebon, 2015; Guillot et al., 2012), and the brain patterns during MI are less distinguishable from rest than motor execution patterns (Wolpaw et al., 2000), which might make MI less efficient for neurofeedback rehabilitation. Lastly, some studies also reported that patients felt that it was less natural and more difficult to perform MI than motor execution, causing focus to drop and fatigue to increase (Chen et al., 2021). Therefore, it will be meaningful to conduct more studies on using motor execution as an alternative task performance for EEG neurofeedback.

Individual Variations in Controlling BCI and Neurofeedback

Furthermore, studies have also shown a large individual variation in the ability to control neurofeedback itself. In fact, as many as 15-30 percent of the participants failed to learn to control a BCI (Blankertz et al., 2009; Halder et al., 2019; Cecotti, 2020). Differences between individuals who show training effects and neuroplasticity with neurofeedback (i.e., responders) and those who do not (i.e.,non-responders) are largely unexplored to date (Ang et al., 2011; Kaiser et al., 2014). The limited spatial resolution offered by EEG data may render it insensitive to individual differences and the functional reorganization brought about by neurofeedback training in some individuals. Thus, it is also imperative for studies to explore factors driving these individual differences and employing other imaging modalities might provide useful insights to this issue.

Considerations for a Low-Density EEG Setup

Lastly, traditional EEG setups used in research settings consist of high-density electrode placements with sophisticated amplifiers. A significant amount of time and expertise is still required to set them up. This makes them less

favourable for use in high intensities, repetitive training across multiple sessions (Langhorne et al., 2011), which is required for rehabilitation to have a clinically and functionally meaningful effect. Therefore, for EEG neurofeedback to attain widespread clinical use, it will be beneficial to develop a cheaper and less complicated system that is easier and less time-intensive to set up and could potentially be adapted for use at home or in community settings.

Objectives of this study

The current study aims to investigate the potential of using a low-cost, mobile, wireless EEG system for neurofeedback training. With 16 electrodes and a small portable amplifier, this setup is substantially reduced from the usual EEG setup used in research settings. However, such a low-density EEG setup will pose several challenges related to spatial resolution (Niedermeyer & Da Silva, 2004), coverage of brain regions (Michel et al., 2004) and source separation (Baillet, 2017). Moreover, the limited number of electrodes may not capture and differentiate signals from artifacts such as muscle activity and eye movements effectively too (McMenamin et al., 2010).

With these potential disadvantages in mind, this study examined the effect of EEG neurofeedback during motor execution on cortical lateralisation in healthy individuals as an initial step before clinical translation to stroke patients. EEG neurofeedback training performance was tracked across multiple sessions, as previous research has suggested that at least four to ten hours of training is required before a person can gain volitional control over mu rhythms (Pineda, 2005). In addition, to assess training effects and possible individual differences more comprehensively, functional MRI before and after the training were also collected.

It is hypothesized that with the presentation of real EEG neurofeedback but not sham neurofeedback, participants would be able to increase laterality of their motor rhythms as measured by the difference in their ERD during motor execution. It is hoped that findings from this study can be the first step to clinical translation for stroke rehabilitation with a low-density, mobile EEG setup.

Methods

Participants

Fourteen healthy volunteers (mean age = 22.4 yo, *SD* = 3.23yo, 7 females) participated in this study. The sample size was determined based on prior studies that had demonstrated neurofeedback effects using similar paradigms (Zich et al., 2015b). All participants were right-handed as assessed by the Edinburgh *Handedness* Inventory (Oldfield, 1971, M = 83.53, SD = 11.42), and had no history of neurological or psychiatric disease. Participants provided written informed consent in accordance with the Declaration of Helsinki and the National Research Ethics service approved the protocol (14/LO/0020).

Experimental Design and Procedure

Using a within-subjects design, participants underwent both real and sham neurofeedback conditions (single-blind, counterbalanced). Each condition consisted of a baseline EEG session, an MRI pre-test, four sessions of real or sham neurofeedback training that took place on different days and an MRI post-test (Figure 4.1). The baseline session was conducted to determine initial EEG

activity during finger tapping in the absence of feedback. In addition, MRI scans were also conducted before and after each set of training to further examine and localise possible training effects. Lastly, electromyography (EMG) data were collected with surface electrodes from the flexor surface of the forearm in all the EEG sessions. All seven sessions (five EEGs and 2 MRIs) were completed within 7 days, and in between the real and sham conditions, a washout period of four to six weeks was implemented. All participants completed the full 14 sessions required by this experiment.

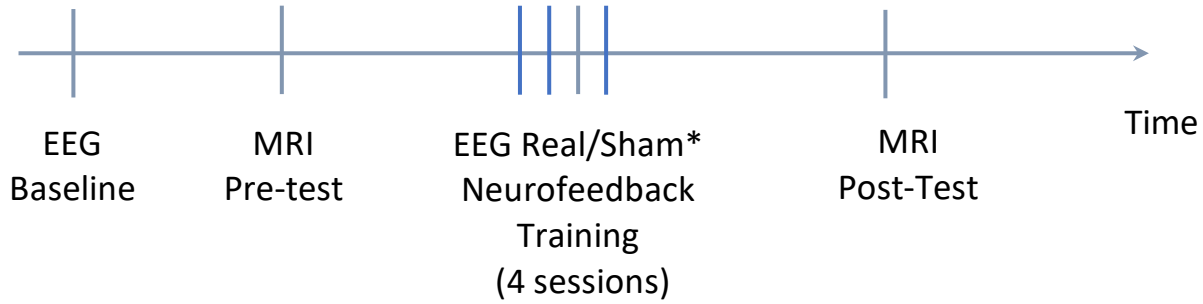

Figure 4.1 Experimental Procedure. The experiment schedule consisted of a baseline EEG session, MRI pre-test, 4 sessions of Real/Sham FB training, MRI Post-Test and a washout period of 4-6 weeks in between the different conditions.

EEG Data Acquisition

EEG data were acquired with a modified wireless and portable Emotiv Epoc amplifier (128 Hz sampling rate, 16 and 45 Hz bandpass, research edition, CA, USA), coupled to 16 Ag/AgCl electrodes. The amplifier (50X44X25mm, 48grams) and electrodes were held in place over bilateral motor cortices on the scalp using EasyCap (Figure 4.2). In addition, EasyCap also allows electrodes to be attached according to the standard 10-20 electrodes placement (Figure 4.3). In this setup, a midline parietal site (Pz) was used as ground and a midline frontopolar electrode (Fz) was used as reference. Electrode impedances were checked regularly at the beginning of each recording to ensure these were below 5 kOhm to minimise noise interference.

Figure 4.2 Example of the portable wireless EEG setup. Instead of a phone, a laptop was used for FB presentation.

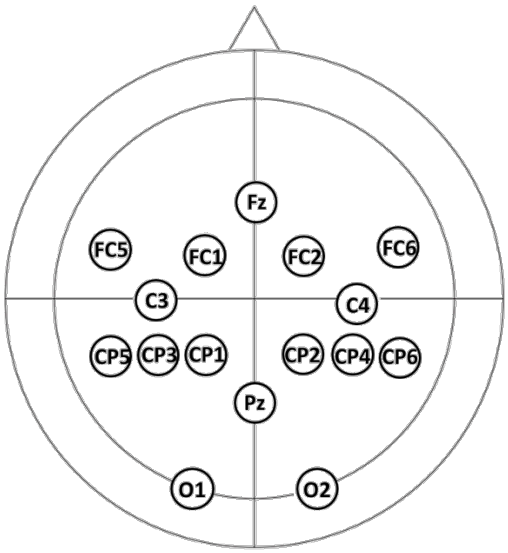

Figure 4.3 Placement of the 16 electrodes used. There were mainly over bilateral motor cortex, with Pz acting as the ground and Fz acting as the reference.

Neurofeedback Trials

Each FB trial started with a fixation cross (2s), followed by an arrow cue to indicate which hand to use (1.25s), and a tapping/feedback period (3.75s) before ending with a jittered inter-trial interval of 1-3.5s (Figure 4.4). Participants were instructed to perform finger tapping movements while attempting to modulate the neurofeedback to the cued direction by varying their order, rate and/or

force of tapping. In the sham condition, a video playback of the feedback from another participant was used instead, but participants were blinded to this manipulation and were instructed to control the feedback shown with finger movements as in the real neurofeedback condition. For each training session, participants completed 5 blocks of 20 FB trials (per hand, presented randomly) in total.

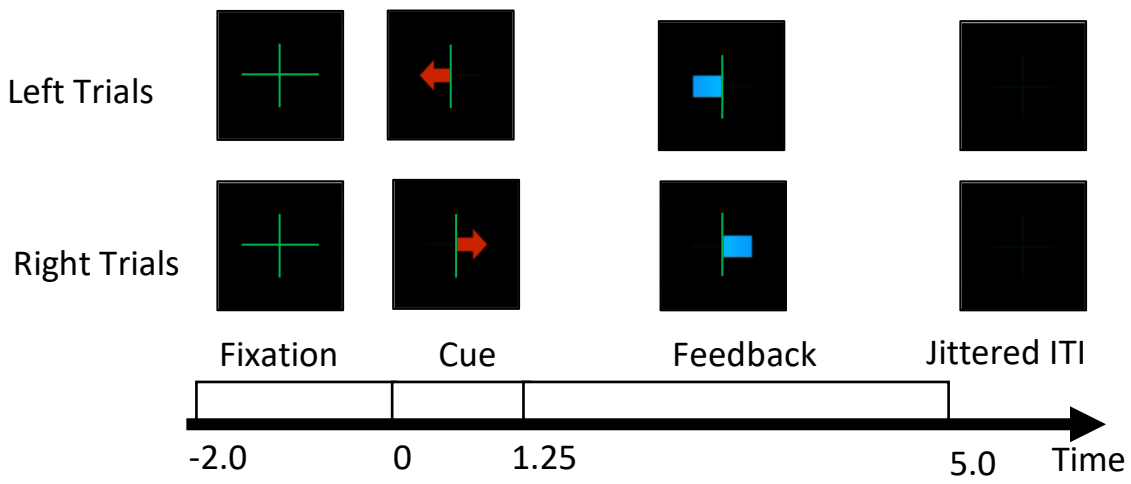

Figure 4.4. Stimulus presentation and timeline used for FB trials. Each trial started with a fixation cross (2s) followed by a directional cue which lasted for 1.25s and before the feedback bar is presented for 3.75s. Lastly a jittered ITI of of 1-3.5s is used.

Online EEG Analyses

Online EEG analyses and FB presented was carried out in OpenViBe 0.18.0 (Renard et al., 2010), an open-source platform for developing BCI applications (Fakhruzzaman, Riksakomara & Suryotrisongko, 2015). As EEG data at the single-trial level are inherently noisy and weak, BCI and machine learning (ML) are employed to identify brain activity without relying on traditional group statistics (Pawan & Dhiman, 2023).

At the beginning of each session, the BCI classifier was trained offline to discriminate between participants' EEG data (from channels C3 and C4) associated with left and right finger tapping. These data were collected from 20 trials of tapping for each hand in the absence of feedback at the beginning of each session. Next the data were preprocessed with a temporal bandpass filter (8-30Hz) and segmented into epochs corresponding to left- and right-hand trials. A running average of 1 second bin, separated by 62.5msec was applied. The averaged epoched data was then feed into a common spatial pattern filter (CSP) for signal enhancement by identifying spatial patterns that maximize the variance for one condition while minimizing the variance for another and vice versa (i.e., right versus left hand trials). Common Spatial Pattern (CSP) filter is a

technique used primarily in the field of electroencephalography (EEG) and brain-computer interfaces (BCIs). It's designed to enhance and extract useful information from multichannel EEG signals by spatially filtering them. CSP calculates a set of spatial filters (or patterns) that maximize the variance of EEG signals for one condition (e.g., left-hand movement) while minimizing it for another condition (e.g., right-hand movement). These filters are derived from the covariance matrix of EEG signals recorded from multiple electrodes placed on the scalp and with the goal of finding a set of spatial filters that can effectively differentiate between the two classes of signals based on their covariance matrices. The end results are separate EEG signal components that are maximally correlated with different mental states or tasks.

Then a ML algorithm, Linear Discriminant Analysis, was applied to learn about the user's intended mental state during the task, by extracting features (such as power spectral density, peak frequency, spatial patterns from CSP filter) from EEG data that can best discriminate between the brain activity associated with left- or right-hand movement. LDA works by identifying a linear combination of features that separates or characterizes two or more classes of objects or events. LDA does this by projecting data with two or more dimensions into one dimension so that it can be more easily classified, referred to as dimensionality

reduction. If there are two classes then the LDA draws one hyperplane and projects the data onto this hyperplane in such a way as to maximize the separation of the two categories. This hyperplane is created to maximise the distance between the means of two classes and minimizing the variation between each category simultaneously. In short, the features used for each participant at each session were computed by ML algorithms with the objective to best discriminate between the two conditions. In this way, the particular combination of features used to drive the classifier might vary between participants.

Then, during the neurofeedback trials, this ML-trained classifier was used to identify EEG data at the single-trial level to derive the FB values. EEG data from the neurofeedback trials also underwent temporal filtering, epoching, CSP spatial filtering. Then features identified from the training data set that could best discriminate between the two conditions were extracted from the current FB trial and fed into the LDA classifier. The output of the LDA classifier is the distance of the feature vector (e.g, the signal band power for each spatially filtered CSP channel) to the LDA separating hyperplane. The larger the outcome (in absolute value), the further away from the separating hyperplane the feature vector. This output, i.e., the distance to the separating LDA hyperplane, is

mapped to the feedback bar, the bar goes left or right depends on whether the LDA output is positive or negative, and the largest the absolute LDA output, the longer the bar (Lotte, 2015). In short, features what could best discriminate between the left- and right-hand trials were first identified from the training data set. These features were then extracted from the NF data in real-time, projected onto the LDA separating hyperplane and the distance of the feature vector to the hyperplane determined the feedback given to the participants. Lastly, this classifier was updated (retrained) once after the third FB block (out of a total of 5 blocks) to take into account possible changes caused by factors such as training and fatigue.

Classification accuracy was calculated based on the percentage of instances or time points where outcomes predicted by the trained classifier were correct over total number of instances. An accuracy rate of 50% indicates that the classifier is performing at a chance level. Effective NFB training will lead to a higher classification accuracy, indicating that the differences between the left- and right-hand are greater, allowing ML algorithms to discriminate between these two conditions more reliably and accurately. This measure of 'Classification Accuracy' was used as the primary measure of individual's ability to control their neurofeedback signal with BCI. To examine the effect of EEG

neurofeedback on classification accuracy, repeated-measure analysis of variance with neurofeedback type (NFB) and Session as factors was carried out in IBM SPSS Statistics (version 25).

Offline EEG analysis

To track the change in laterality across sessions, event-related de-synchronisation (ERD) was computed offline using EEGLAB B 10.2.2.4b (Delorme and Makeig, 2004) and MATLAB R2011b (Mathworks, Inc, Natick, MA).

EEG data were first band-pass filtered from 1 to 40 Hz, and artefacts such as eye blinks, movements and heart beat were removed using independent component analysis (ICA) and manual rejection. Data were epoched from -0.5s to +5.0s with respect to cue onset time (Figure 4.4) and a common spatial patterns filter was applied to improve spatial resolution and signal-to-noise ratio. To identify the most sensitive frequency bands for the analysis, event-related spectral perturbations (ERSP) maps were created using bootstrapping with *t*-statistics for channels C3 and C4 (covering left and right primary motor area respectively). These time-frequency maps showed statistically significant changes of spectral power over time (Figure 4.5). Peak frequency was

determined from the time-frequency map for each subject, each session and each condition to calculate the ERD.

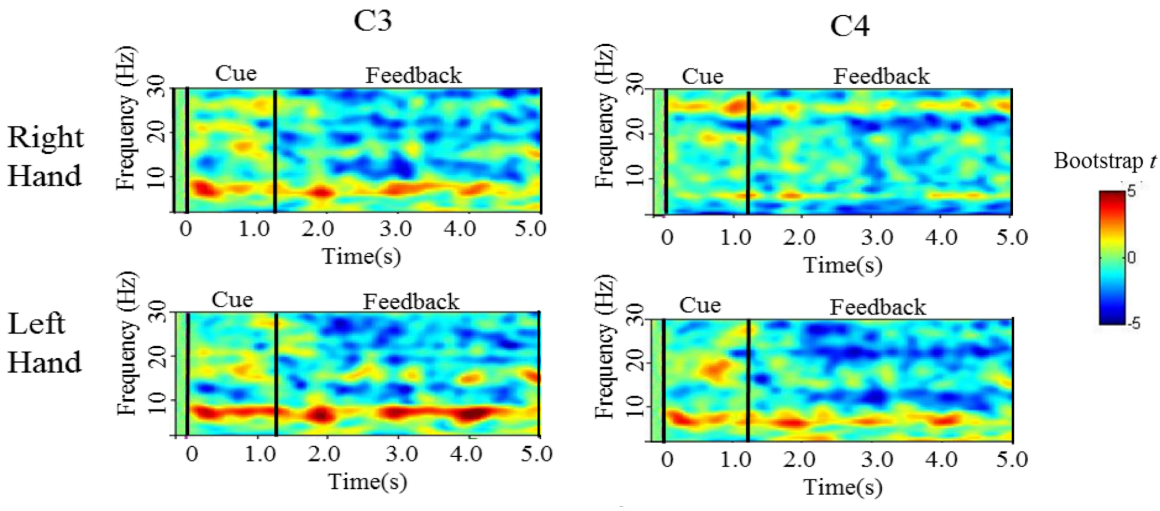

Figure 4.5 Example of ERSP maps from a single subject. These time-frequency maps show statistically significant changes in ERD for C3 and C4 during right- and left-hand trials. ERSP was used to determine subject-specific peak frequency. (Desynchronisation is represented in blue).

ERD was then computed by band-pass filtering of each trial based on the identified peak frequency (peak frequency +/- 2Hz), squaring of sample points to obtain EEG power, averaging over trials, and smoothing with a moving window of 750ms (spaced 6.25ms apart). Change in ERD was then expressed as a percentage change from the reference baseline period (defined as the window -0.5s before cue onset to cue onset, Figure 4.2).

- $\Delta ERD(\%) = \frac{Power_{baseline} - Power_{event}}{Power_{baseline}}$ x 100

Lateralised ERD was then computed, as with the change in ERD, as follows (Eimer, 1998; Nam, Jeon, Kim, Lee, & Park, 2011):

- Overall lateralised ERD = $[(C3\text{-}C4)_{\text{right hand}} - (C3\text{-}C4)_{\text{left hand}}]$
  - Lateralised ERD for left-hand trials = C3-C4
  - Lateralised ERD for right-hand trials = C4-C3

To examine the effect of EEG neurofeedback training across sessions on lateralised ERD, RM-ANOVA with FB type (Real/Sham) and Session (1 to 4) as factors, was carried out in IBM SPSS Statistics (version 25).

Electromyography (EMG) acquisition and analysis

EMG data were collected with surface electrodes from the flexor carpi radialis muscle on each arm in all the EEG sessions to assess for possible behavioural changes with neurofeedback training. Signals were sampled at 5 kHz, amplified, filtered (10 Hz-1 kHz), and recorded using a CED 1902 amplifier, a CED micro1401 A/D converter, and Signal software version 3.13 (Cambridge Electronic Design). Subsequently, the data were analysed in MATLAB R2011b

(Mathworks, Inc, Natick, MA): denoised, rectified, converted to root mean squares (RMS) and epoched according to conditions. RMS values were summed during the task active period (during motor execution when FB was presented) and averaged across trials. To investigate the possible changes in EMG activity across training sessions with Real and Sham NFB, RM-ANOVA was carried out in IBM SPSS Statistics (version 25) using NFB and Session as factors.

MRI acquisition and analyses for Pre-test and Post-test

MRI data were acquired on a 3 T Siemens Magnetom Prisma MRI scanner (Siemens AG) using a 32-channel head coil. A whole brain anatomical T1-weighted [magnetization prepared rapid gradient echo (MPRAGE), voxel-size = 1 × 1 × 1 mm3, TR = 1900 ms, 192 slices] image was collected. Task fMRI was acquired using multiband gradient echo-planer imaging (72 slices, whole brain coverage, voxel-size = 2 × 2 × 2 mm3, TR = 933 ms). During the task fMRI scans, participants were told to perform finger tapping in the absence of feedback in a block design sequence with 1s cue, followed by 15s of tapping and 20s of rest (Figure 4.6).

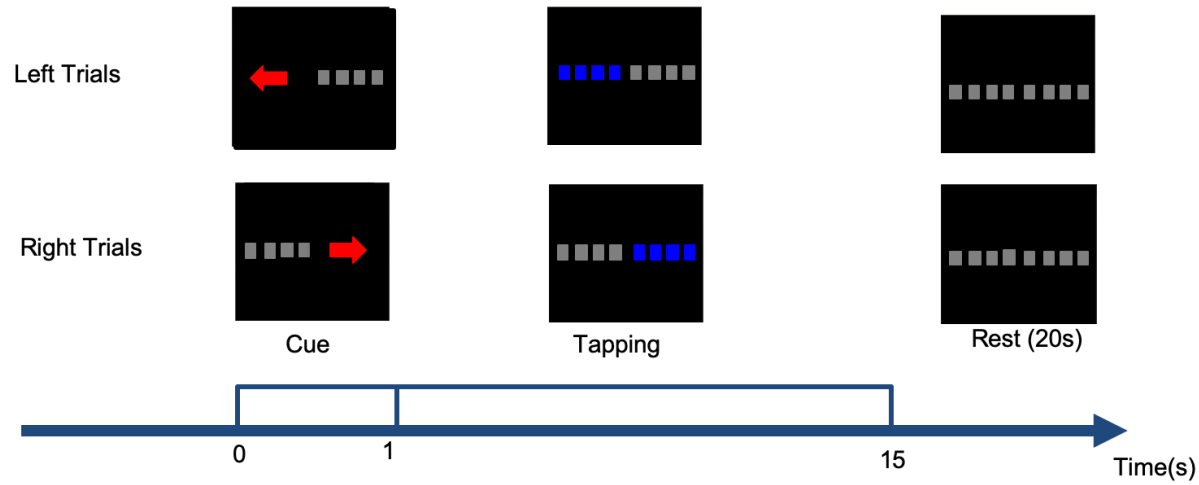

Figure 4.6 Stimulus presentation and time line used for task fMRI scans trials. Each block started with a directional cue for 1s, 15s of tapping and 20s of rest.

Data were analysed in FMRIB Software Library (www.fmrib.ox.ac.uk/fsl), with standard preprocessing steps including motion correction, brain extraction, fieldmap-based EPI distortion correction using FUGUE, Gaussian spatial smoothing (FWHM of 5mm), denoising with FIX and 100s high-pass temporal filtering. Co-registration was achieved by first using linear registration (FLIRT); to register the multiband functional data to a single volume, high-contrast (single-band) EPI image. Next, the high-contrast EPI image was linearly registered to the T1-weighted image using boundary-based registration (6 degrees of freedom). Data were then registered nonlinearly with FNIRT to the standard MNI 2mm template brain to allow voxel-wise group analysis. Group level analysis was carried out using FMRIB's Local Analysis of Mixed Effects

(FLAME) to compare difference maps between the Real and the Sham condition, before and after EEG NFB training (i.e., NFB-by-Session interaction) for each hand. Group Z-statistic images were thresholded using clusters determined by $Z > 3.1$ and a family-wise corrected cluster significance threshold of $p<0.05$ was applied.

In addition, parameter estimates (*PEs*) from the right and left M1 ROIs (identified with Harvard-Oxford Structural atlases) during the task period was extracted. A two-way (ROI-by-Session) rm-ANOVA was applied to test for changes in activity in these ROIs before and after neurofeedback training.

To investigate possible neural correlates of EEG neurofeedback control, classification accuracy from the first EEG FB session was included in FEAT as additional covariate (EV). This allows for investigation of brain regions that show positive linear relationship between initial classification accuracy (i.e., neurofeedback control) and initial fMRI BOLD activity at pre-test.

Results

Classification Accuracy during EEG Neurofeedback

To test whether NFB altered classification accuracy, these values were compared over the four sessions of NF, for Real and Sham NF groups (Figure 4.7A). Repeated measures analysis of variance (RM-ANOVA) revealed no NFB*Session interaction for classification accuracy ($F_{(2.51, 32.6)}$ = 1.31, p = .548). To investigate possible ceiling effect given that classification accuracies were already quite high from the first session (mean = 79.3%), participants were divided into High and Low Accuracy Group based on their performance in the first real feedback session with a median spilt. This post-hoc analysis revealed a significant Group*NFB*Session interaction ($F_{(2.83, 28.6)}$ = 2.72, p = .044)., followed by a significant Group*Session interaction in the Real NFB training condition ($F_{(2.18, 28.3)}$ = 2.61, p = .041). Specifically, there was a significant change, i.e., simple main effect, in classification accuracy for the Low Accuracy Group with Real NFB training ($F_{(2.65, 34.3)}$ = 2.94, p = .039) but no change in classification accuracy for this group when they underwent Sham FB (Figure 4.7B). For the Low Accuracy Group with Real NFB training, classification accuracy was higher

in Session 3 vs Session 1 (paired $t_{(6)}$ = 2.47, p = 0.48, two-way) and Session 4 vs Session 1 (paired $t_{(6)}$ = 2.61, p = 0.37, two-way) but not between session 2 and 1 (p >.1) (Figure 4.7B). There was also no significant interaction or main effects for the High Accuracy Group (ps > .1) (Figure 4.7C).

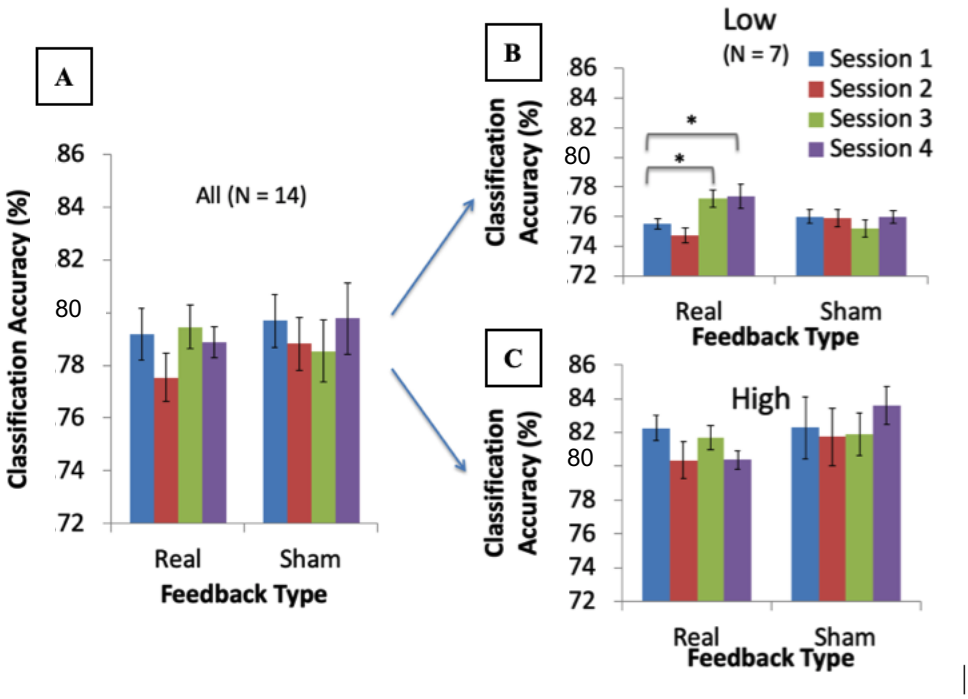

Figure 4.7 Classification Accuracy during EEG Neurofeedback. (A) RM-ANOVA revealed no NFB*Session interaction for classification accuracy ($F_{(2.51, 32.6)}$ = 1.31, p = .548). After grouping the participants using median spilt on their accuracy results from the first Real FB session, there is a significant Group*NFB*Session interaction, $F_{(2.83, 28.6)}$ = 2.72, p = .044. (B)There is a significant Group*Session interaction in the Real NFB training condition ($F_{(2.18, 28.3)}$ = 2.61, p = .041). There is a significant change in classification accuracy for the Low group with Real NFB training ($F_{(2.65, 34.3)}$ = 2.94, p = .039). Classification accuracy was higher in session 3 vs session 1 (paired $t_{(6)}$ = 2.47, p = 0.48, two-way) and session 4 vs session 1 (paired $t_{(6)}$ = 2.61, p = 0.37, two-way). There is no change in classification accuracy for this group when they underwent Sham FB. (C)There is no significant interaction and main effects for the High Accuracy Group.

Change in ERD with EEG Neurofeedback

To test whether NF altered ERD, these values were compared over the 4 NF sessions and between Real and Sham NF groups. RM ANOVA shows a NFB*Session interaction for overall lateralised ERD, $F_{(2.61, 34.0)} = 4.17$, $p = .017$ (Figure 4.8A). More specifically, change in overall lateralised ERD is significant in the Real NFB condition (i.e simple main effect of session) in Real NFB group, $F_{(2.57, 32.1)} = 3.17$, $p = .037$ but not in the Sham NFB condition ($p > .1$). For the Real NFB condition, the difference between session 4 and 1 was significant (paired $t_{(13)} = 2.51$, $p = 0.26$, two-way) , but not between sessions 3 and 1, nor between sessions 2 and 1 (ps > .1).

To further localise the change, ERD values were separately analysed for left hand trials (i.e., C4 – C3) and right-hand trials (C3 – C4). Lateralised ERD for left-hand trials revealed a significant NFB*Session interaction ($F_{(2.71, 38.1)} = 4.67$, $p = .011$), followed by a significant simple main effect of Session in the real NFB condition ($F_{(2.57, 32.1)} = 3.52$, $p = .028$) but not in the Sham NFB condition ($F_{(2.23, 29.1)} = 2.59$, $p = .087$) (Figure 4.8B). For the Real NFB condition, the difference between session 4 and 1 was significant (paired $t_{(13)} = 2.44$, $p = 0.29$, two-way), but not

between sessions 3 and 1, not between sessions 2 and 1 (ps > .1) (Figure 4.8B). On the other hand, there were no significant effects of interaction, NFB or Session in the right-hand trials (*p*s > .1) (Figure 4.8C)

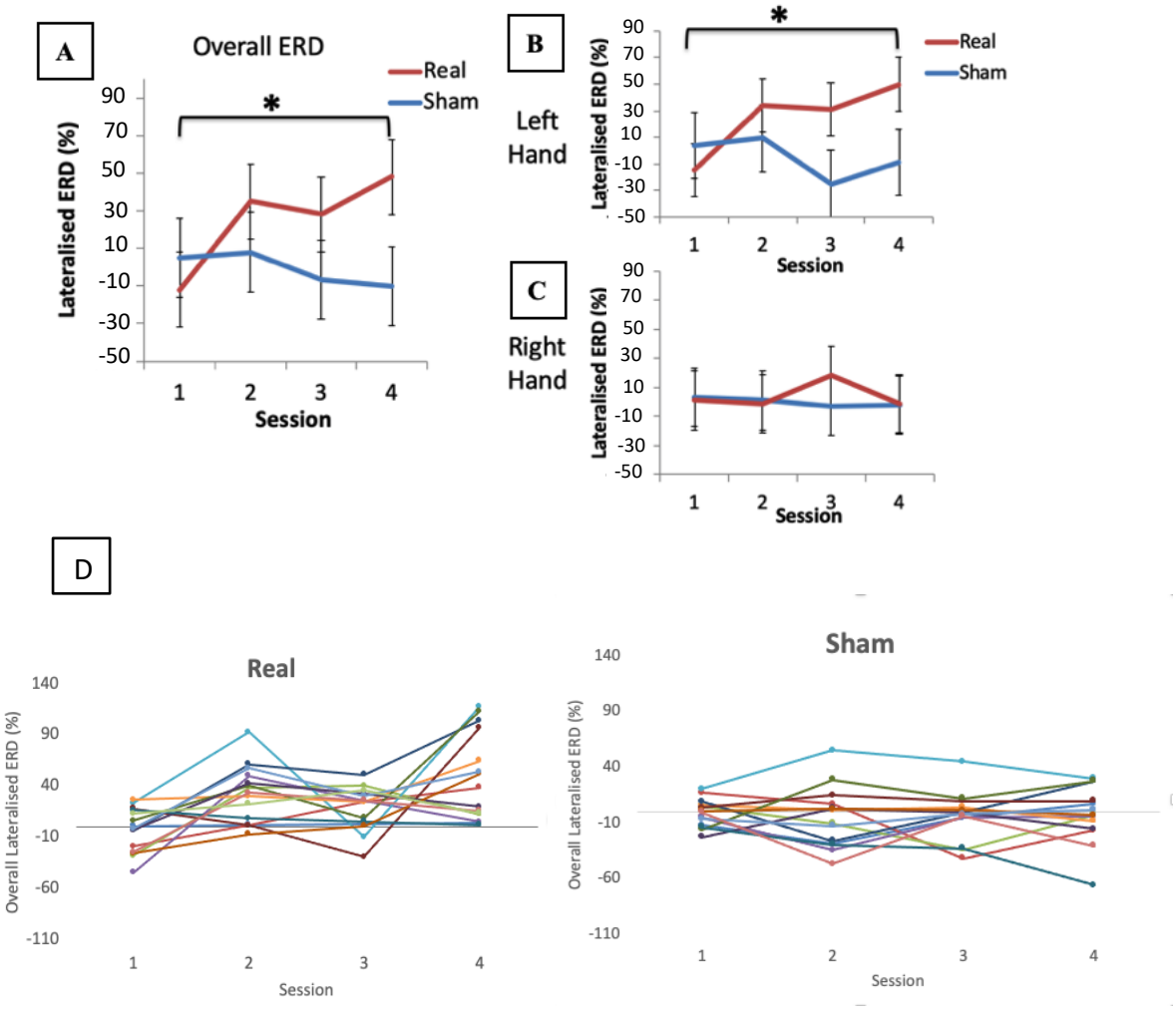

Figure 4.8 Change in ERD with EEG Neurofeedback. (A) There is a NFB*session interaction for overall lateralised ERD ($F_{(2.61, 34.0)} = 4.17$, $p = .017$), with the change in overall lateralised ERD significant in the Real NFB condition (simple main effect of session for Real NFB, $F_{(2.57, 32.1)} = 3.17$, $p = .037$) but not in the Sham NFB condition. There was an increase in ERD at Session 4 when compared to Session

1 (paired $t_{(13)}$ = 2.51, p = 0.26, two-way). (B) To further localize the change, ERD values were separately analysed for left hand and right-hand. Lateralised ERD for left-hand trials revealed a significant NFB*Session interaction ($F_{(2.71,\ 38.1)}$ = 4.67, p = .011), followed by a significant simple main effect of Session in the Real NFB ($F_{(2.57,\ 32.1)}$ = 3.52, p = .028) but not in the Sham NFB condition. ERD was also higher in Session 4 when compared to Session 1 (paired $t_{(13)}$ = 2.44, p = 0.29, two-way) when receiving Real FB. (C) On the other hand, there were no significant interaction and main effects of NFB or Session in the right-hand trials. (D) Overall lateralised ERD for individual subjects across sessions 1 to 4.

Change in EMG with EEG Neurofeedback

To test whether NF altered forearm muscle activity during movement, EMG signals were compared over the 4 NFB sessions and between Real and Sham groups (Figure 4.9). For EMG averaged across both hands, there was no significant NFB*Session interaction ($F_{(2.18,\ 28.1)}$ = 0.671, p = .71) and no main effect of Session ($F_{(2.14,\ 27.1)}$ = 0.378, p = .82). However, there was a significant main effect of NFB, $F_{(1,\ 13)}$ = 5.87, p = .031, indicating the EMG outputs from participants were higher during Real NFB conditions regardless of Session (Figure 4.9). Analysing EMG for each hand separately did not yield any significant interaction of Hand*Session interaction or main effects in Real and Sham NFB conditions (ps > .1)

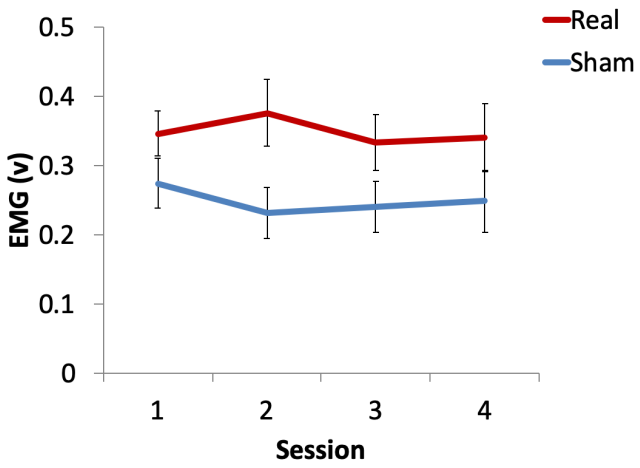

Figure 4.9 Change in EMG with EEG Neurofeedback. There is a significant main effect of NFB, $F_{(1, 13)} = 5.87$, p = .031, indicating the EMG outputs from participants were higher during Real NFB conditions regardless of session.

Transfer Effects: MRI Pre-test vs Post-Test

Voxel-wise group analyses using the contrast NFB-by-Session interaction (ie. Real(Post – Pre) – Sham(Post – Pre)) for each hand revealed a significant cluster at prefrontal context (PFC). Increase in activity in PFC after FB training was greater in the Real NFB condition than in the Sham NFB condition (Figure 4.10)

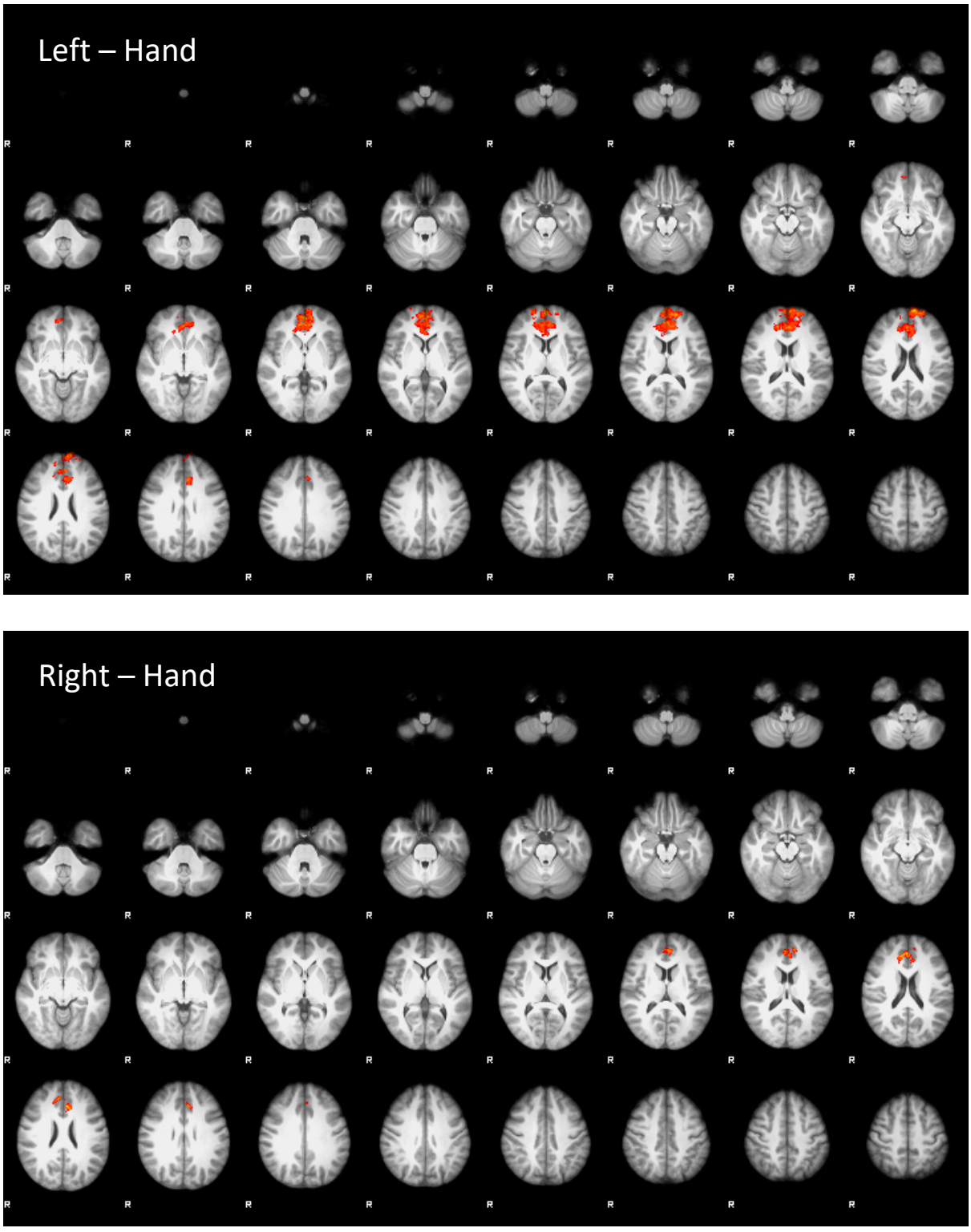

Figure 4.10. Voxel-wise group analyses using the contrast NFB-by-Session interaction for each hand revealed a significant cluster at prefrontal context (PFC).

To test whether NFB resulted in any persistent changes in movement-related activity, even after NFB was removed, fMRI signals were compared between Pre and Post NFB scans for Real and Sham conditions. RM ANOVA performed on fMRI parameter estimates (*Pe*s) did not reveal any significant NFB*Session interaction or main effects for both the left primary motor cortex (M1) and Right M1 (ps > .1) (Figure 4.11).

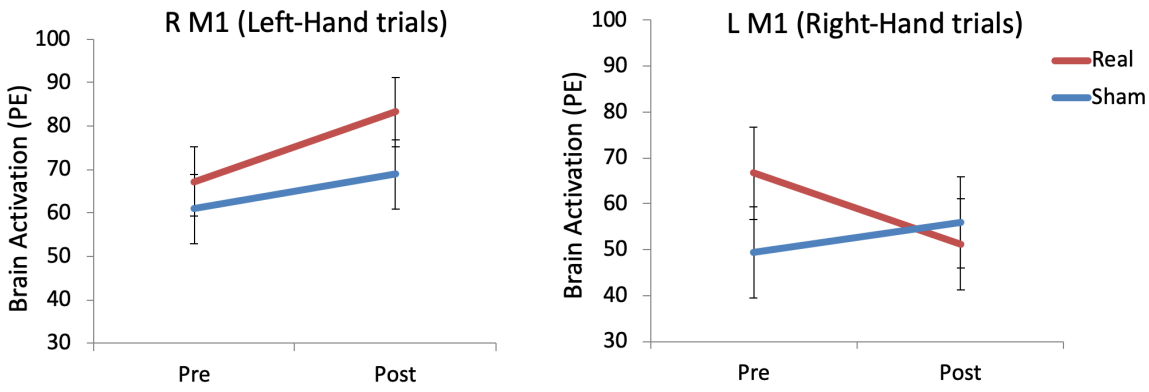

Figure 4.11 Transfer Effects: MRI Pre-test vs Post-Test. There is no significant interaction or main effects for both the left primary motor cortex (M1) and Right M1 for the PEs obtained from fMRI task sessions.

Neural correlates of EEG Neurofeedback Control

To examine whether individual differences in baseline brain activity predict control of NFB with BCI (i.e., potential differences between responders and non-responders), fMRI activity during the pre-NFB scan was related to classification

accuracy during the first NF session. FEAT analysis revealed significant correlation between classification accuracy and fMRI BOLD activity in non-dominant right M1 (Figure 4.12). To visualise the distribution of data underlying the correlation between BOLD response and Classification Accuracy shown in Figure 4.12, the mean values within the significant cluster are plotted in a scatter plot in Figure 4.13.

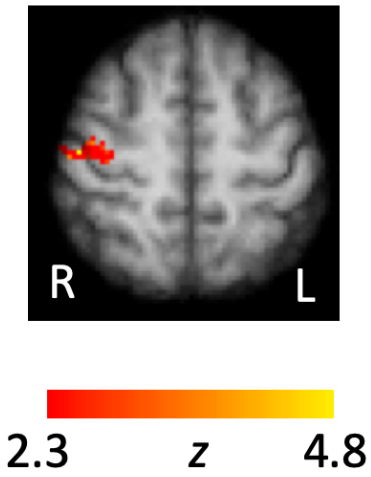

Figure 4.12 A significant correlation between classification accuracy and fMRI BOLD activity in non-dominant right M1. fMRI activity during the pre-NFB scan was related to classification accuracy during the first NF session. FEAT analysis revealed significant correlation between classification accuracy and fMRI BOLD activity in non-dominant right M1.

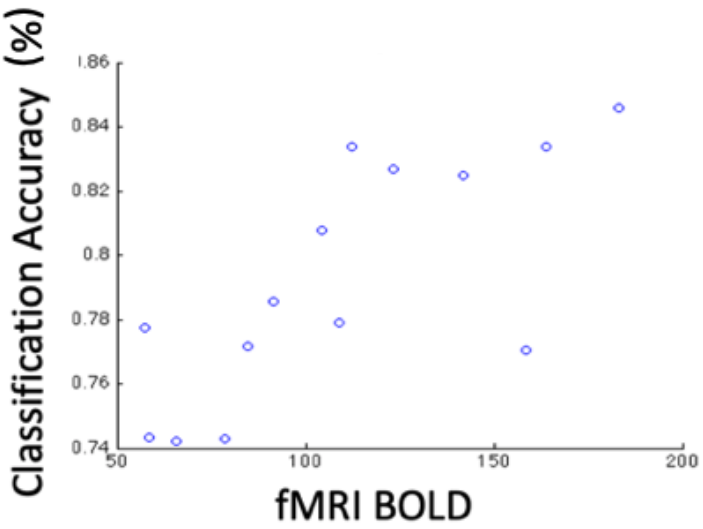

Figure 4.13 Scatter plot of parameter estimates from the right M1 during left-hand tapping with classification accuracy during the first session of NF.

Discussion

Summary of Findings

The current study investigated the use of a low-cost, mobile EEG system (Debener et al., 2012) for neurofeedback training to increase brain lateralization during motor execution in healthy individuals. Results suggest that classification accuracy and lateralised ERD during movement execution can increase with neurofeedback training. These results provide some preliminary evidence that neurofeedback training can be an effective means in promoting self-regulation of brain activity and specifically, hemispheric lateralisation during motor execution. Behaviourally, EMG output during real neurofeedback was higher than EMG output during sham neurofeedback, indicating that movement parameters (e.g.,velocity, force) were greater when real neurofeedback was provided. Correlating classification accuracy and fMRI BOLD activity at baseline suggests that activity in the non-dominant M1 predicted participants' ability to control neurofeedback with self-regulated ERD activities. However, in the absence of neurofeedback, increase in activity in PFC is greater after participants

received real feedback than sham feedback. However, no change in BOLD activity between the Pre-test and Post-test was observed for M1.

EEG neurofeedback promotes cortical reorganisation

Findings from the current study suggests that a low-density concise EEG neurofeedback setup can be a potential useful approach for stroke rehabilitation. Consistent with research using a full EEG setup, lateralized ERD increased with EEG neurofeedback training, suggesting that EEG neurofeedback can bring about greater cortical lateralisation. However, the results are mainly observed in the non-dominant right hemisphere when moving the non-dominant left hand. This could be because of the task design employed in this study. As a simple motor execution task in healthy participants for the dominant hand is already quite effortless, no change was observed in the dominant hemisphere.

Neural Correlates of ability to control EEG Neurofeedback

To address possible individual differences more comprehensively, functional MRI before and after the NFB training were also collected Correlating classification accuracy and fMRI BOLD activity at baseline suggests that activity

in the non-dominant M1 predicted participants' ability to control neurofeedback with self-regulated ERD activities. This is probably because classification algorithms work by maximising the difference between two conditions. As activity in the dominant hemisphere is relatively stable, as seen from the lack of change in ERD, when brain activity in the non-dominant hemisphere increases, it leads to greater differences between the two conditions. This increased difference between conditions that leads to better classification.

Laterality of motor ERD during Motor Execution

Most EEG neurofeedback research in stroke or patients with hemiplegia has also been focusing on motor imagery (MI) instead of motor execution or motor attempt. The current study investigated the effect of EEG neurofeedback with motor execution as it offers advantages such as avoiding individual differences in the ability to perform MI and MI was generally thought to be less natural and more difficult to perform than motor execution (Chen et al., 2021).

However, the results in this study seems to suggest that the ERD during motor execution is quite bilateral process. Interestingly, this was also observed in a few studies. Li et al. (2018) applied a comprehensive electroencephalography (EEG) analysis to understand movement-related brain activity changes during

movement preparation and execution stage of a cued unilateral wrist extension task in 34 healthy subjects. In the movement preparation stage, motor ERD presented mainly in the contralateral sensory motor cortex area (C3 and C4 for right and left wrist movements, respectively) and showed significant differences between different locations. However, during the motor execution phrase, ERD was observed at both locations and the change in ERD do not differ significantly between the locations. Similarly, in the studies by Stancák and Pfurtscheller (1996), and Dolye, Yarrow and Brown (2005) with healthy participants, motor ERD was observed to be lateralised during the movement preparation period and it became bilateral during motor movement for both hands. These studies suggest that motor ERD was found to have stronger contra-lateralisation features in the movement preparation stage and might be a better indicator for detecting movement intentions and planning.

Nonetheless, there are also studies where laterality of ERD was observed during motor execution. For example, Zich et al. (2015a) investigated lateralisation patterns of covert (MI) and overt movements (execution) in 39 young and 36 older healthy adults using EEG neurofeedback. Findings from this study show that ERD lateralization was observed in both overt and covert movements, but laterality was lower in the older adults. More studies are needed to reconcile

the differences in the time course of the laterality of ERD during motor execution.

Post stroke, both decrease in ERD (indicating impaired processing or difficulty engaging in specific tasks) and increase in ERD (compensatory mechanisms employed by the brain to overcome processing deficits) have been observed (Babil et al., 2017, Lotze et al., 2006; Sitaram et al., 2013). Rebalancing these abnormal EEG brain oscillations has been shown to promote recovery in various clinical settings, suggesting that developing a neurofeedback paradigm for self-regulation of EEG desynchronization can be beneficial for rehabilitation (Melnikov 2021, Ray et al., 2020, Viviani & Vallesi 2021). However, given the conflicting results regarding the laterality of motor ERD during movement execution, more studies are needed to ascertain whether motor execution is the ideal task to use with neurofeedback to promote changes in ERD laterality. In addition, other measures such as motor attempt (i.e., attempting to move a paralyzed body part, which may or may not result in visible movement) for neurofeedback can also be explored. A meta-analysis by Bai et al. (2020) revealed that using movement attempt as the trigger task in BCI training appeared to be more effective than using motor imagery, suggesting that motor attempt might also be a potential task for use with neurofeedback training.

The Role of Prefrontal Cortex in Neurofeedback

The PFC is responsible for higher-order cognitive functions such as executive control, decision-making, self-regulation, and goal setting. In the context of neurofeedback, the PFC is important because it is involved in self-regulation and attentional control, which are key aspects of learning to modulate brain activity. Neurofeedback is a psychophysiological procedure in which online feedback of neural activation is provided to the participant for the purpose of self-regulation (Sitaram et al., 2016). It has been proposed that PFC is one of the regions that is involved in learning self-regulation of brain activity through neurofeedback, i.e.,a regulating network that is independent of the targeted brain areas used for the feedback (Mirifar, Keil & Ehrlenspiel, 2022). For instance, a study aiming at down regulation of the auditory cortex found that the PFC were simultaneously up-regulated, suggesting that this area might be involved in the regulation process (Haller et al., 2010)

Higher EMG output in the presence of Real Neurofeedback

EMG output during real neurofeedback was higher than EMG output during sham neurofeedback, indicating that movement parameters (e.g.,velocity, force) were greater when real neurofeedback was provided. These findings suggest that presenting real neurofeedback promote more hand movements in the participants. However, such change does not parallel the change in classification accuracies and lateralised ERD.

In effect, many studies failed to find association between beta ERD or ERS magnitude and movement parameters such as speed (Stancák and Pfurtscheller, 1995, 1996), force (Pistohl et al., 2012; Cremoux et al., 2013) and muscle pattern (Salmelin et al., 1995). Additionally, other studies found that beta ERS amplitude increased with increasing movement speed or force (Stančák et al., 1997; Parkes et al., 2006; Fry et al., 2016). For instance, findings of higher rate finger extensions linked to greater beta event-related synchronisation (ERS) amplitude (Parkes et al., 2006); as movement onsets and offsets were controlled by finger contacts with a button, the blocks with faster movements might have resulted in greater somatosensory input. In general, beta activity reflects inhibition of the motor system, as it is associated with

increased local GABAergic tone (Cassim et al., 2001; Gaetz et al., 2011; Muthukumaraswamy et al., 2013) and decreased cortical excitability (Hsu et al., 2011; Noh et al., 2012; McAllister et al., 2013). Hence, beta ERD may release motor areas from idle state to plan and execute movements, while beta ERS may reflect post-movement active inhibition of the motor network and reactivation of somatosensory areas (Alegre et al., 2008; Solis-Escalante et al., 2012).

Limitations

Ceiling Effect in Classification Accuracies?

Classification accuracies observed in this study (79% on the first day) are higher than those reported in other studies using EEG neurofeedback with motor imagery (MI) as opposed to the motor execution task used here. Using a similar BCI setup with OpenViBe, Zich et al (2015) reported classification accuracies for MI to be about 68% on the first day of the training, which increased to about 74% at the end of the three-day training. Likewise in another study with MI, the mean classification rate reported was 72.4% and the mean maximum accuracy observed was 80.7% (Irimia et al., 2018). The classification accuracy observed in the current study from the beginning was already close 80%. It is therefore quite possible that the participants' or the classification algorithms performance were

already at ceiling. Once again. this could be due to the fact that this study used motor execution in a healthy population instead of motor imagery, which is more difficult to perform.

Low-Density EEG setup

However, the low-density EEG setup used in the current study will pose several challenges related to lower signal-to-noise ratio, spatial resolution (Niedermeyer & Da Silva, 2004), coverage of brain regions (Michel et al., 2004) and source separation (Baillet, 2017). With fewer electrodes, LDEEG setups are more susceptible to noise and artifacts, which can interfere with the detection of ERD. Noise from muscle activity, eye movements, and external sources can have a more pronounced impact on the data quality. (McMenamin et al., 2010). Advanced algorithms that enhance EEG signal processing, such as independent component analysis (ICA) and source reconstruction methods, may have less data to work with in low-density EEG setups. This can limit their effectiveness compared to when they are applied to high-density EEG setup (Soler et al., 2020). These might be the reason why the ERD observed in this study is more bilateral that other studies performed on healthy populations (Nam, 2011).

Future directions

Findings from this study offer preliminary evidence that a small mobile EEG neurofeedback setup is capable of promoting cortical lateralisation during motor execution in healthy adults. Future directions would be to extend the study to stroke patients. A large-scale clinical study of 54 stroke patients has already revealed that 87% of stroke patients were still able to generate EEG motor activity that can be detected by brain-computer machines at a single-trial level despite their neurological damage (Ang et al., 2009). However, using a low-density EEG setup, with limitations such as lower spatial resolution and increased sensitivity to artifacts on lesioned brains, might pose extra challenges not present in standard experimental settings. Hence, the next steps would be to extend the current study to stroke patients in order to evaluate whether a low-density EEG setup can be clinically translated to rehabilitation settings.

Chapter 5

General Discussion

Overview of this thesis

This thesis examines the use of neurofeedback for increasing cortical lateralisation during motor execution as a tool for the promotion of stroke recovery. Two different imaging modalities were used as neurofeedback. The first imaging method studied was fMRI BOLD signal (Chapter Three), which offers a better spatial resolution and a more direct measure of the underlying hemodynamic activities in the cortical motor regions (Huettel, Song, & McCarthy, 2004; Ogawa et al., 1990; Moerel et al., 2020). On the other hand, EEG neurofeedback used in Chapter Four is a more affordable and portable alternative, with good temporal resolution and few contraindications (Luck, 2014; Niedermeyer & da Silva, 2004).

This thesis begins with an overview of the reorganization and recovery of brain activity following a stroke incident. It is reviewed that self-regulation of brain activity to rebalance the abnormal bilateral activation in cortical motor cortex post-stroke can be beneficial to rehabilitation. At the same time, research has also suggested that neurofeedback training can be a means to encourage volitional control over an individual's brain activity, making it a potential tool for

promoting motor recovery. Then two common modes of neurofeedback, fMRI and EEG, were highlighted together with their pros and cons outlined. Lastly, challenges and limitations faced in neurofeedback research currently were considered.

In the next chapter on Methods, biological basis, principles and methodologies behind the two imaging modalities used in this thesis were discussed. Data analysis approaches for both modalities were also outlined.

In Chapter 3, using a sham-controlled double-blind design, I examined the effect of neurofeedback using real-time fMRI on increasing laterality of cortical motor activity during movement execution in 24 chronic stroke patients. Results suggest that in the presence of real neurofeedback, lateralisation was higher during the movement of the affected hand but not in the presence of sham feedback. In addition, voxel-wise group comparison suggests that the difference in brain activities between the real and sham NFB group was localised in the ipsilesional M1, i.e., greater brain activity was observed in the ipsilesional hemisphere in the real NFB group. However, when comparing laterality scores (LS) in Pre-FB and Post-FB scans for both groups, there was no statistical differences observed.

In chapter 4, effects of EEG neurofeedback training were carried out across multiple sessions with a low-density EEG setup, and compared to sham-controlled feedback sessions in healthy young participants. Results suggest that classification accuracy and lateralised ERD during movement execution can increase with neurofeedback training. However, no transfer effect was observed when neurofeedback was removed. In addition, attempt to study individual differences in EEG neurofeedback control indicates that activity in the non-dominant M1 predicted participants' ability to control neurofeedback with self-regulated ERD activities. The findings from this study highlight the potential of using a cheap, portable EEG device as a tool for promoting self-regulation of brain activity.

Future directions and Challenges

The current thesis set out to address some of the challenges faced in the present literature of neurofeedback. By using a double-blind, sham-controlled procedure in Experiment 3, it is hoped that the effects of fMRI neurofeedback can be investigated without confounds such as biases and placebo effects. In Experiment 4, a low-density, portable EEG neurofeedback system was explored with healthy participants as an initial step to develop an economical and convenient tool crucial for the widespread adoption of neurofeedback in stroke

rehabilitation. However, several challenges remain to be addressed in future studies before neurofeedback can be successfully integrated into standard clinical treatment.

Retaining effects of fMRI neurofeedback with longitudinal studies

In the current thesis (Chapter 3), an increase in laterality during motor execution with fMRI neurofeedback was not retained in the absence of the neurofeedback. This could be due to insufficient training or fatigue taking place over a single long training session. Future studies should investigate neurofeedback effects with a longitudinal design across multiple days to further explore possible transfer effects associated with longer neurofeedback training. In effect, Sanders et al. (2022) were able to demonstrate that with three days of fMRI neurofeedback training, stroke survivors show increase in laterality of motor brain activity within session but not across sessions (this deviation from the current study where increase in laterality was not preserved within the same session might be due difference in characteristics of stroke participants recruited. For instance, the average time post stroke was about 35 months shorter and patients with more than one stroke incident were not recruited in the current thesis). More importantly, there was also improvement in gross motor subtasks on the Jebsen Taylor Test and decrease in white-matter asymmetry in the corticospinal tract.

This shows the potential of repeated fMRI neurofeedback in inducing meaningful functional performance and structural changes in the brain. For fMRI neurofeedback to become a useful rehabilitation tool, future studies would be required to explore how to maintain the gains acquired with neurofeedback training across sessions and whether meaningful functional and behavioural improvements can be achieved.

Examining the effect of EEG neurofeedback on stroke survivors

Results from this thesis (Chapter 4) have suggested that it is possible to use a cheap and convenient low-density EEG neurofeedback to increase laterality in EEG motor activity with healthy young participants. However, this has to be extended to stroke survivors to investigate whether: A) neurologically-impaired brains are capable of producing EEG/ERD activity during motor execution that can be classified by current BCI signal processing reliably; B) EEG neurofeedback training can change laterality of motor ERD in this population; C) the effect of neurofeedback training can be maintained in the absence of feedback; D) there is any behaviour and structural changes associated with longer EEG neurofeedback training, and lastly E) the effect of neurofeedback training can

achieve any clinical and functional changes for the patients, e.g.,in performing activities of daily livings.

Further studies on EEG NFB can be potentially useful for stroke rehabilitation. Post stroke, both decrease in ERD (indicating impaired processing or difficulty engaging in specific tasks) and increase in ERD (compensatory mechanisms employed by the brain to overcome processing deficits) have been observed (Babil et al., 2017, Lotze et al., 2006; Sitaram et al., 2013). Rebalancing these abnormal EEG brain oscillations has been shown to promote clinical recovery in various clinical populations (Melnikov 2021, Viviani & Vallesi 2021). For instance, Ray et al., 2020 investigated the relationship of oscillatory sensorimotor brain activity to motor recovery in 30 chronic stroke patients with severe upper-limb paralysis. These patients underwent an intervention including movement training based on combined brain–machine interfaces and physiotherapy of several weeks recorded in a double-blinded randomized clinical trial. Heterogeneity in training outcome was observed in patients with different levels of alpha desynchronization at baseline. Patients showing a strong ipsilesional alpha desynchronization at the beginning of the training improved clinically as assessed with Fugl-Meyer scale if they increased their alpha desynchronization. Patients showing a weak ipsilesional alpha

desynchronization at initial training stages improved clinically if they decreased it further in both hemispheres. In all patients, a progressive shift of desynchronization toward the ipsilesional hemisphere correlate significantly with clinical improvement assessed with Fugl-Meyer scale regardless of lesion location (no differences in ERD for subjects with lesions in pre/postcentral gyrus and those without). This study suggests that developing a neurofeedback for self-regulation of EEG desynchronization might be clinical beneficial.

Conclusions

Addressing the challenges outlined above is essential for advancing the field of neurofeedback in stroke rehabilitation. Future research should focus on large-scale, well-designed studies with diverse stroke populations to enhance the generalizability of findings (Bowman et al., 2021, Franc et al., 2022; Mane, Chouhan & Guan 2020). Additionally, understanding the neurobiological mechanisms underlying neurofeedback effects will contribute to the refinement of treatment protocols and addressing heterogeneity in treatment response. As the field matures, overcoming these challenges will pave the way for the integration of neurofeedback into routine stroke rehabilitation programs, offering personalized and effective strategies for motor and cognitive recovery.

References

Andersson, J. L., Jenkinson, M., & Smith, S. (2007). Non-linear registration, aka spatial normalisation FMRIB technical report TR07JA2. *FMRIB Analysis Group of the University of Oxford*, 2(1), e21.

Alegre M., Alvarez-Gerriko I., Valencia M., Iriarte J., Artieda J. (2008). Oscillatory changes related to the forced termination of a movement. *Clin. Neurophysiol.* 119, 290–300. 10.1016/j.clinph.2007.10.017

Baillet, S. (2017). Magnetoencephalography for brain electrophysiology and imaging. *Nature Neuroscience*, 20(3), 327-339. https://doi.org/10.1038/nn.4504

Ballester, B. R., Maier, M., Duff, A., Cameirão, M., Bermúdez, S., Duarte, E., Cuxart, A., Rodríguez, S., San Segundo Mozo, R. M., & Verschure, P. F. M. J. (2019). A critical time window for recovery extends beyond one-year post-stroke. *Journal of Neurophysiology*, 122(1), 350–357. https://doi.org/10.1152/jn.00762.2018

Bandettini, P. A., Wong, E. C., Hinks, R. S., Tikofsky, R. S., & Hyde, J. S. (1992). Time course EPI of human brain function during task activation. *Magnetic Resonance in Medicine*, 25(2), 390–397. https://doi.org/10.1002/mrm.1910250220

Başar, E. (2012). A review of alpha activity in integrative brain function: fundamental physiology, sensory coding, cognition and pathology. *International Journal of Psychophysiology*, 86(1), 1-24. https://doi.org/10.1016/j.ijpsycho.2012.07.002

Behboodi, A., Lee, W. A., Hinchberger, V. S., & Damiano, D. L. (2022). Determining optimal mobile neurofeedback methods for motor neurorehabilitation in children and adults with non-progressive neurological disorders: a scoping review. *Journal of NeuroEngineering and*

Berger, H. (1929). Über das Elektrenkephalogramm des Menschen. *Archiv Für Psychiatrie Und Nervenkrankheiten*, 87, 527–570. https://doi.org/10.1007/BF01797193

Bergmann, T. O., & Hartwigsen, G. (2021). Inferring causality from noninvasive brain stimulation in cognitive neuroscience. *Journal of cognitive neuroscience*, *33*(2), 195-225.

Bertolucci, F., Chisari, C., & Fregni, F. (2018). The potential dual role of transcallosal inhibition in post-stroke motor recovery. *Restorative Neurology and Neuroscience*, *36*(1), 83-97.

Bezmaternykh, D. D., Kalgin, K. V., Maximova, P. E., Mel'nikov, M. Y., Petrovskii, E. D., Predtechenskaya, E. V., ... & Shurunova, A. V. (2021). Application of fMRI and simultaneous fMRI-EEG neurofeedback in post-stroke motor rehabilitation. *Bulletin of Experimental Biology and Medicine*, *171*(3), 379-383.

Bhagat, N. A., Yozbatiran, N., Sullivan, J. L., Paranjape, R., Losey, C., Hernandez, Z., Keser, Z., Grossman, R., Francisco, G. E., O'Malley, M. K., & Contreras-Vidal, J. L. (2020). Neural activity modulations and motor recovery following brain-exoskeleton interface mediated stroke rehabilitation. *NeuroImage Clinical*, 28, 102502–102502. https://doi.org/10.1016/j.nicl.2020.102502

Birbaumer, N., Murguialday, A. R., Weber, C., & Montoya, P. (2009). Neurofeedback and brain–computer interface: clinical applications. *International Review of Neurobiology*, 86, 107-117. https://doi.org/10.1016/S0074-7742(09)86008-X

Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, 34(4), 537–541. https://doi.org/10.1002/mrm.1910340409

Bowman, T., Gervasoni, E., Arienti, C., Lazzarini, S. G., Negrini, S., Crea, S., Cattaneo, D., & Carrozza, M. C. (2021). Wearable Devices for Biofeedback Rehabilitation: A Systematic Review and Meta-Analysis to Design Application Rules and Estimate the Effectiveness on Balance and Gait Outcomes in Neurological Diseases. *Sensors (Basel, Switzerland)*, *21*(10), 3444. https://doi.org/10.3390/s21103444

Boynton, G. M., Engel, S. A., Glover, G. H., & Heeger, D. J. (1996). Linear systems analysis of functional magnetic resonance imaging in human V1.

Journal of Neuroscience, 16(13), 4207-4221. https://doi.org/10.1523/JNEUROSCI.16-13-04207.1996

Brancaccio, A., Tabarelli, D., & Belardinelli, P. (2022). A new framework to interpret individual inter-hemispheric compensatory communication after stroke. *Journal of Personalized Medicine*, *12*(1), 59.

Buxton, R. B. (2013). The physics of functional magnetic resonance imaging (fMRI). *Reports on Progress in Physics*, 76(9), 096601–096601. https://doi.org/10.1088/0034-4885/76/9/096601

Carrera, E., & Tononi, G. (2014). Diaschisis: past, present, future. *Brain*, 137(Pt 9), 2408. https://doi.org/10.1093/brain/awu101

Cassim F., Monaca C., Szurhaj W., Bourriez J. L., Defebvre L., Derambure P., et al.. (2001). Does post-movement beta synchronization reflect an idling motor cortex? *Neuroreport* 12, 3859–3863. 10.1097/00001756-200112040-00051

Cecotti, H. (2020). Adaptive time segment analysis for steady-state visual evoked potential based brain–computer interfaces. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 28(3), 552-560. https://doi.org/10.1109/TNSRE.2020.2968307

Chen, S., Shu, X., Wang, H., Ding, L., Fu, J., & Jia, J. (2021). The differences between motor attempt and motor imagery in brain-computer interface accuracy and event-related desynchronization of patients with hemiplegia. *Frontiers in Neurorobotics*, 15, 706630. https://doi.org/10.3389/fnbot.2021.706630

Cheng, N., Phua, K. S., Lai, H. S., Tam, P. K., Tang, K. Y., Cheng, K. K., Yeow, R. C., Ang, K. K., Guan, C., & Lim, J. H. (2020). Brain-computer interface-based soft robotic glove rehabilitation for stroke. *IEEE Transactions on Biomedical Engineering,* 67(12), 3339–3351. https://doi.org/10.1109/TBME.2020.2984003

Cho, H. Y., Kim, K. T., & Jung, J. H. (2016). Effects of neurofeedback and computer-assisted cognitive rehabilitation on relative brain wave ratios and activities of daily living of stroke patients: A randomized control trial. *Journal*

of Physical Therapy Science, 28(7), 2154-2158. https://doi.org/10.1589/jpts.28.2154

Cramer, S. C. (2008). Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Annals of neurology*, *63*(3), 272-287.

Cramer, S. C., Nelles, G., Benson, R. R., Kaplan, J. D., Parker, R. A., Kwong, K. K., Kennedy, D. N., Finklestein, S. P., & Rosen, B. R. (1997). A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke*, 28(12), 2518–2527. https://doi.org/10.1161/01.STR.28.12.2518

Cremoux S., Tallet J., Berton E., Dal Maso F., Amarantini D. (2013). Does the force level modulate the cortical activity during isometric contractions after a cervical spinal cord injury? *Clin. Neurophysiol.* 124, 1005–1012. 10.1016/j.clinph.2012.11.007

Dancause, N. (2006). Vicarious function of remote cortex following stroke: Recent evidence from human and animal studies. *The Neuroscientist,* 12(6), pp. 489–499). https://doi.org/10.1177/1073858406292782

Dickhaus, T., Sannelli, C., Müller, K.-R., Curio, G., & Blankertz, B. (2009). Predicting BCI performance to study BCI illiteracy. *BMC Neuroscience*, 10(S1), P84–P84. https://doi.org/10.1186/1471-2202-10-S1-P84

Di Pino, G., Pellegrino, G., Assenza, G., Capone, F., Ferreri, F., Formica, D., ... & Di Lazzaro, V. (2014). Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. *Nature Reviews Neurology*, *10*(10), 597-608.

Edelman, R. R., Hesselink, J. R., & Zlatkin, M. B. (1996). MRI: clinical magnetic resonance imaging (2nd ed.). *Saunders*, USA.

El Nahas, N., Roushdy, T. M., Shokri, H. M., Moustafa, R. R., Elsayed, A. M., Amin, R. M., Ashour, A. A., Abd Eldayem, E. H., Elhawary, G. A., & Elbokl, A. M. (2022). Lateralized readiness potentials can identify hemisphere of recovery in stroke patients. *Restorative Neurology and Neuroscience*, 40(2), 63–71. https://doi.org/10.3233/rnn-211222

Engel, A. K., & Fries, P. (2010). Beta-band oscillations — signalling the status quo? *Current Opinion in Neurobiology*, 20(2), 156–165. https://doi.org/10.1016/j.conb.2010.02.015

Esteves, I., Nan, W., Alves, C., Calapez, A., Melício, F., & Rosa, A. (2021). An Exploratory Study of Training Intensity in EEG Neurofeedback. *Neural plasticity*, *2021*, 8881059. https://doi.org/10.1155/2021/8881059

Fede, S. J., Dean, S. F., Manuweera, T., & Momenan, R. (2020). A guide to literature informed decisions in the design of real time fMRI neurofeedback studies: a systematic review. *Frontiers in human neuroscience*, *14*, 60.

Fridman, E. A., Hanakawa, T., Chung, M., Hummel, F., Leiguarda, R. C., & Cohen, L. G. (2004). Reorganization of the human ipsilesional premotor cortex after stroke. *Brain*, 127(4), 747–758. https://doi.org/10.1093/brain/awh082

Friston, K. J., Holmes, A. P., Poline, J.-B., Grasby, P. J., Williams, S. C. R., Frackowiak, R. S. J., & Turner, R. (1995). Analysis of fMRI time-series revisited. *NeuroImage*, 2(1), 45–53. https://doi.org/10.1006/nimg.1995.1007

Gaetz W., Edgar J. C., Wang D. J., Roberts T. P. L. (2011). Relating MEG measured motor cortical oscillations to resting gamma-aminobutyric acid (GABA) concentration. *Neuroimage* 55, 616–621. 10.1016/j.neuroimage.2010.12.077

Garcia Pimenta, M., Brown, T., Arns, M., & Enriquez-Geppert, S. (2021). Treatment efficacy and clinical effectiveness of EEG neurofeedback as a personalized and multimodal treatment in ADHD: A critical Review. *Neuropsychiatric Disease and Treatment*, 17, 637–648. https://doi.org/10.2147/NDT.S251547

Gelineau, A., Perrochon, A., Daviet, J. C., & Mandigout, S. (2022). Compliance with Upper Limb Home-Based Exergaming Interventions for Stroke Patients: A Narrative Review. *Journal of rehabilitation medicine*, *54*, jrm00325. https://doi.org/10.2340/jrm.v54.2270

Ghadimi M, Sapra A. Magnetic Resonance Imaging Contraindications. [Updated 2023 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551669/, retrieval date: 23 Sept 2023

Giulia, L., Adolfo, V., Julie, C., Quentin, D., Simon, B., Fleury, M., Leveque-Le Bars, E., Bannier, E., Lécuyer, A., Barillot, C., & Bonan, I. (2021). The impact of neurofeedback on effective connectivity networks in chronic stroke patients: an exploratory study. *Journal of Neural Engineering,* 18(5), 56052. https://doi.org/10.1088/1741-2552/ac291e

Gong, A., Gu, F., Nan, W., Qu, Y., Jiang, C., & Fu, Y. (2021). A review of neurofeedback training for improving sport performance from the perspective of user experience. *Frontiers in Neuroscience*, 15, 638369–638369. https://doi.org/10.3389/fnins.2021.638369

Gopura, R. A. R. C., Lalitharatne, T. D., Kiguchi, K., & Zhang, D. (2022). EMG/EEG Signals-based control of assistive and rehabilitation robots. *Frontiers in Neurorobotics*, 16, 840321. https://doi.org/10.3389/fnbot.2022.840321

Gonzalez, C. L., Ganel, T., & Goodale, M. A. (2006). Hemispheric specialization for the visual control of action is independent of handedness. *Journal of neurophysiology*, *95*(6), 3496-3501.

Grefkes, C., & Fink, G. R. (2011). Reorganization of cerebral networks after stroke: new insights from neuroimaging with connectivity approaches. *Brain,* 134(Pt 5), 1264–1276. https://doi.org/10.1093/brain/awr033

Greve, D. N., & Fischl, B. (2009). Accurate and robust brain image alignment using boundary-based registration. *Neuroimage*, 48(1), 63-72. https://doi.org/10.1016/j.neuroimage.2009.06.060

Grosprêtre, S., Ruffino, C., & Lebon, F. (2016). Motor imagery and cortico-spinal excitability: A review. *European Journal of Sport Science*, 16(3), 317-324. https://doi.org/10.1080/17461391.2015.1024756

Guillot, A., Di Rienzo, F., MacIntyre, T., Moran, A., & Collet, C. (2012). Imagining is not doing but involves specific motor commands: a review of experimental data related to motor inhibition. *Frontiers in Human Neuroscience*, 6, 247. https://doi.org/10.3389/fnhum.2012.00247

Fry A., Mullinger K. J., O'Neill G. C., Barratt E. L., Morris P. G., Bauer M., et al.. (2016). Modulation of post-movement beta rebound by contraction force and rate of force development. *Hum. Brain Mapp.* 37, 2493–2511.

Haaland, K. Y., Elsinger, C. L., Mayer, A. R., Durgerian, S., & Rao, S. M. (2004). Motor sequence complexity and performing hand produce differential patterns of hemispheric lateralization. *Journal of cognitive neuroscience*, *16*(4), 621-636.

Halder, S., Leinfelder, T., Schulz, S. M., & Kübler, A. (2019). Neural mechanisms of training an auditory event-related potential task in a brain–computer interface context. *Human Brain Mapping*, 40(8), 2399-2412. https://doi.org/10.1002/hbm.24531

Haller, S., Birbaumer, N., & Veit, R. (2010). Real-time fMRI feedback training may improve chronic tinnitus. *European radiology*, *20*, 696-703.
Hasslinger, J., D'Agostini Souto, M., Folkesson Hellstadius, L., & Bölte, S. (2020). Neurofeedback in ADHD: A qualitative study of strategy use in slow cortical potential training. *PLoS One*, *15*(6), e0233343.

Hatem, S. M., Saussez, G., Della Faille, M., Prist, V., Zhang, X., Dispa, D., & Bleyenheuft, Y. (2016). Rehabilitation of motor function after stroke: a multiple systematic review focused on techniques to stimulate upper extremity recovery. *Frontiers in human neuroscience*, *10*, 442.

Herrmann, C. S., Rach, S., Neuling, T., & Strüber, D. (2013). Transcranial alternating current stimulation: A review of the underlying mechanisms and modulation of cognitive processes. *Frontiers in Human Neuroscience,* 7, 279. https://doi.org/10.3389/fnhum.2013.00279

Hoult, D. I., & Richards, R. E. (1976). The signal-to-noise ratio of the nuclear magnetic resonance experiment. *Journal of Magnetic Resonance*, 24(1), 71-85. https://doi.org/10.1016/0022-2364(76)90233-X

Hróbjartsson, A., & Gøtzsche, P. C. (2010). Placebo interventions for all clinical conditions. *Cochrane Database of Systematic Reviews*, 2010(1), CD003974. https://doi.org/10.1002/14651858.CD003974.pub3

Hsu Y. F., Liao K. K., Lee P. L., Tsai Y. A., Yeh C. L., Lai K. L., et al.. (2011). Intermittent θ burst stimulation over primary motor cortex enhances movement-related β synchronisation. *Clin. Neurophysiol.* 122, 2260–2267.

Huettel, S. A., Song, A. W., & McCarthy, G. (2004). Functional magnetic resonance imaging (1st ed.). *Sinauer Associates*, USA.

Huettel, S. A., Song, A. W., & McCarthy, G. (2009). Functional magnetic resonance imaging (2nd ed.). *Sinauer Associates*, USA.

Ikeda, Y., Nishimura, Y., Shin, N., & Higuchi, S. (2020). A study of EEG mu neurofeedback during action observation. Experimental Brain Research, 1-8.

Langhorne, P., Coupar, F., & Pollock, A. (2009). *Motor recovery after stroke: a systematic review. The Lancet Neurology, 8(8), 741–754.* doi:10.1016/s1474-4422(09)70150-4

Lee, G. J., & Suhr, J. A. (2020). Expectancy effects of placebo neurofeedback in ADHD treatment seekers: A neuropsychological investigation. *Neuropsychology*, *34*(7), 774–782. https://doi.org/10.1037/neu0000689

Li, L. M., Uehara, K., & Hanakawa, T. (2015). The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Frontiers in cellular neuroscience*, *9*, 181.

Liu, X., Zhang, W., Li, W., Zhang, S., Lv, P., & Yin, Y. (2023). Effects of motor imagery based brain-computer interface on upper limb function and attention in stroke patients with hemiplegia: a randomized controlled trial. *BMC neurology*, *23*(1), 1-14.

Irimia, D. C., Ortner, R., Poboroniuc, M. S., Ignat, B. E., & Guger, C. (2018). High classification accuracy of a motor imagery based brain-computer interface for stroke rehabilitation training. *Frontiers in Robotics and AI*, 5, 130. https://doi.org/10.3389/frobt.2018.00130

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, 5(2), 143-156. https://doi.org/10.1016/S1361-8415(01)00036-6

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*, 17(2), 825-841. https://doi.org/10.1006/nimg.2002.1132

Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). FSL. *Neuroimage*, 62(2), 782-790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Jenkinson, M., Pechaud, M., & Smith, S. (2005, June). BET2: MR-based estimation of brain, skull and scalp surfaces. In *Eleventh Annual Meeting of the Organization for Human Brain Mapping* (Vol. 17, No. 3, p. 167).

Jung, M. W., & Shim, S. H. (2012). Effects of neurofeedback training and computer-assisted cognitive rehabilitation on cognition and upper extremity function in post stroke. *Therapeutic Science for Rehabilitation*, 1(1), 57-70. https://doi.org/10.22683/tsnr.2012.1.1.057

Kaiser, V., Bauernfeind, G., Kreilinger, A., Kaufmann, T., Kübler, A., Neuper, C., & Müller-Putz, G. R. (2014). Cortical effects of user training in a motor imagery based brain–computer interface measured by fNIRS and EEG. *NeuroImage*, 85, 432–444. https://doi.org/10.1016/j.neuroimage.2013.04.097

Kim, T., Kim, S., & Lee, B. (2016). Effects of action observational training plus brain–computer interface-based functional electrical stimulation on paretic arm motor recovery in patient with stroke: a randomized controlled trial. *Occupational Therapy International,* 23(1), 39-47. https://doi.org/10.1002/oti.1403

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. *Brain Research Reviews,* 29 (2), pp. 169–195). https://doi.org/10.1016/S0165-0173(98)00056-3

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: The inhibition–timing hypothesis. *Brain Research Reviews*, 53(1), 63–88. https://doi.org/10.1016/j.brainresrev.2006.06.003

Kober, S. E., Schweiger, D., Witte, M., Reichert, J. L., Grieshofer, P., Neuper, C., & Wood, G. (2015). Specific effects of EEG based neurofeedback training

on memory functions in post-stroke victims. *Journal of neuroengineering and rehabilitation*, *12*, 1-13.

Knyazev, G. G., Slobodskoj-Plusnin, J. Y., Bocharov, A. V., & Pylkova, L. V. (2011). The default mode network and EEG alpha oscillations: An independent component analysis. *Brain Research*, 1402, 67–79. https://doi.org/10.1016/j.brainres.2011.05.052

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., Kennedy, D. N., Hoppel, B. E., Cohen, M. S., Turner, R., Cheng, H.-M., Brady, T. J., & Rosen, B. R. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proceedings of the National Academy of Sciences - PNAS, 89(12), 5675–5679. https://doi.org/10.1073/pnas.89.12.5675

Langhorne, P., Coupar, F., & Pollock, A. (2009). Motor recovery after stroke: a systematic review. The Lancet Neurology, 8(8), 741–754. doi:10.1016/s1474-4422(09)70150-4

Langhorne, P., Bernhardt, J., & Kwakkel, G. (2011). Stroke rehabilitation. The Lancet, 377(9778), 1693-1702. https://doi.org/10.1016/S0140-6736(11)60325-5

Lauritzen, M., & Gold, L. (2003). Brain function and neurophysiological correlates of signals used in functional neuroimaging. *The Journal of Neuroscience*, 23(10), 3972–3980. https://doi.org/10.1523/JNEUROSCI.23-10-03972.2003

Lauterbur, P. C. (1973). Image formation by induced local interactions: Examples employing nuclear magnetic resonance. *Nature*, *242*(5394), 190–191. https://doi.org/10.1038/242190a0

Le Franc, S., Herrera Altamira, G., Guillen, M., Butet, S., Fleck, S., Lécuyer, A., Bougrain, L., & Bonan, I. (2022). Toward an adapted neurofeedback for post-stroke motor rehabilitation: State of the art and perspectives. *Frontiers in Human Neuroscience*, 16, 917909–917909. https://doi.org/10.3389/fnhum.2022.917909

Liew, S.-L., Rana, M., Cornelsen, S., Fortunato de Barros Filho, M., Birbaumer, N., Sitaram, R., Cohen, L. G., & Soekadar, S. R. (2016). Improving motor

corticothalamic communication after stroke using real-time fMRI connectivity-based neurofeedback. *Neurorehabilitation and Neural Repair*, 30(7), 671–675. https://doi.org/10.1177/1545968315619699

Li, H., Huang, G., Lin, Q., Zhao, J. L., Lo, W. A., Mao, Y. R., Chen, L., Zhang, Z. G., Huang, D. F., & Li, L. (2018). Combining Movement-Related Cortical Potentials and Event-Related Desynchronization to Study Movement Preparation and Execution. *Frontiers in neurology*, *9*, 822. https://doi.org/10.3389/fneur.2018.00822

Liu, Y., Liang, M., Zhou, Y., He, Y., Hao, Y., Song, M., Yu, C., Liu, H., Liu, Z., & Jiang, T. (2008). Disrupted small-world networks in schizophrenia. *Brain*, 131(4), 945–961. https://doi.org/10.1093/brain/awn018

Logothetis, N. K. (2002). The neural basis of the blood–oxygen–level–dependent functional magnetic resonance imaging signal. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 357(1424), 1003–1037. https://doi.org/10.1098/rstb.2002.1114

Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature*, 453(7197), 869-878. https://doi.org/10.1038/nature06976

Logothetis, N. K., & Wandell, B. A. (2004). Interpreting the BOLD signal. *Annual Review of Physiology*, 66, 735-769. https://doi.org/10.1146/annurev.physiol.66.082602.092845

Luck, S. J. (2014). An introduction to the event-related potential technique (2nd ed.). *MIT press*, USA.

Luft, A. R., Waller, S., Forrester, L., Smith, G. V., Whitall, J., Macko, R. F., Schulz, J. B., & Hanley, D. F. (2004). Lesion location alters brain activation in chronically impaired stroke survivors. *NeuroImage*, *21*(3), 924–935. https://doi.org/10.1016/j.neuroimage.2003.10.026

Mane, R., Chouhan, T., & Guan, C. (2020). BCI for stroke rehabilitation: motor and beyond. *Journal of neural engineering*, *17*(4), 041001.

Marzbani, H., Marateb, H., & Mansourian, M. (2016). Methodological note: Neurofeedback: A comprehensive review on system design, methodology and clinical applications. *Basic and Clinical Neuroscience*, 7(2), 143.

https://doi.org/10.15412/J.BCN.03070208

Mathiowetz, V., Weber, K., Kashman, N., & Volland, G. (1985). Adult norms for the nine hole peg test of finger dexterity. Occupational Therapy Journal of Research, 5, 24 -33.

McAllister C. J., Ronnqvist K. C., Stanford I. M., Woodhall G. L., Furlong P. L., Hall S. D. (2013). Oscillatory beta activity mediates neuroplastic effects of motor cortex stimulation in humans. *J. Neurosci.* 33, 7919–7927. 10.1523/JNEUROSCI.5624-12.2013

McDonnell, M. N., & Stinear, C. M. (2017). TMS measures of motor cortex function after stroke: a meta-analysis. *Brain stimulation*, *10*(4), 721-734.

McGough, J. J. (2022). Neurofeedback for ADHD: time to call it quits? *American Journal of Psychiatry*, 179(12), 888-889. https://doi.org/10.1176/appi.ajp.20220861

McMenamin, B. W., Shackman, A. J., Maxwell, J. S., Bachhuber, D. R., Koppenhaver, A. M., Greischar, L. L., & Davidson, R. J. (2010). Validation of ICA-based myogenic artifact correction for scalp and source-localized EEG. *Neuroimage*, 49(3), 2416-2432. https://doi.org/10.1016/j.neuroimage.2009.10.010

Melnikov M. Y. (2021). The Current Evidence Levels for Biofeedback and Neurofeedback Interventions in Treating Depression: A Narrative Review. *Neural plasticity*, *2021*, 8878857. https://doi.org/10.1155/2021/8878857

Michel, C. M., Murray, M. M., Lantz, G., Gonzalez, S., Spinelli, L., & De Peralta, R. G. (2004). EEG source imaging. *Clinical Neurophysiology*, 115(10), 2195-2222. https://doi.org/10.1016/j.clinph.2004.06.001

Miller, F. G., & Kaptchuk, T. J. (2004). Sham procedures and the ethics of clinical trials. J*ournal of the Royal Society of Medicine*, 97(12), 576-578. https://doi.org/10.1258/jrsm.97.12.576

Mirifar, A., Keil, A., & Ehrlenspiel, F. (2022). Neurofeedback and neural self-regulation: a new perspective based on allostasis. *Reviews in the neurosciences*, *33*(6), 607–629. https://doi.org/10.1515/revneuro-2021-0133

Moisello C., Blanco D., Lin J., Panday P., Kelly S. P., Quartarone A., et al.. (2015). Practice changes beta power at rest and its modulation during movement in healthy subjects but not in patients with Parkinson's disease. *Brain Behav.* 5:e00374. 10.1002/brb3.374

Murman D. L. (2015). The Impact of Age on Cognition. *Seminars in hearing*, *36*(3), 111–121. https://doi.org/10.1055/s-0035-1555115

Murphy, T. H., & Corbett, D. (2009). Plasticity during stroke recovery: from synapse to behaviour. *Nature reviews neuroscience*, *10*(12), 861-872.

Muthukumaraswamy, S. D., & Johnson, B. W. (2004). Primary motor cortex activation during action observation revealed by wavelet analysis of the EEG. Clinical Neurophysiology, 115(8), 1760-1766. https://doi.org/10.1016/j.clinph.2004.03.004

Muthukumaraswamy S. D., Myers J. F. M., Wilson S. J., Nutt D. J., Lingford-Hughes A., Singh K. D., et al.. (2013). The effects of elevated endogenous GABA levels on movement-related network oscillations. *Neuroimage* 66, 36–41. 10.1016/j.neuroimage.2012.10.054

Nelson A. B., Moisello C., Lin J., Panday P., Ricci S., Canessa A., et al.. (2017). Beta oscillatory changes and retention of motor skills during practice in healthy subjects and in patients with Parkinson's disease. *Front. Hum. Neurosci.* 11:104. 10.3389/fnhum.2017.00104

Neuper, C., & Pfurtscheller, G. (2001). Event-related dynamics of cortical rhythms: frequency-specific features and functional correlates. International journal of psychophysiology, 43(1), 41-58. https://doi.org/10.1016/S0167-8760(01)00178-7

Neuper, C., & Pfurtscheller, G. (2001). Evidence for distinct beta resonance frequencies in human EEG related to specific sensorimotor cortical areas. Clinical Neurophysiology, 112(11), 2084-2097. https://doi.org/10.1016/S1388-2457(01)00661-7

Neuper, C., Wörtz, M., & Pfurtscheller, G. (2006). ERD/ERS patterns reflecting sensorimotor activation and deactivation. Progress in brain research, 159, 211-222. https://doi.org/10.1016/S0079-6123(06)59014-4

Niedermeyer, E., & da Silva, F. L. (2017). Electroencephalography: basic principles, clinical applications, and related fields (7th ed.). *Lippincott Williams & Wilkins*, USA.

Noh N. A., Fuggetta G., Manganotti P., Fiaschi A. (2012). Long lasting modulation of cortical oscillations after continuous theta burst transcranial magnetic stimulation. *PLoS One* 7:e35080. 10.1371/journal.pone.0035080

Nunez, P. L., & Srinivasan, R. (2006). Electric fields of the brain: the neurophysics of EEG (2nd ed.). *Oxford University Press*, USA.

Oberman, L. M., Hubbard, E. M., McCleery, J. P., Altschuler, E. L., Ramachandran, V. S., & Pineda, J. A. (2005). EEG evidence for mirror neuron dysfunction in autism spectrum disorders. *Cognitive Brain Research*, 24(2), 190-198. https://doi.org/10.1016/j.cogbrainres.2005.01.014

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *National Academy of Sciences*, 87(24), 9868-9872. https://doi.org/10.1073/pnas.87.24.9868

Ogawa, S., Lee, T. M., Nayak, A. S., & Glynn, P. (1990). Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magnetic Resonance in Medicine*, 14(1), 68-78. https://doi.org/10.1002/mrm.1910140108

Oyake, K., Suzuki, M., Otaka, Y., & Tanaka, S. (2020). Motivational strategies for stroke rehabilitation: A descriptive cross-sectional study. *Frontiers in Neurology*, 11, 553. https://doi.org/10.3389/fneur.2020.00553

Parkes L. M., Bastiaansen M. C. M., Norris D. G. (2006). Combining EEG and fMRI to investigate the post-movement beta rebound. *Neuroimage* 29, 685–696. 10.1016/j.neuroimage.2005.08.018

Pfurtscheller, G., & Da Silva, F. H. (1999). Event-related EEG/MEG synchronization and desynchronization: Basic principles. *Clinical Neurophysiology*, 110(11), 1842-1857. https://doi.org/10.1016/S1388-2457(99)00141-8

Pfurtscheller, G., & Neuper, C. (2006). Future prospects of ERD/ERS in the context of brain–computer interface (BCI) developments. *Progress in Brain Research,* 159, 433-437. https://doi.org/10.1016/S0079-6123(06)59028-4

Pfurtscheller, G., Neuper, C., & Mohl, W. (1994). Event-related desynchronization (ERD) during visual processing. *International Journal of Psychophysiology*, 16(2-3), 147-153. https://doi.org/10.1016/0167-8760(89)90041-X

Pfurtscheller, G., Neuper, C., Andrew, C., & Edlinger, G. (1997). Foot and hand area mu rhythms. *International Journal of Psychophysiology*, 26(1-3), 121-135. https://doi.org/10.1016/S0167-8760(97)00760-5

Pineda, J. A. (2005). The functional significance of mu rhythms: translating "seeing" and "hearing" into "doing". *Brain Research Reviews*, 50(1), 57-68. https://doi.org/10.1016/j.brainresrev.2005.04.005

Pistohl T., Schulze-Bonhage A., Aertsen A., Mehring C., Ball T. (2012). Decoding natural grasp types from human ECoG. *Neuroimage* 59, 248–260. 10.1016/j.neuroimage.2011.06.084

Pollock, A., Farmer, S. E., Brady, M. C., Langhorne, P., Mead, G. E., Mehrholz, J., van Wijck, F., & Pollock, A. (2014). Interventions for improving upper limb function after stroke. *Cochrane Database of Systematic Reviews*, 2014(11), CD010820–CD010820. https://doi.org/10.1002/14651858.CD010820.pub2

Ray, A. M., Figueiredo, T. D. C., López-Larraz, E., Birbaumer, N., & Ramos-Murguialday, A. (2020). Brain oscillatory activity as a biomarker of motor recovery in chronic stroke. Human brain mapping, 41(5), 1296–1308. https://doi.org/10.1002/hbm.24876

Rayegani, S. M., Raeissadat, S. A., Sedighipour, L., Mohammad Rezazadeh, I., Bahrami, M. H., Eliaspour, D., & Khosrawi, S. (2014). Effect of neurofeedback and electromyographic-biofeedback therapy on improving hand function in stroke patients. *Topics in Stroke Rehabilitation*, 21(2), 137-151. https://doi.org/10.1310/tsr2102-137

Renton T, Tibbles A, Topolovec-Vranic J (2017) Neurofeedback as a form of cognitive rehabilitation therapy following stroke: A systematic review. PLoS ONE 12(5): e0177290. https://doi.org/10.1371/journal.pone.0177290

Robineau, F., Saj, A., Neveu, R., Van De Ville, D., Scharnowski, F., & Vuilleumier, P. (2019). Using real-time fMRI neurofeedback to restore right occipital cortex activity in patients with left visuo-spatial neglect: proof-of-principle and preliminary results. *Neuropsychological Rehabilitation*, 29(3), 339-360. https://doi.org/10.1080/09602011.2017.1301262

Ros, T., Théberge, J., Frewen, P. A., Kluetsch, R., Densmore, M., Calhoun, V. D., & Lanius, R. A. (2013). Mind over chatter: plastic up-regulation of the fMRI salience network directly after EEG neurofeedback. Neuroimage, 65, 324-335. https://doi.org/10.1016/j.neuroimage.2012.09.046

Saghaei, M., & Saghaei, S. (2011). Implementation of an open-source customizable minimization program for allocation of patients to parallel groups in clinical trials. J Biomed Sci Eng, 4(11), 734-739.

Sainburg, R. L. (2002). Evidence for a dynamic-dominance hypothesis of handedness. Experimental brain research, 142, 241-258.

Sampaio-Baptista, C., Neyedli, H. F., Sanders, Z.-B., Diosi, K., Havard, D., Huang, Y. Y., Andersson, J. L. R., Lühr, M., Goebel, R., & Johansen-Berg, H. (2021). fMRI neurofeedback in the motor system elicits bidirectional changes in activity and in white matter structure in the adult human brain. *Cell Reports*, 37(4), 109890. https://doi.org/10.1016/j.celrep.2021.109890

Sanders, Z.-B., Fleming, M. K., Smejka, T., Marzolla, M. C., Zich, C., Rieger, S. W., Lührs, M., Goebel, R., Sampaio-Baptista, C., & Johansen-Berg, H. (2022). Self-modulation of motor cortex activity after stroke: a randomized controlled trial. *Brain*, 145(10), 3391–3404. https://doi.org/10.1093/brain/awac239

Schulz, K. F., & Grimes, D. A. (2002). Blinding in randomised trials: hiding who got what. *The Lancet*, 359(9307), 696-700. https://doi.org/10.1016/S0140-6736(02)07816-9

Serrien, D. J. (2009). Functional connectivity patterns during motor behaviour: the impact of past on present activity. *Human Brain Mapping*, *30*(2), 523-531.

Shellock, F. G. (2002). Biomedical implants and devices: assessment of magnetic field interactions with a 3.0-Tesla MR system. *Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine*, 16(6), 721-732. https://doi.org/10.1002/jmri.10207

Sitaram, R., Ros, T., Stoeckel, L., Haller, S., Scharnowski, F., Lewis-Peacock, J., Weiskopf, N., Blefari, M. L., Rana, M., Oblak, E., Birbaumer, N., & Sulzer, J. (2017). Closed-loop brain training: the science of neurofeedback. *Nature Reviews. Neuroscience*, 18(2), 86–100. https://doi.org/10.1038/nrn.2016.164

Sitaram, R., Veit, R., Stevens, B., Caria, A., Gerloff, C., Birbaumer, N., & Hummel, F. (2012). Acquired control of ventral premotor cortex activity by feedback training: An exploratory real-time fMRI and TMS study. *Neurorehabilitation and Neural Repair*, 26(3), 256–265. https://doi.org/10.1177/1545968311418345

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, 23(SUPPL. 1), S208–S219. https://doi.org/10.1016/j.neuroimage.2004.07.051

Soler, A., Muñoz-Gutiérrez, P. A., Bueno-López, M., Giraldo, E., & Molinas, M. (2020). Low-density EEG for neural activity reconstruction using multivariate empirical mode decomposition. *Frontiers in neuroscience*, *14*, 175.

Solis-Escalante T., Müller-Putz G. R., Pfurtscheller G., Neuper C. (2012). Cue-induced beta rebound during withholding of overt and covert foot movement. *Clin. Neurophysiol.* 123, 1182–1190. 10.1016/j.clinph.2012.01.013

Sreedharan, S., Sitaram, R., Paul, J. S., & Kesavadas, C. (2013). Brain-computer interfaces for neurorehabilitation. *Critical Reviews™ in Biomedical Engineering*, 41(3), 269–279. https://doi.org/10.1615/CritRevBiomedEng.2014010697

Stancák A., Pfurtscheller G. (1995). Desynchronization and recovery of β rhythms during brisk and slow self-paced finger movements in man. *Neurosci. Lett.* 196, 21–24. 10.1016/0304-3940(95)11827-j

Stancák A., Pfurtscheller G. (1996). Event-related desynchronisation of central beta-rhythms during brisk and slow self-paced finger movements of dominant and nondominant hand. *Brain Res.* 4, 171–183. 10.1016/s0926-6410(96)00031-6

Stančák A., Riml A., Pfurtscheller G. (1997). The effects of external load on movement-related changes of the senorimotor EEG rhythms. *Electroencephalogr. Clin. Neurophysiol.* 102, 495–504. 10.1016/s0013-4694(96)96623-0

Steingrimsson, S., Bilonic, G., Ekelund, A.-C., Larson, T., Stadig, I., Svensson, M., Vukovic, I. S., Wartenberg, C., Wrede, O., Bernhardsson, S., (2020). Electroencephalography-based neurofeedback as treatment for post-traumatic stress disorder: A systematic review and meta-analysis. *European Psychiatry*, 63(1), e7–e7. https://doi.org/10.1192/j.eurpsy.2019.7

Stinear, C. M., Petoe, M. A., & Byblow, W. D. (2015). Primary motor cortex excitability during recovery after stroke: implications for neuromodulation. *Brain Stimulation*, 8(6), 1183-1190. https://doi.org/10.1016/j.brs.2015.06.015

Takata, Norio & Hirase, Hajime. (2008). Cortical Layer 1 and Layer 2/3 Astrocytes Exhibit Distinct Calcium Dynamics In Vivo. PloS one. 3. e2525. 10.1371/journal.pone.0002525.

Tatti, E., Ricci, S., Mehraram, R., Lin, N., George, S., Nelson, A. B., & Ghilardi, M. F. (2019). Beta Modulation Depth Is Not Linked to Movement Features. Frontiers in behavioral neuroscience, 13, 49. https://doi.org/10.3389/fnbeh.2019.00049

Thibault, R. T., Lifshitz, M., Birbaumer, N., & Raz, A. (2015). Neurofeedback, self-regulation, and brain imaging: clinical science and fad in the service of mental disorders. *Psychotherapy and psychosomatics*, *84*(4), 193-207.

Tsao, C. W., Aday, A. W., Almarzooq, Z. I., Alonso, A., Beaton, A. Z., Bittencourt, M. S., ... & American Heart Association Council on Epidemiology

and Prevention Statistics Committee and Stroke Statistics Subcommittee. (2022). Heart disease and stroke statistics—2022 update: a report from the American Heart Association. *Circulation*, *145*(8), e153-e639.

Tscherpel, C., Hensel, L., Lemberg, K., Vollmer, M., Volz, L. J., Fink, G. R., & Grefkes, C. (2020). The differential roles of contralesional frontoparietal areas in cortical reorganization after stroke. *Brain stimulation*, *13*(3), 614-624.

Veerbeek, J. M., Koolstra, M., Ket, J. C., van Wegen, E. E., & Kwakkel, G. (2011). Effects of augmented exercise therapy on outcome of gait and gait-related activities in the first 6 months after stroke: a meta-analysis. *Stroke*, 42(11), 3311-3315. https://doi.org/10.1161/STROKEAHA.111.623819

Veldsman, M., Cumming, T., & Brodtmann, A. (2015). Beyond BOLD: optimizing functional imaging in stroke populations. *Human brain mapping*, *36*(4), 1620-1636

Vidaurre, C., Irastorza-Landa, N., Sarasola-Sanz, A., Insausti-Delgado, A., Ray, A. M., Bibián, C., Helmhold, F., Mahmoud, W. J., Ortego-Isasa, I., López-Larraz, E., Lozano Peiteado, H., & Ramos-Murguialday, A. (2023). Challenges of neural interfaces for stroke motor rehabilitation. *Frontiers in human neuroscience*, *17*, 1070404. https://doi.org/10.3389/fnhum.2023.1070404

Viviani, G., & Vallesi, A. (2021). EEG-neurofeedback and executive function enhancement in healthy adults: A systematic review. *Psychophysiology*, *58*(9), e13874. https://doi.org/10.1111/psyp.13874

Wada, K., Ono, Y., Kurata, M., Ito, M. I., Minakuchi, M. T., Kono, M., & Tominaga, T. (2019). Development of a brain-machine interface for stroke rehabilitation using event-related desynchronization and proprioceptive feedback. *Advanced Biomedical Engineering*, 8, 53-59. https://doi.org/10.14326/abe.8.53

Wang, T., Mantini, D., & Gillebert, C. R. (2018). The potential of real-time fMRI neurofeedback for stroke rehabilitation: A systematic review. *Cortex*, 107, 148-165. https://doi.org/10.1016/j.cortex.2017.09.006

Ward, N. S. (2017). Restoring brain function after stroke—bridging the gap between animals and humans. *Nature Reviews Neurology*, 13(4), 244-255. https://doi.org/10.1038/nrneurol.2017.34

Ward, N. S., & Cohen, L. G. (2004). Mechanisms underlying recovery of motor function after stroke. *Archives of Neurology*, 61(12), 1844-1848. https://doi.org/10.1001/archneur.61.12.1844

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *Neuroimage*, 92, 381-397. https://doi.org/10.1016/j.neuroimage.2014.01.060

Włodarczyk, L., Cichon, N., Saluk-Bijak, J., Bijak, M., Majos, A., & Miller, E. (2022). Neuroimaging Techniques as Potential Tools for Assessment of Angiogenesis and Neuroplasticity Processes after Stroke and Their Clinical Implications for Rehabilitation and Stroke Recovery Prognosis. *Journal of clinical medicine*, *11*(9), 2473. https://doi.org/10.3390/jcm11092473

Woolrich, M. W., Behrens, T. E., Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2004). Multilevel linear modelling for fMRI group analysis using Bayesian inference. *Neuroimage*, 21(4), 1732-1747. https://doi.org/10.1016/j.neuroimage.2003.12.023

Worsley, K. J. (2001). Statistical analysis of activation images. Functional MRI: An introduction to methods, pages: 251-270.*Oxford University Press*, UK. https://doi.org/10.1093/acprof:oso/9780192630711.003.0014

Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Friston, K. J., & Evans, A. C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Human Bbrain Mapping,* 4(1), 58-73. https://doi.org/10.1002/(SICI)1097-0193(1996)4:1%3C58::AID-HBM4%3E3.0.CO;2-O

Yoo, I. G. (2021). Electroencephalogram-based neurofeedback training in persons with stroke: a scoping review in occupational therapy. NeuroRehabilitation, 48(1), 9-18. https://doi.org/10.3233/NRE-201579

Yozbatiran, N., Der-Yerghiaian, L., & Cramer, S.C. (2008). A standardized approach to performing the action research arm test. Neurorehabilitation & Neural Repair, 22(1), 78-90.

Zich, C., Debener, S., De Vos, M., Frerichs, S., Maurer, S., & Kranczioch, C. (2015a). Lateralization patterns of covert but not overt movements change with age: An EEG neurofeedback study. NeuroImage, 116, 80–91.

Zich, C., Debener, S., Kranczioch, C., Bleichner, M. G., Gutberlet, I., & De Vos, M. (2015b). Real-time EEG feedback during simultaneous EEG-fMRI identifies the cortical signature of motor imagery. NeuroImage, 114, 438–447. https://doi.org/10.1016/j.neuroimage.2015.04.020

Zich, C., Debener, S., Kranczioch, C., Bleichner, M. G., Gutberlet, I., & De Vos, M. (2015c). Real-time EEG feedback during simultaneous EEG-fMRI identifies the cortical signature of motor imagery. NeuroImage, 114, 438–447. https://doi.org/10.1016/j.neuroimage.2015.04.020