COMBINED ACTION OBSERVATION AND MOTOR IMAGERY NEUROFEEDBACK UP-REGULATES CONTRALATERAL SENSORIMOTOR ACTIVITY

by

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ABSTRACT

Motor imagery (MI) and action observation have proven to be efficacious adjuncts to traditional physiotherapy, to enhance motor recovery from stroke. Recently, researchers have used a combined approach called imagined imitation (II), where an individual watches a motor task being performed, while simultaneously imagining they are performing the movement. While neurofeedback (NFB) has been used extensively with MI to improve patients' ability to modulate sensorimotor activity and enhance motor recovery, the feasibility of using NFB with II is unknown. *This project tested whether healthy controls could modulate sensorimotor lateralization during II-NFB of a unilateral handshake using electroencephalography*, *and whether this ability transferred to subsequent MI.* Thirty-two subjects, receiving real or sham NFB attended four sessions where they engaged in II-NFB training and subsequent MI. Results showed the NFB group demonstrated more sensorimotor activity during sessions three and four, and that this NFB effect transferred to subsequent MI.

LIST OF ABBREVIATIONS USED

ANS	Autonomic Nervous System
AO	Action Observation
BCI	Brain Computer Interface
CNS	Central Nervous System
EEG	Electroencephalography
ERD	Event-related Desynchronization
ERS	Event-related Synchronization
EOG	Electrooculogram
fNIRS	Functional Near-Infrared Spectroscopy
fMRI	Functional Magnetic Resonance Imaging
II	Imagined Imitation
KVIQ	Kinesthetic and Visual Imagery Questionnaire
MEG	Magnetoencephalography
mIHI	Maladaptive Interhemispheric Inhibition
M1	Primary Motor Cortex
MEP	Motor Evoked Potential
ME	Motor Execution
MI	Motor Imagery
NFB	Neurofeedback
PCA	Principal Component Analysis

PNS	Peripheral Nervous System
PFC	Prefrontal Cortex
S1	Primary Somatosensory Cortex
SPL	Superior Parietal Lobe
SMA	Supplemental Motor Area
TMS	Transcranial Magnetic Stimulation
UX	User Experience
V1	Primary Visual Cortex

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CHAPTER 1 INTRODUCTION

Therapies involving the mental simulation of movements have been drawing increased attention from researchers in the past ten years. Such therapies have been shown to hold utility as adjuncts to use-dependent therapies in stroke rehabilitation, or as gateway therapies for those whose limbs are too impaired to engage in traditional (i.e., movement-based) rehabilitation. The two types of mental simulation therapy with the strongest claims to efficacy are motor imagery (MI)[1-3] and action observation (AO)[4,5]. Recently, researchers have used a combined MI/AO approach: here an individual *watches* a motor task being performed repetitively, *while simultaneously imagining* they are performing the movement themselves. This approach of 'Imagined Imitation' (II) has been shown to facilitate corticospinal excitability to a greater degree than either AO or MI alone [6-9], and to increase brain activity in several regions critical for motor learning and performance over and above that seen in AO or MI [10-13]. Another innovation, recently garnering much attention for its applications in neuro-prosthetics and as a supplement to the use of MI for stroke rehabilitation, is neurofeedback (NFB). And while NFB has been successfully used to allow users to more efficiently engage the sensorimotor network in MI [14-16], this approach has not yet been applied to II.

To investigate the feasibility of using NFB during II—and to test the transfer of NFB learning to subsequent MI—we designed, created, and tested an II-NFB system. This system allowed users to watch first-person videos of a complex handshake, and while imagining that they themselves were executing the handshake, receive real-time feedback regarding the

quality of their II. 'Quality' in this instance referred to the as the ability to up-regulate contralateral sensorimotor activity, and down-regulate ipsilateral sensorimotor activity—a correlate of the re-balancing of interhemispheric inhibition which has been associated with more complete motor recovery from stroke[17-19]. Feedback was provided in the form of varying video color—the videos started black-and-white, and turned to colour on the basis of the electroencephalography (EEG) data being collected over the subjects' sensorimotor cortices. The II-NFB system contained titrated difficulty, incentivizing contralateral sensorimotor up-regulation at easy difficulty levels, and ipsilateral down-regulation at higher difficulty levels.

To measure the efficacy of this system for allowing healthy controls to modulate sensorimotor activity during II, we compared the pattern of sensorimotor activity of subjects receiving genuine NFB, with subjects receiving sham NFB through the same system. Subjects in both groups attended 4 experimental sessions within a 7-day period. We hypothesized (1) that subjects receiving genuine NFB would produce more sensorimotor activity than sham subjects, and that this NFB learning effect would emerge sometime after the first session. To test the transfer of NFB learning, we had subjects perform MI of the video from the II-NFB training at the end of each experimental day. We hypothesized (2) that any NFB learning we observed during II-NFB sessions 2-4 would transfer to MI alone.

Our results showed that participants in the NFB group demonstrated increased contralateral sensorimotor activation in sessions 3-4 compared to sham, both during II-NFB as well as subsequent MI. However, this pattern of NFB learning was not seen for the down-regulation of ipsilateral sensorimotor activity.

This partial success demonstrates that II-NFB is a feasible design possibility for those attempting to integrate feedback into mental simulation therapy.

CHAPTER 2 BACKGROUND AND RATIONALE

2.1 Motivation

2.1.1 The Impact of Stroke

Stroke is the third leading cause of death in Canada[20,21]. In Canada alone over 50,000 strokes occur each year, and over 300,000 people live with disability resulting from stroke. The estimated cost of care for stroke survivors in 2009 was $3.6 billion in Canada alone. Given the forecasted aging of the population in Canada and other developed countries[22], the societal challenges posed by stroke will only intensify[23].

Moreover, given that stroke is most likely to occur in the elderly, the process of travelling to a clinic for treatment, once released from the hospital, will become increasingly onerous as the population ages. Findings show that rural stroke survivors have a depressed trajectory of functional recovery compared with urban-dwellers[24], suggesting that the distance a patient has to travel to receive therapy can have measurable impacts on their recovery. The fact that the majority of our clinical efforts take place in a highly-centralized fashion (i.e., therapists performing rehabilitation in a clinical setting) suggests that innovations to help deliver stroke rehabilitation therapy in a more decentralized manner would be of great utility.

All this suggests that innovations that make stroke care more economical, and decentralized are desperately needed.

2.2 The Role of Mental Stimulation in Neurorehabilitation from Stroke

Recovery from stroke is due largely to the brain's ability to 're-wire' itself. Rehabilitative therapies help survivors of stroke regain lost motor abilities by having them practice actions like reaching and grasping. These interventions are called 'use-dependent' therapies, and are based on principles of motor skill acquisition or learning[25-30]. Use-dependent therapies involve the repetitive practice of a skilled motor task, with an emphasis on completion and accuracy[31]. The theory behind use-dependent therapies is that repetitive practice induces changes in the brain regions responsible for these functions, and these changes allow the individual to regain functional capacity[30,32]. The exact nature and/or sequence of these neural changes is not precisely defined, and likely differs between individuals and individual pathologies—however functional motor improvement during stroke rehabilitation is surely caused by a combination of synaptogenesis[27], neurogenesis[26], changes in myelination[33], epigenetic changes[34] and/or an increase in the production of growth factors[35,36]. It is important to highlight that the utility of use-dependent therapies for motor rehabilitation from stroke is contingent on its abilities to catalyze these neural processes, which in turn manifest at the level of behavior.

While use-dependent therapies are quite effective in helping survivors of stroke regain motor function[37-39], there are three impediments limiting their effectiveness. ***Firstly***, individuals who have recently experienced a stroke are often easily fatigued[40-42], limiting the amount of therapy they can receive, and thus hindering their recovery, as the amount of therapy an individual engages in has been shown to correlate with increased recovery[43-45].

Second, the severity of impairment resulting from the stroke precludes many survivors from engaging in traditional, use-dependent therapies at all[46,47]. And ***thirdly***, this method of treatment is very time-consuming and expensive for the health care system, meaning many patients cannot afford as much therapy as they need[48,49].

One way to both extend the amount of use-dependent therapy survivors of stroke receive, as well as allow more severely impaired individuals to start on the path to functional recovery, is to use therapies based on motor simulation—where the brain areas involved in movements are targeted, without any physical movement. Two methods of activating motor areas of the brain, in the absence of movement, have been previously shown to improve movement outcomes for survivors of stroke. The first is by imagining performing a movement, but not actually doing it. This is called ***motor imagery (MI)***. The second is by repetitively watching videos of people moving the affected limbs. This is called ***action observation (AO)***.

2.3 Motor Imagery

A wealth of neuroimaging studies have shown that the neural activity present during MI is similar to that of motor execution (ME)[50-55] (for a review see[56]). Furthermore, it has also been shown that MI activates descending corticospinal motor pathways, measured as increased muscle tone in action-relevant effector muscles,[57-60] and induces autonomic nervous system (ANS) responses comparable to that of ME[61-65] (for a review see[66]).

However, while neuroimaging studies of MI demonstrate neural activation in many areas of the ME network (primary motor cortex[67-69] [M1], supplementary motor[70] [SMA] and

pre-motor areas[70], somatosensory cortex [S1], basal ganglia[71], the parietal lobe[70] as well as the cerebellum), the exact area of activation within these regions often differs between MI and ME. Specifically, the area of activation in MI preferentially involves sub-regions responsible for motor planning[71,72]. For example, the anterior portion of M1 and the SMA, the head of the caudate nucleus in the basal ganglia, as well as a more posterior/ventral foci in the cerebellum are found to have greater activation in MI relative to ME. In addition, both the parietal lobe (involved in initiating shifts in attention required for conscious actions[73], visuo-motor integration,[74,75] and neural representation of body parts[76]) and premotor cortex (critical for assembling and sequencing motor plans[77,78]) show preferential activation for MI compared to ME[70].

While the evidence noted above suggests MI is not neurally equivalent to ME, and does not contain sensory and proprioceptive feedback, it has been shown to improve motor learning [79-82]. One transfer study used TMS to demonstrate the interaction between MI and ME, which is hypothesized to the reason repeated MI can manifest in changes at the level of behavior. This group[68] demonstrated that physically practicing a finger abduction task, prior to MI of that same movement, results in greater activity in the brain regions responsible for hand/finger movement during MI. The researchers quantified motor activity by recording motor evoked potentials (MEPs) resulting from transcranial magnetic stimulation (TMS) of the first dorsal interosseous muscle area of the primary motor cortex (M1). Specifically, researchers collected MEPs for subjects both at rest and during MI, prior to and after physical practice. They found that the increase in MEP amplitude from rest to MI was greater after,

compared to before, physical practice. This priming effect, where ME increases the motor activity seen in subsequent MI, suggests that these two systems (ME and MI) do not operate in isolation of each other (i.e., that performing ME affects the properties of subsequent MI), and has been shown to be bi-directional (MI prior to ME has been shown to affect the neural activity[83,84] and behavioral characteristics[85-87] of subsequent ME as well). These findings provide support for the theory that MI consists of a simulation of the motor system[88,89], and thus represents a valid way to augment movement abilities[90,91].

Motor imagery has also been shown to be effective as an adjunct therapy for motor recovery following stroke [1-3]. For example, one recent randomized control trial[92] in 44 stroke patients showed that 6 weeks of daily training featuring MI of walking resulted in greater functional gains in walking ability (measured via a 10-meter walking test and the Fugl-Meyer assessment) than a control group who received the equivalent amount of muscle relaxation training in addition to their traditional physiotherapy.

2.4 Action Observation

Action observation refers to the observation of movement. A useful organizing principle for describing the neural activity taking place during AO is ***abstraction****;* where ***abstract*** is used in a way that combines two of its dictionary meanings: (1) to extract or remove and (2) to consider something theoretically, (and thus in a sense) constructing semantic meaning that is separate from 'the thing' itself. For our purposes, it is useful to consider the process of abstraction on a continuum—somewhere between simply classifying, pulling out features

from ‘raw data’ (i.e., the first definition), and the creation of ***new structures*** out of the information that has been pulled out from the raw data (i.e., the second definition).

For example, while brain regions upstream in the AO network (secondary occipital and superior temporal) ***abstract*** according to the first definition, as information is passed through the AO network, other brain regions take these pieces of information (i.e., salient features of the visual scene) and connect them in accordance with an individual’s semantic knowledge. These new structures are what are often casually referred to as ***neural representations.***

Action observation is supported by a wide range of brain regions: secondary occipital and superior temporal regions are thought to highlight visually-salient features of the actions being observed[93-95]; parietal and secondary motor cortices (i.e., pre- and supplementary motor) represent the motor movements most likely being observed[70,96,97]; by forward-modeling a motor plan, they may allow the brain to make inferences about the movements that will be coming next. These regions are thought to provide input to M1, leading researchers to speculate that these motor representations and plans or predictions are being used to create a motor simulation[98-101]. Lastly, various regions of the prefrontal cortex (PFC) have also been shown to be active during AO[102,103], perhaps reflecting the need to use AO to deduce action goals or motivations in order to infer something of a motor-centric theory of mind.

Furthermore, like MI, repetitive AO has been shown to promote plasticity in motor and secondary-motor regions [104,105] and bolster motor skill acquisition [8,106,107]. Work in Paul

Gribble's lab has shown that skill acquisition through observation has been shown to require activity of both M1 and S1 respectively. Their design for demonstrating this required subjects to hold a robotic arm by a handle, and move the arm to target areas in the presence of a force field that could push the subject's arm in any direction as they moved to the target. Subjects first watched a video of a person performing the task with a force field pushing the arm *to the right*. Subjects then engaged in the task, with the force field now (unbeknownst to them) pushing in the opposite direction. The idea (supported by similar studies[104]) is that, if watching the video imparted any motor learning to the individual, change in the force field's direction would decrease the subjects' accuracy. Specifically, the trajectory of their reach would be more curved, and this curvature was taken as a measure of motor learning through action observation. In separate studies, the group used inhibitory TMS[108] and median nerve stimulation[109] to show that interfering with M1 and S1 respectively extinguishes motor learning that occurs via observation.

And lastly, AO has also been shown to improve motor recovery from stroke [4,5,110-112], and to enhance occupational performance following stroke[113] (for a review see[114]). For example, a randomized clinical trial[115] of 102 stroke patients found that adding observation of upper-body action videos to traditional physiotherapy for 4 weeks garnered patient's greater functional outcomes (tested with a multitude of measures) versus patients who were presented with static images in conjunction with physiotherapy. The AO group showed functional gains over the control group both immediately following the 4-week training, as

well as at a 4-5 month follow-up.

2.5 Imagined Imitation

2.5.1 *A tale of Two Simulations: Understanding Imagery and the Observation of Actions Together*

It is important to pursue a coherent conceptual framework of II—of how the processes of MI and AO might relate to each other as they are being performed simultaneously. This will help researchers better contextualize their experimental data, and hopefully allow them to better leverage II in the development of clinical or commercial learning products. Only one work[116] has attempted to delineate the neural underpinnings of II thus far, and these authors did not bring the network of brain regions responsible for MI and AO explicitly into their discussion. What they did is theorize that II is a mental process that falls somewhere between purely intentional motor simulation, and completely automatic sensory resonance. The authors specifically drew attention to the fact that MI and AO differ in regards to temporal structure: with the individual 'setting the pace' of their MI, whereas the timing of AO is dictated by the speed of the observed action. The authors refer to their conceptualization of II as the "dual simulation view".

The concept of a 'simulation' is a useful one to utilize in attempting to square the circle of just what MI and AO ***are***—i.e., how to conceptualize their effects on the central (CNS) and peripheral nervous system (PNS) in an interrelated manner. The most basic procedural definition of a ***simulation*** is the representation of an operation of a system by that

of another system. Given this, it is easy to understand MI and AO both as *simulations* of ME. Whereas MI is the conscious initiation of a ME simulation of the individuals choosing, AO is an automatically elicited ME simulation of the action being observed.

Motor execution can be conceptualized as a process initiated by a conscious or unconscious thought regarding a specific end state which involves some movement of the body, which then is forward-modeled by the brain[117,118], and carried out by the interconnected subsystems of the CNS and PNS.

Motor imagery, then, would be a consciously initiated emulation of the ME process (here the 'specific end state' is simply a desire to carry out the simulation), carried out by the same interconnected systems. Thus ***MI differs from ME in two fundamental ways. Firstly,*** the catalyst initiating MI must be a conscious thought, and the end state being forward-modeled is simply to ***replicate*** the experience of movement ***without*** actually eliciting movement. And ***secondly,*** stemming from this first difference, while MI still requires information processing by the same set of interconnecting neural systems, the nature of that processing differs (see the above discussion of MI's neural activity compared with ME).

Whereas the sequence in which MI and ME are carried out are quite similar (initiation by internal decision making processes, forward-modeling, then simulation [MI] or execution [ME]), AO differs from this temporal sequence, starting with how it is catalyzed (by external stimuli vs. internal decision making), and then requiring both inverse ***and*** forward modeling in order to simulate ME. While extra-striate and superior temporal activity (highlighting salient features of the action being observed) represent the inverse modeling of

the action being observed, premotor and parietal activity represents the forward-modeling of this reverse-engineered motor plan—i.e., the creation of a 'mirrored' version of the action being observed. And finally, the sensorimotor and prefrontal activity seen in AO is responsible for the simulation of this motor plan.

2.5.2 *Imagined Imitation as Dual Motor Simulation*

What is ***crucial*** to our discussion of performing MI and AO simultaneously, is the theory that the neural regions associated with both types of internal modeling that take place during AO (discussed in the previous section) exert a causal influence over each other—posterior regions involved in reverse-engineering the action being observed ***both influence and are influenced by*** more anterior forward-modeling and simulation regions[119-121]. This is consistent with Jeannerod's theory of motor cognition[89], as well as a host of recent data. For example, the finding that more corticospinal excitability is produced in II than AO or MI alone[7] suggests a synergistic effect of combining MI and AO. Moreover, recent neuroimaging data (using magnetoencephalography [MEG])[120] has demonstrated that information transfer (measured as event-related desynchronization (ERD) within the alpha and beta bands) during AO moves ***bi-directionally*** between posterior and anterior regions of the AO network. This indicates that inverse- and forward-models in AO, as well as in II, can be thought of as symbiotic processes, where an ebb and flow of information transfer allows an improvement in the quality (i.e., increased neural differentiation) of one model to improve the quality of the other.

While clearly an oversimplification (the cerebellum and other subcortical structures involved in AO are not mentioned here), a brain-based version of the dual simulation model[116] provides a clear explanation for the findings that regions of the motor network are more active in II than MI or AO alone. On the basis of this theoretical model, it is possible that II could provide more utility than either MI or AO alone for stroke rehabilitation.

2.6 Impediments to Motor Simulation's Utility for Enhancing Stroke Recovery

As mentioned above, both MI and AO have proven to be effective ways to improve rehabilitation following a stroke, both as an adjunct to traditional therapy (allowing recovering patients to increase the dosage of therapy) and as a gateway therapy for those whose motor impairments are so severe they are unable to engage in traditional therapies. Based on recent studies (discussed in the previous section), it is highly probable that II holds similar or greater promise to improve rehabilitation for motor impairment in stroke as well.

Despite the fact that motor simulation therapies have proved to be effective adjuncts to facilitate motor recovery following stroke, they have not become a facet of usual clinical care alongside use-dependent therapies[122,123]. While the lack of uptake in routine clinical practice is no doubt multifactorial, one reason is likely related to the fact that these therapies are dull, solitary activities, where the patient does not receive any immediate feedback on their performance, or on their progression over time. Because MI and AO both work by driving changes in the brain, the therapist cannot tell if the patient is doing it optimally, or doing it at all. Furthermore, given that rehabilitation is a slow process, the patient cannot

immediately tell if doing MI or AO is making a positive impact in their functional recovery. Both the nature of the therapies and the lack of feedback can negatively impact a patient's compliance to the therapy, which in-turn reduces the amount of the therapy they are willing to complete.

2.7 Neurofeedback

The issues discussed in the previous section suggest that innovations are needed in order to make motor simulations' contribution to recovery perceptible and easily apparent, as well as to make motor simulation therapies more engaging. A potential remedy to these two issues with mental simulation therapies is their integration with NFB. Neurofeedback is where an individual is presented with easily-understandable information about an aspect of their brain activity (e.g., via visual, auditory or haptic feedback), and asked to induce a simple change to the representation of their brain activity they see, thus reinforcing this new pattern of neural activity[124]. The decreasing difficulty an individual has in eliciting this change is *NFB learning*.

2.7.1 Neurofeedback Mechanisms

Neurofeedback begins simply by presenting the individual with the system (giving them sensory access to the aspect of brain function of interest), then allowing the individual to 'find a way' to move the system to the state explicitly defined as optimal. The result is the creation of a control-theoretic closed feedback loop [125-127] between an individual and their

brain activity: where the individual creates an association between the neural modulation required to elicit the system's win-state and the reward of success[128].

Single cell recording work[129] and computational modeling of neural networks[130] both suggest that the ability to 'find the right behaviour' in a closed behavioural feedback loop is accomplished by distinct changes in the patterns of neural activation which produce that behaviour. This has been directly demonstrated in an experiment that used single-neuron recording to show that NFB learning of gamma up-regulation in monkeys led to increased spiking synchrony of individual neurons in M1[131]. Moreover, the ability to quickly learn a new association connected to a reward in this way has been shown to be supported by short-term synaptic plasticity[132,133]. Such activity-dependent plasticity is thought to be accomplished via the formation of new dendritic spines [134], as well as axon re-modeling[135]. Given these findings, it is not surprising that NFB learning has been shown to induce task-related changes in both white and gray matter volume,[136,137] suggesting these transient changes can lead to lasting effects on the architecture of various functional neural networks. This finding is consistent with results showing that NFB learning leads to *NFB transfer*—a change in brain activity or behaviour observable subsequent to NFB learning, when the individual is no longer receiving NFB. In humans, NFB transfer has been demonstrated six months [138], two years [139], or even *nine years*[124] following NFB learning.

The exact nature of the changes in brain activity that take place in response to NFB learning in humans will obviously vary based on individual differences and the type of NFB used. However, several inferences can be made about the nature of these changes in general.

The first is that the changes in neural activity that result from NFB learning are not restricted to the discrete region or regions that the NFB signal is taken from. After learning to modulate the activity in a particular region, studies have shown[140-143] that NFB learning leads to changes in the activity of areas functionally connected to the region the NFB signal is taken from. For example, one functional magnetic resonance imaging (fMRI) NFB study[140] showed that subjects who learned to up-regulate activity of the primary visual cortex (V1) showed increased connectivity between V1 and the superior parietal lobe (SPL) during NFB. The authors then used dynamic casual modeling (informed by prior work on these regions' interactions[73]) to infer that this increased connectivity was the result of increased top-down control—specifically, the SPL was causing the up-regulation in V1, and their findings also suggested that this was accompanied by a decrease in bottom-up information transfer from V1 to the SPL. Furthermore, the finding that NFB learning on a narrow metric of brain function (e.g., up-regulation of one region) can lead to change in the behavior of larger functional neural networks is the basis of NFB's clinical utility[138,144].

While the pattern of neural adaption that takes place in response to NFB undoubtedly changes with the type of NFB employed, one brain region that appears to be critical for all NFB learning is the basal ganglia. Using intracellular recordings in rats, it has been shown that cortico-striatal plasticity is necessary for NFB learning to take place[145], as knockout rats lacking N-methl-D-aspartate receptors (required for long term potentiation at the striatum) showed no NFB learning. Another study[146] found that NFB learners (compared to non-learners) showed increased activity in the basal ganglia as well as various areas of the motor

network. It is possible that dopaminergic neurons innervating M1 from the basal ganglia[147] could be crucial for NFB learning to take place.

Another brain region likely important for NFB learning is the cingulate cortex. The cingulate cortex is important for self-monitoring (i.e., error detection) and reward processing, and up-regulation of the cingulate cortex has been shown to predict NFB learning[148]. Moreover, greater volume and white matter concentration surrounding the mid-cingulate cortex has been found in NFB learners compared with non-learners[149]. And lastly, it has been shown that, compared to subjects receiving sham NFB, NFB subjects show increased connectivity in the dorsal anterior cingulate cortex, both during and 30 minutes following NFB training[150]. Given that the different areas of the cingulate have been shown to support different functions[151], it is difficult to draw any specific conclusions about the cingulate cortices' contribution to NFB learning—however, given its close anatomical connections to the basal ganglia,[151-153] it is likely that the basal ganglia-cingulate circuit is important for NFB learning.

Lastly, various types of NFB learning have also been associated with increased PFC activity[154-156], and white matter density in the fronto-occipital fascicle[148] has been associated with NFB learning aptitude. Moreover, human lesion studies have shown that PFC damage extinguishes the ability for NFB learning[157], suggesting the PFC cortex plays a critical role in NFB learning.

2.7.2 Advantages of Neurofeedback for Mental Practice

The core advantage of delivering motor simulation therapies alongside a closed-loop NFB system, as opposed to in isolation, is of course feedback. Feedback is a well-established means of improving the ability to learn a wide variety of skills[158-161], and NFB systems in particular are able to seamlessly combine negative feedback (i.e., the error correction that takes place in real time as the individual attempts to alter their brain activity) and positive feedback (i.e., highlighting the individuals progress through the use of reinforcing stimuli). The combination of positive and negative feedback is highly advantageous for the promotion of motor learning, as it has been shown that negative feedback enhances procedural[162,163] and skill motor learning[91], while positive feedback has been shown to improve retention skills gained through motor learning[164,165].

While various types of feedback are clearly beneficial in promoting learning, the increase in interactivity inherent in the provision of feedback—in and of itself—has been shown to result in increased learner persistence[166-168]. Hence, another major advantage of using NFB for motor rehabilitation is the element of structure and interaction it brings to a task that may otherwise become boring easily. Given that the mechanism of action for MI and AO both crucially require ***repetitive*** task performance [88], this aspect is far from trivial. Moreover, when compared to mental practice without feedback, NFB of a motor task has been shown to increase attention[169] as well as activation of the motor cortex[170]. Tethering the user to the task via NFB endows an otherwise unregulated task with a sense of achievement, as the individual receives immediate positive feedback about their performance [171,172]. The

NFB system can also be made flexible and adaptive, by designing systems where the difficulty is modulated by the performance of the user. By titrating the feedback the individual receives to their performance in real time, a NFB system can provide constant challenge to users of any ability[15,173].

Another advantage to integrating NFB into these rehabilitative therapies is the increased precision it affords an individual to modulate their neural activity. Given that these therapies are predicated on causing physiological changes in the brain through the repetitive activation of specific neural networks, increasing the specificity with which we are able to intervene in changing a patient's pattern of functional brain activation could surely improve the efficacy of these therapies. Moreover, given that NFB control at the level of single neurons has been shown in mice [174], and the wide variety of NFB techniques that individuals have been shown to be capable of learning[175], it is really only our theory (about what neural modulations are desirable for what goal) and our neuroimaging hardware that limit the potential specificity of NFB. By delineating the neural changes that occur in individuals with stroke who recover well, as well as those who recover poorly, in theory we could improve the efficacy of our therapeutic interventions through the use of increasingly complex NFB metrics.

2.8 Neurofeedback and Motor Imagery

Given that both MI and AO contribute to motor recovery following stroke by modulating brain activity, NFB could potentially allow individuals to directly observe the progress they are making in rehabilitating their brain. This could allow patients to track their

progress over time, so that they can demonstrate compliance for their clinicians and family members. Neurofeedback could potentially even make these therapies fun, interactive experiences that patients are willing to pour many hours into.

Indeed, many researchers have combined MI with neurofeedback[13-16,176,177]. In these studies feedback is based on a correlate of neural activity provided to the individual in real-time, or at a short delay, creating an interactive digital system akin to a video game (with the individual's brain replacing the typical 'controller'). Furthermore, to date several studies have demonstrated the ability of NFB-MI systems to modulate neural activity in the motor system[17,27-31]. The hypothesis underlying these tests on healthy controls, is that if NFB systems can be designed to allow individuals to modulate brain activity during MI (which has, on its own, been proven efficacious as a therapeutic adjunct[1-3]) in a manner that previous literature has shown to correlate with motor recovery from stroke, the effectiveness of MI therapy will be enhanced. An example using this approach comes from our lab's previous work[14], which showed that healthy controls were able to learn to lateralize sensorimotor activity using MEG NFB. The specific rationale for this NFB metric is the presence of maladaptive interhemispheric inhibition (mIHI) in the brain following a stroke. mIHI refers to a situation where patients' contra-lesional motor cortex shows increased activity during motor execution, a pattern of activity linked to complete functional recovery. [26,178-183]. Moreover, it has been shown that stroke patients who show less mIHI attain greater functional outcomes[17-19].

The underlying premise of this work, again, is that if healthy controls are able to produce more sensorimotor activation in one cortex, and less in another, during MI, a stroke patient could do the same, and this would lead to an enhancement of their functional recovery. And while this field is still in its infancy, the results of several recent studies suggest that the underlying premise is not erroneous. For example, one study using functional near-infrared spectroscopy (fNIRS) demonstrated that the addition of ipsilesional pre-motor NFB to MI enhanced the functional motor recovery of stroke patients compared with sham feedback[184], while another found that a group of stroke patients receiving NFB during MI showed a greater motor recovery compared to a control group that used MI without NFB[185]. Moreover, a decrease in alpha and beta ERD (a proxy for sensorimotor activity[186-189]) over the ipsilesional motor cortex during MI predicted an increase in functional motor recovery. While a third study found that a patient group receiving NFB (specifically training to decrease power in the alpha band over the ipsilesional motor cortex) while performing MI of movements congruent with a hand prostheses showed enhanced motor recovery compared with a patient group who were not provided with NFB[185].

2.9 Modulating Motor Cortex Activity in Stroke Recovery

Neurofeedback of course offers more than just the opportunity to make these therapies engaging and user-friendly. As alluded to in the previous section, NFB can allow individuals to *systematically* drive changes in their brain in a manner specified by the NFB metrics being used. To fully harness this potential, it is important to understand what changes in brain

activity the literature indicates lead to good outcomes, as well as what patterns of brain activity are indicative of an incomplete or poor recovery.

As mentioned in the previous section, researchers have highlighted the importance of mIHI in preventing the synaptogenesis required to restore the ipsi-lesional motor network (see Figure 1). Specifically, contra-lesional motor activity during unilateral movement of the affected limb, and a corresponding IHI of ipsi-lesional sensorimotor areas has been shown to be associated with worse motor outcomes [178-182]. A reduction in GABA-A receptors, both in the tissue surrounding the lesion, as well as in the contra-lesional hemisphere is thought to be the mechanism initiating this imbalance [190,191]. Starting in the sub-acute phase of recovery, this widespread disinhibition causes increased levels of plasticity across the brain [192,193]. The cumulative result of these events is often maladaptive plasticity—the contra-lesional hemisphere taking over motor functions, inhibiting the ipsi-leisonal hemisphere and thereby preventing the restoration of the damaged neural networks.

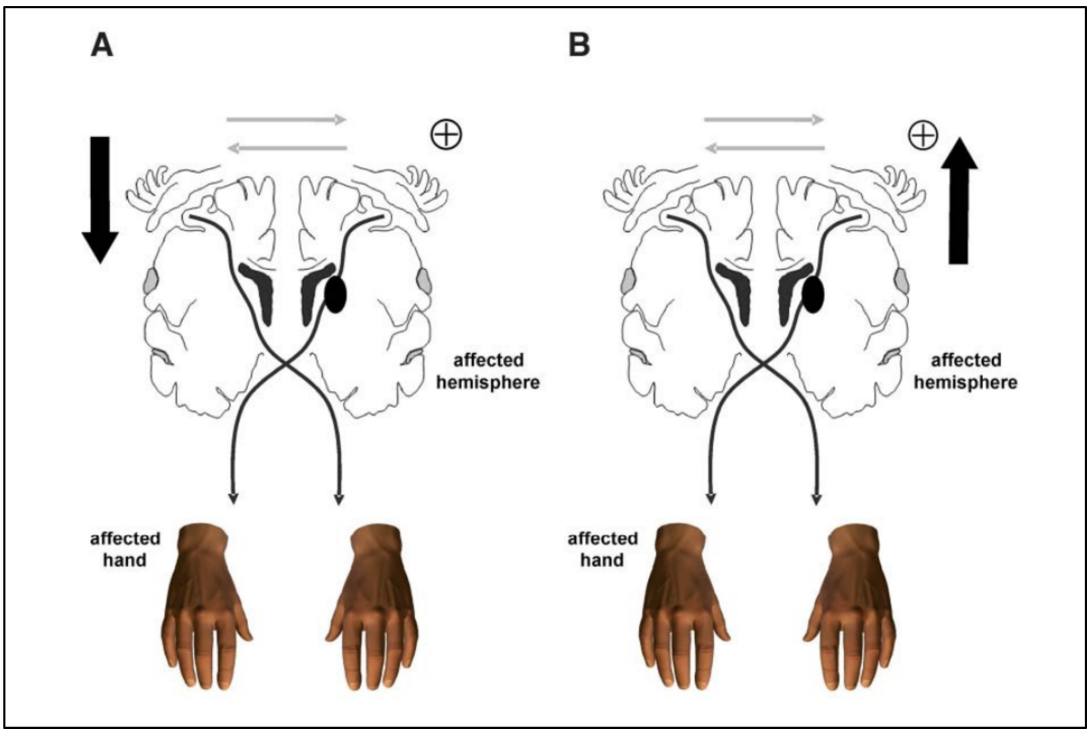

Figure 1 *Illustration of how maladaptive IHI can be rebalanced in a post-stroke motor network in two steps: first (A) the unaffected hemisphere decreases its compensatory activity, then (B) the affected hemisphere, free of excessive IHI, increases its activity*[180].

Several recent studies have shown that rebalancing IHI, by encouraging ipsi-lesional inhibition of the contra-lesional hemisphere's sensorimotor cortex, allows individuals to recover their motor function from stroke more fully than in those for whom this maladaptive plasticity still exists [17-19]. Several TMS studies have demonstrated that inhibiting the contra-lesional sensorimotor cortex during unilateral movement of a paretic arm leads to greater ipsi-lesional sensorimotor activity and better motor recovery [194,195]. However, the use of inhibitory TMS has also been shown to *reduce* recovery efficacy in some cases [196,197]. This may be because the ipsi-lesional hemisphere needs to be capable of reasserting its dominant

neural-processing role in contralateral movement; and thus when the contra-lesional sensorimotor hemisphere is inhibited in this scenario, maladaptive plasticity takes place. One way to circumvent this problem may be training individuals to correct maladaptive hemispheric imbalance via NFB, rather than through the use of inhibitory TMS.

In support for the possibility of using NFB to rebalance IHI, NFB based on suppression of the alpha rhythm has been shown to disinhibit intracortical inhibition (as measured via TMS) both immediately after as well as 20 minutes following NFB[198]. Furthermore, the ability to rebalance IHI in the visual cortex (using fMRI NFB) has also been demonstrated[199]. Lastly, studies using NFB of MI have demonstrated that individuals can learn to lateralize neural activity in the motor system using this technique[14-16].

2.9.1 The Use of Difficulty Titration in Neurofeedback

While choosing the right metric of brain activity to feed back to the NFB-user is crucial for any NFB to have its intended effect, another important, interrelated issue, is the way the NFB system is designed. One topic that has been discussed in the NFB literature is the use of difficulty titration, to ensure that NFB learning takes place.

As discussed in section 2.7, the provision of NFB has been shown to enhance functional motor recovery from stroke[185,200,201]. However, in some of these studies NFB learning (i.e., the ability to modulate brain activity in real-time in response to NFB) did not actually take place, as subjects in the NFB group did not show significantly better control of motor activity during NFB training compared to sham. One group[202] has speculated that the reason these patients in the NFB group showed enhanced functional outcomes was that the process of

interacting with the NFB system primed the patients brain more effectively than those engaging in a sham or randomized feedback interaction. These authors then conclude that the therapy these patients engaged in subsequent to the failed NFB training had an enhanced effect on their functional recovery (relative to those who engaged in sham NFB), *despite the fact* they did not demonstrate an enhanced ability to modulate brain activity during the *actual* NFB training. This view, held by others as well[203], posits that in order to increase the effectiveness of NFB for stroke rehabilitation beyond a priming effect, NFB must allow patients true operant control of their brain activity, and that the best way to ensure this takes place is to resist the urge to adapt the NFB metric to the idiosyncrasies of each individuals brain activity, but rather to use a fixed NFB metric, and to titrate the difficulty carefully to the abilities of the individual, in keeping with the best practices of cognitive load theory[204]. In the context of designing a NFB system to enhance the efficacy of mental simulation therapy, having explicitly defined NFB metrics is the optimal design choice, given that the outcomes (i.e., the modulations of functional neural activity to be incentivized by the system, to bring about the goal of behavioral change) can be based on previous literature—for example those discussed in section 2.9. Moreover, this perspective has also been supported by a recent Bayesian simulation study[205], that found that an adaptive difficulty increased the ability of NFB to produce reinforcement learning (i.e., operant conditioning).

2.10 Research Rationale

In the past ten years, MI coupled with neurofeedback has intensified the research community's interest in MI. This is undoubtedly driven by the fact that we have just entered

the era of affordable, mobile EEG systems—meaning any breakthrough interface created for MI has the potential to be far more accessible and user-friendly than anything we could have imagined previously [206,207]. Given the nascent though self-evident utility of combining MI and AO (as discussed in the *Imagined Imitation* section), it seems only a matter of time before this combined modality is designed in ways that incorporate neurofeedback. This type of brain-computer-interface (BCI) would also circumvent a limitation of current MI-neurofeedback systems: the fact that imagery is best accomplished with the eyes closed limits designers, making the delivery of visual, real-time visual feedback suboptimal. Making it ***advantageous*** to perform imagery with the eyes open, by combining MI and AO, opens up many possibilities with respect to interface design.

In addition, as we learn more about the specific functional perturbations of the sensorimotor network following stroke, increasingly complex metrics of neural activity can be integrated into NFB systems for stroke recovery. For example, post-stroke NFB for upper limb rehabilitation has traditionally used some measure of contralateral motor activity during a unilateral movement, with 'more activity' taken to represent better neurofeedback performance. The use of this metric is supported by a wealth of research showing an association between ipsilesional motor activity during paretic limb movement and motor recovery [18,208].

Given NFB's well documented ability to alter inhibition-excitation coupling of brain networks[209], and the finding that healthy controls utilizing MI-NFB systems are able to lateralize sensorimotor activity[14], it would be interesting to test whether an II-NFB system

could allow individuals to simultaneously up-regulate one hemisphere's sensorimotor activity, while disinhibiting the ipsilesional hemisphere's sensorimotor activity. However, before this type of NFB system could be compared with MI-NFB systems, and potentially integrated into a clinical rehabilitation setting, a study on healthy controls is required.

Moreover, previous studies have shown that MI-NFB learning transfers to subsequent MI[210,211], a finding of great clinical interest given that this means that the use of NFB with mental simulation could facilitate more effective mental simulation later on, when NFB is not being used. For this reason, the present study is interested in determining if any NFB learning that takes place using an II-NFB system to lateralize sensorimotor activity shows a transfer in this ability to subsequent MI.

Given the above discussion, the present study seeks to determine the utility of NFB in II. This research will be the first to attempt to demonstrate that closed-loop NFB can be used to augment a user's engagement of the sensorimotor network during II. It is expected that this study will expand our idea of what types of NFB designs and metrics can feasibly be integrated into BCI-based stroke rehabilitation, and contribute to the overarching goal of proliferating safe, effective home treatments for the motor impairments caused by stroke.

CHAPTER 3 OBJECTIVES AND HYPOTHESES

3.1 Objectives

The objectives of the present work are to:

1. Determine if NFB can be used to up-regulate contralateral sensorimotor activity and down-regulate ipsilateral brain activity during II. Lateralization here refers specifically to the process of (1a) up-regulating contralateral sensorimotor activation and (1b) down-regulating ipsilateral sensorimotor activation.
2. Determine if the effects on sensorimotor activity seen in NFB (i.e., objective 1) transfer to subsequent MI.

3.2 Hypotheses

1. We hypothesize (1) that subjects receiving EEG-based NFB during II of a unilateral motor task will show greater alpha (7.5-14.5 Hz) event-related desynchronization (ERD; a proxy for sensorimotor activity[186-189]) in the contralateral hemisphere, and more alpha event-related synchronization (ERS; a proxy for sensorimotor inactivity[186-189]) during II than those in the Sham group. Specifically, we expect to see a group by session effect; given previous findings[14,176,212], we expect that NFB learning will require >1 session.
2. We also hypothesize that individuals who received genuine NFB will show these same effects on sensorimotor activity compared to those in the sham group during a block of MI occurring subsequent to the II-NFB session.

CHAPTER 4 METHODS

4.1 Subjects

Thirty-two right-handed[213], non-disabled adults (10 males; 23.7 ± 3.4 years) agreed to participate. This age-range is based on research showing age-related changes in motor processing and brain structure between young and older and middle-aged adults [214,215]. Subjects were recruited via word-of-mouth, posters and online advertising. All subjects had normal or corrected-to-normal vision, were free of neurological and movement disorders and each provided written, informed consent. Subjects were assigned to either the NFB (n = 17) or sham feedback (n = 15) group based on a pre-determined recruiting schedule to ensure that each member of the sham feedback group would have a unique member of the neurofeedback group to be yoked to (yoking is described in detail below). Subjects attended 4 II-NFB training sessions within 7 days, with all sessions taking place at approximately the same time of the day. Other researchers, using a single session design, have seen a significant effect of neurofeedback on their metric of interest using group sizes of 5-10[16,150],[81]. The study was conducted with approval from the Research Ethics Board at the IWK Health Centre.

4.2 Questionnaires

4.2.1 Edinburgh Handedness Inventory

The Edinburgh Handedness Inventory[213] was used to assess the dominance of a person's right or left hand in daily activities[213].

4.2.2 *The Kinesthetic and Visual Imagery Questionnaire (KVIQ)*

The KVIQ is an adapted MI questionnaire intended for individuals who may need guidance in rating their imagery and who cannot perform complex movements[216]. The KVIQ is used to assess the vividness of both the visual and kinesthetic dimensions of MI. Within the visual dimension, a self-report rating of 5 indicates the individual imagines the movement as clear as seeing, while a score of 1 is reflective of seeing no image at all; within the kinesthetic dimension, a participant rating of 5 indicates the MI is as intense as actually executing the movement, where a score of 1 is representative of feeling no sensation[217]. Importantly, application of the KVIQ has shown reliability in both non-disabled controls and stroke patients[217]. In the present study, the KVIQ was used primarily to ensure that no subjects demonstrated a drastically low ability to perform MI.

4.3 Electroencephalography

Electroencephalography is the detection of electrical activity along the scalp produced by the discharge of neurons within the brain. The resultant EEG signal is the summation of the synchronous activity of the neurons that have a similar spatial orientation relative to a given scalp electrode location.

The EEG signal was detected using a QuikCap (Compumedics Neuroscan, Charlotte, NC) attached to a Synamps RT system (Compumedics Neuroscan, Charlotte, NC). The *QuikCap* is an electrode placement system manufactured of highly elastic, breathable Lycra material that houses the electrodes used to detect the EEG signal. The electrodes consist of

soft, neoprene reservoirs that house the electrode itself. The reservoirs are filled with gel to conduct the signal from the scalp to the electrode, as the electrode does not actually contact the participant's scalp. QuikCaps are cleaned following each use, and a number of sizes are available to ensure a comfortable fit. At the onset of the experiment, the QuikCap is placed on the individual's head and the gel reservoirs are filled with the electrode gel. To accomplish this, large gauge, disposable, blunt needles are used. The needle is inserted into a hole on the outside of the cap and placed gently against the scalp. The needle head is then moved in a circular motion to move the hair under the electrode out of the way and to allow for the electrode gel to be injected, a process continued as the needle is removed from the hole. This process is then repeated at each of the electrode sites.

Electroencephalography data was acquired at a sampling rate of 1000 Hz with a band-pass of DC-333 Hz. The ground electrode on the 128-channel QuikCap was used as a ground. Impedances for all electrodes was maintained at <15 kΩ throughout the experiment. Eight electrode sites on the cap were used in the present study: ground, reference, bilateral mastoid electrodes (to provide re-referencing of the signal) as well as electrodes C3, CP3 (left sensorimotor input) and C4, CP4 (right sensorimotor input). The selection of these four sensors is informed by multiple EEG studies of motor execution and imagery [218-221] (see Figure 2 for illustration). In addition, a study conducted at our lab (McWhinney, unpublished data) was also used to inform the addition of CP3 and CP4 to the array. In this study participants received bilateral median nerve stimulation, and the amplitude change of all sensors was used

to in order to determine which sensors responded most strongly to the stimulation—with sensors CP3 and CP4 selected most often.

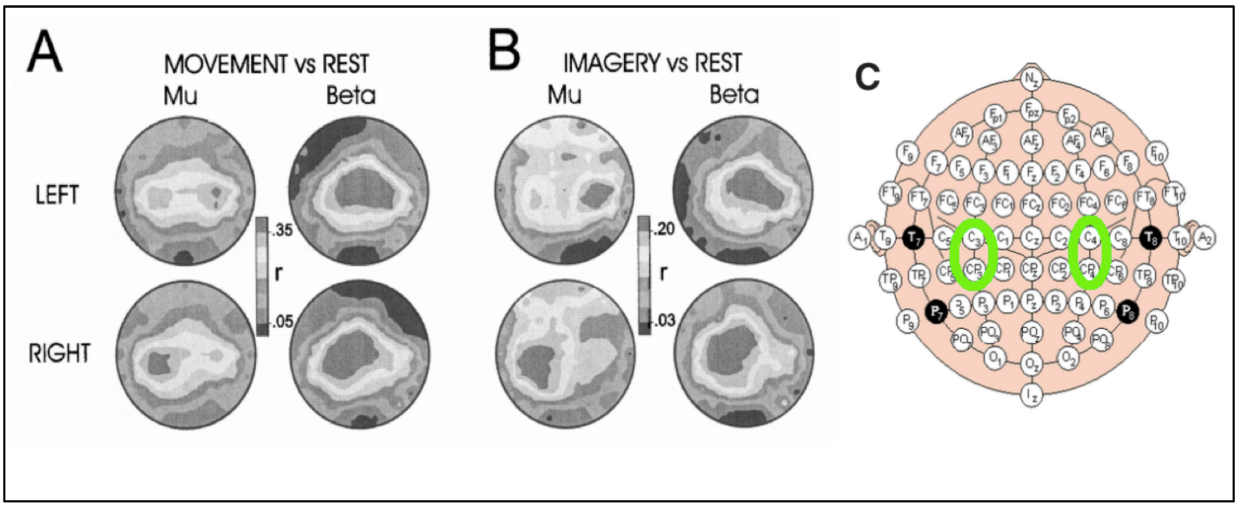

Figure 2 *EEG topography[222] for ME (A) and MI (B) of both left and right hand movements in Mu (7.5-12.5 Hz) and Beta (15-30 Hz) bands, with the EEG channels chosen to measure the NFB signal from (C; modified from[223]).*

In order to detect and reduce artifacts produced by eye movements and blinking, an electrooculogram (EOG) was obtained using self-adhering ring electrodes placed above and below the left eye, and just lateral to the left and right eye.

4.4 Electromyography

During the II-NFB and MI tasks, electromyography (EMG) was recorded to allow for monitoring (and subsequent quantification) of muscle activity. Activity of the extensor (i.e., extensor carpi radialis longus) and flexor (i.e., flexor carpi radialis) muscles of the wrists was acquired throughout using self-adhering electrodes (3 x 3 cm; Kendall-LTP, Chicopee, MA) arranged in a bi-polar configuration (inter-electrode distance of 2 cm) using the EEG

electronics as described in the preceding section. The raw EMG signal was bandpass filtered (0-333 Hz) and sampled at 1000 Hz (128-channel SynAmps RT, Compumedics Neuroscan, Charlotte, NC), stored for offline analysis and fed back to the real time computer. Lastly, the EMG signals from the NFB and MI task blocks were analyzed off-line to monitor the amount of muscle activity occurring during II-NFB and MI (see Offline Preprocessing, section 4.7.2).

4.5 **Experimental Design**

Subjects in both groups were to attend four experimental sessions performed at approximately the same time of day within a 7-day period. At the beginning of the first session subjects completed the KVIQ[217] and the Edinburgh Handedness Inventory[213] to confirm ability to perform MI and hand dominance respectively. Following completion of these questionnaires, subjects watched a 2-minute video describing the NFB task (see Appendix 1 for script), which included 2 replays of a 7-second video of a complex handshake. Following the introduction video, and at the outset of sessions 2-4, subjects were prepared for EEG and EMG recording. On all study days, subjects performed 3 blocks of II-NFB training, and a single block of MI. Figure 3 outlines the experimental timeline.

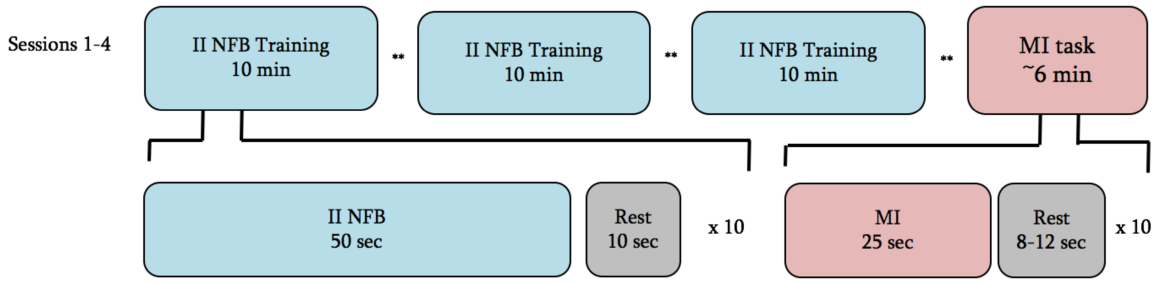

Figure 3 *Experimental timeline for a single experimental session.*

*** indicates a junction at which subjects were permitted to take as much time as they liked to prepare for the following block(s)*

4.5.1 Imagined Imitation Neurofeedback Training

Each II session consisted of three training blocks broken up by two rest blocks. Each of the three training blocks consisted of ten sets of a task block, where the subject engaged in the II task, followed by a rest block, where the subject could take as much time as they wanted to rest and assess the metrics of their performance up till that point. This design, with frequent rest periods, has been shown to both minimize fatigue and maximize post-training synchronization measures associated with better behavioural transfer [224,225].

Each II block consisted of 50s of II, followed by a 10s rest block, where the subject's performance (i.e., the difficulty levels achieved) during that day's session was plotted. The II session required the subject to watch a video depicting a complex handshake involving the right arm, while imagining they were performing the handshake themselves. This handshake used the right hand only, was filmed from the first person perspective by the experimenter and had 6 major components (a traditional handshake grip, an alternative handshake grip, wiggling of the fingers, slapping of both sides of the hands, bumping of fists vertically, and bumping of fists straight on; see figure 4 for depiction). The handshake was chosen because of its visual interest, and because it is a movement that would seem plausible to all subjects, but that no subject had done before. The video used the first person perspective, given the findings that imagery from this perspective induces more motor-network activity[226,227], and

has been shown to facilitate learning more effectively[228,229], than imagery taking a third person perspective.

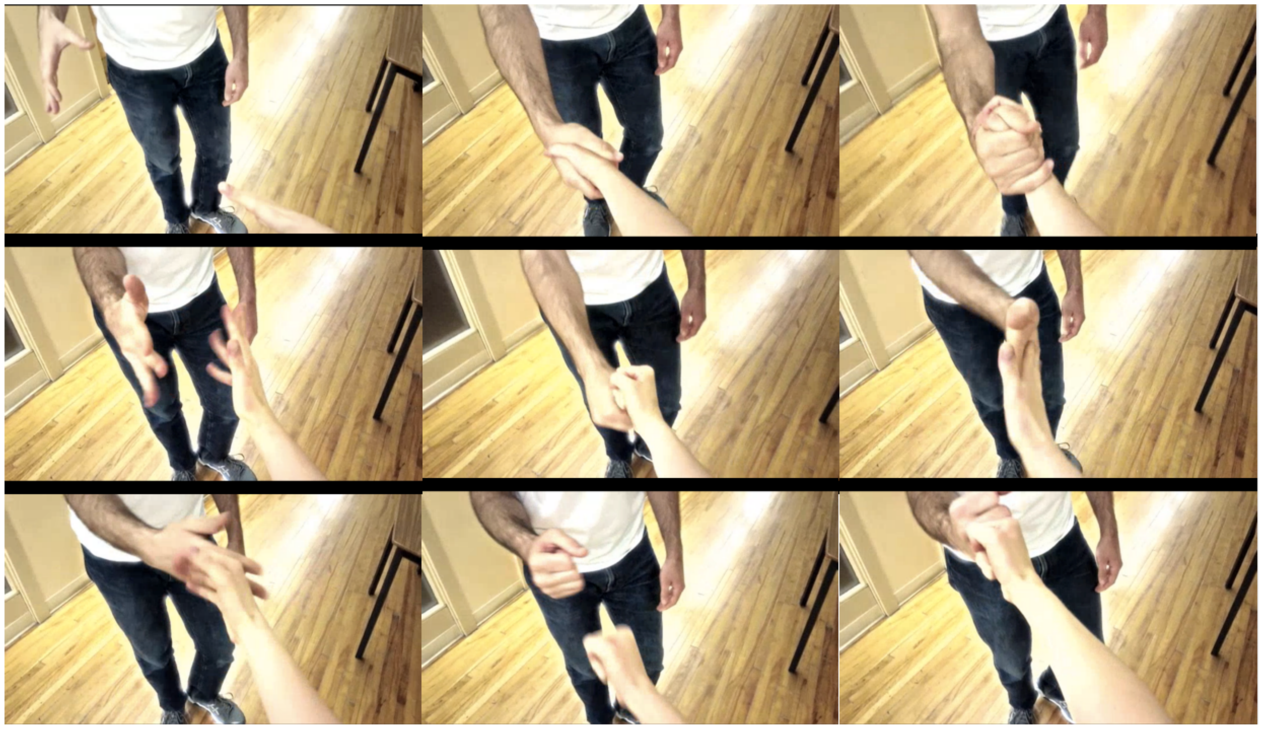

Figure 4 Illustration of handshake video

The script (Appendix 1) played for the subject at the beginning of the first session simply told the subject to imagine they are executing the arm movements they see on the screen, and that their goal is to make the video become and stay as colourful as possible. They were also told that they will start on level 1, and can move up levels by imagining well (i.e., making the video play in colour). No more instruction or information about the NFB system was given, as giving an excessive tutorial concerning the underlying methodology and physiology of the NFB system has been shown to inhibit subsequent NFB system mastery [230,231]. This feedback modality (i.e., incremental color modulation of the video) was chosen

given the findings that visual feedback is preferable to auditory feedback[232,233], that feedback providing immediate, incremental information about performance is superior to binary [234] or delayed feedback [235].

At the end of each task block, if their performance was above or below the threshold to change difficulty level a happy or sad sound (respectively; these sounds were taken from a popular video game) played[236], indicating they had gone up or down a difficulty level. The sounds were selected for their positive or negative valences, as it has been shown that using moderately affective stimuli can enhance NFB learning[237].

Total time for the II NFB session was 30 minutes plus the time taken in the two rests between II blocks. This is in line with other neurofeedback studies, which generally use session lengths between 30-60 minutes [15,209,238,239].

Finally, while half of the participants received genuine neurofeedback (as described above), the other half received sham feedback. Participants in the sham[240] feedback group were presented with the exact same changes in video colour gradient as another participant in the neurofeedback group produced during their II sessions. By 'yoking' sham feedback with neurofeedback participants in this manner it was possible to equate the stimuli each group was exposed to while keeping the attention level of each group equal.

4.5.2 Motor Imagery Task

Following II feedback training, subjects completed a block of kinesthetic MI. Subjects were instructed (via on-screen prompts, which they were given as much time as needed to read) to sit with their eyes closed, and that when they hear a voice say "go", they should

begin imagining the handshake they practiced imagining in the II-NFB feedback training (at the same pace as it was presented during the II-NFB training), and that when they hear a voice say "rest", they should cease the imagery, and rest with their eyes closed until instructed to engage in imagery again. Each participant completed 10, 25s blocks of imagery, for a total time of ~6 minutes.

4.5.3 Experimental Blinding

Given the requirements of the experimental set up, the experimenter was not blinded. However, to control for experimenter effects[241,242], a structured script was created (Appendix 2) to make sure all experimenters responded in a similar manner to questions about the experiment from subjects in either group. The use of an instructional video to inform the subject about the expectations of the study and the performance of the II NFB system, further helped ensure that all subjects' interactions with the experimenter were identical. Moreover, the experimenters' script did not include any specific advice (e.g., different strategies) for how subjects might optimize NFB performance, as it has been shown that NFB learning is not enhanced by the specification of specific strategies[243].

4.6 Online Processing and Calculation of Neurofeedback Metric

Acquisition of the EEG and EMG data was performed in Curry 7 (Compumedics Neuroscan, Charlotte, NC). The following procedures were applied online to the continuous EEG data: high- and low-pass filters at 1 and 100 Hz respectively; a notch filter at 60 Hz; baseline correction (using the first 3s of data acquired); artifact reduction via principal

component analysis (PCA) as implemented in Curry 7, using a threshold of ±360mV at both vertical and horizontal occular electrodes to identify eye blinks and movements, attenuating the first component within a window of -200ms to 500ms relative to the peak of the detected artifact.

Following preprocessing, 500 ms data segments were passed from Curry to MATLAB (MATLAB 8.03, The MathWorks Inc., Natick, MA, 2014) for analysis using a custom script. The custom MATLAB script continuously estimated the magnitude of power changes in the alpha frequency band for the most recent 500ms data segment passed to MATLAB from Curry 7. Power change in the alpha frequency band (measured via a fast Fourier transform) was compared to the alpha power during a 15s block obtained immediately prior to the first II- NFB block. During this 15s block the subject silently counted backwards from 100 by 3s, while staring at a fixation cross and keeping their arms as relaxed as possible. A single, fixed baseline (i.e., the 15s block) was required in order to titrate the difficulty of the NFB system. A log2 function was applied to the alpha power during II-NFB divided by the baseline power, producing a negative integer for all ERD segments, and a positive integer for all ERS segments. A running average of the most recent 6 data segments (i.e., 3s in total) was used as the metric of current alpha power relative to baseline. A running average of the previous 3s of alpha power change was used in order to present the modulation of alpha power in a comprehensible way to the subject, as presenting real-time changes can become incomprehensible to the subject given the speed at which these changes can occur.

In order to incentivize contralateral ERD and ipsilateral ERS during the unilateral right-handed task (described in section 4.5.1), log2 values from both the left and right hemisphere (obtained by averaging the alpha power between the two sensors, then dividing this value by the baseline power) were multiplied by -1 (rendering positive values for ERD, and negative for ERS), and these two values then had a weighting applied (see following section) depending on the difficulty level of the current NFB trial. The resulting integers, representing each hemisphere's contribution to the NFB metric, were then summed, resulting in a singular *NFB Score,* with higher values representing more sensorimotor lateralization towards the contralateral hemisphere.

4.6.1 Imagined Imitation Neurofeedback System

The II-NFB system consisted of Presentation® (Version 16.05.09, www.neurobs.com) code designed to repetitively loop the video of the complex handshake. The color of each frame depended on a value (Video Score) passed from MATLAB to Presentation every 500ms. The Video Score ranged from 1-6, corresponding to a range from black-and-white to full color saturation (Figure 5).

Figure 5 *Example of the range of colors the II video displays.*

The Video Score value at each 500ms instance was determined by comparing the current L Score (described in the preceding section) to the L Score thresholds for the current Difficulty Level. For example, if the current L Score was 4, and the thresholds for moving the Video Score up and down were -3 and 3 respectively, the Video score would increase by one from its previous value, as it exceeded the threshold required to raise the video score (see Figure 6 for an illustration). If the L Score had been <-3, the Video Score would be one less than the previous value (or 1, if the previous value was 1), and the Video Score would remain at its previous value if the L Score was >-3 and <3. At the beginning of each NFB trial, the default Video Score value was 1 (i.e., at the beginning of each block the video started black-and-white).

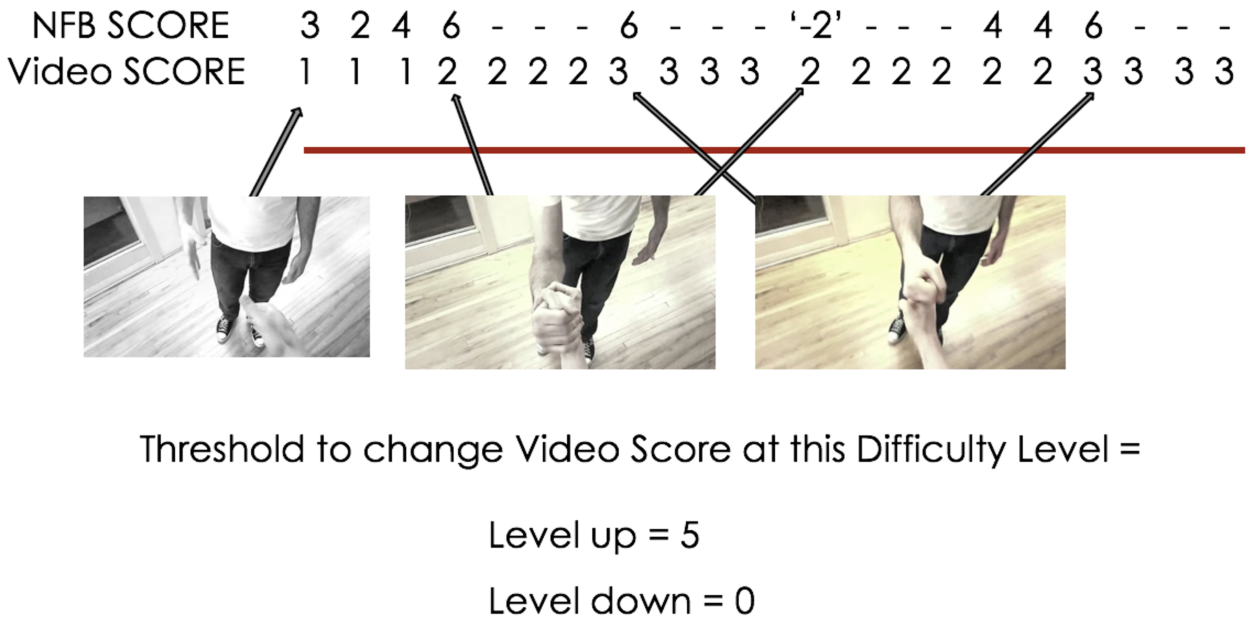

Figure 6 *Example of the interaction between NFB score and the video's colour during II-NFB (with a new L score calculated every 500ms).*

The choice to have the Video Score only more up or down one increment at a time, was to ensure that the movement of the changes in the colour gradient (i.e., the representation of NFB performance) were easily perceptible.

At the beginning of each experimental day, subjects began at Difficulty Level 1. If subjects remained at Difficulty Level 1 for three trials in a row, there were two difficulty levels below one (0 and -1; where the thresholds required to increase the Video Score were lowered considerably from Difficulty Level 1), in order to prevent any participants' initial level of competence from precluding them from progression on the II-NFB system. Upon completion of each NFB trial, the Video Score values from the last 20s were averaged, and this value determined whether the difficulty-level increased (average color-level >4)

decreased (average color-level <2), or stayed the same (average color-level 2-4). The calculation of the NFB metric also varied based on the difficulty level. At low difficulty-levels (1-4) the ipsilateral hemisphere's II-NFB metric was not factored into the II-NFB value, however the threshold values determining the video color-level increased. Conversely, at each medium difficulty-level (5-14) the ipsilateral hemisphere's II-NFB metric was factored in 10% more. At high difficulty-levels (>14) ipsilateral and contralateral II-NFB metrics contributed equally to the final II-NFB metric, with the thresholds determining the changes in color-level increasing with each difficulty level.

During each rest period, a line graph depicting the Difficulty Level achieved by the subject throughout the day's NFB blocks was presented (Figure 7). In conjunction with the presentation of the line graph, a happy or sad sound played if the difficulty level moved up or down respectively. Upon completion of each II-NFB session, a screen appeared thanking the subject for their effort, and stating the average difficulty level they achieved.

In addition to the above, the MATLAB script calculated the Difficulty Level the sham subjects would be on if their brain activity were in the NFB condition. The Difficulty Levels the sham subjects would have achieved throughout the entire session were saved to file upon completion of the experimental day. Video score and corresponding color-level for each video frame was saved to file to enable the provision of sham NFB.

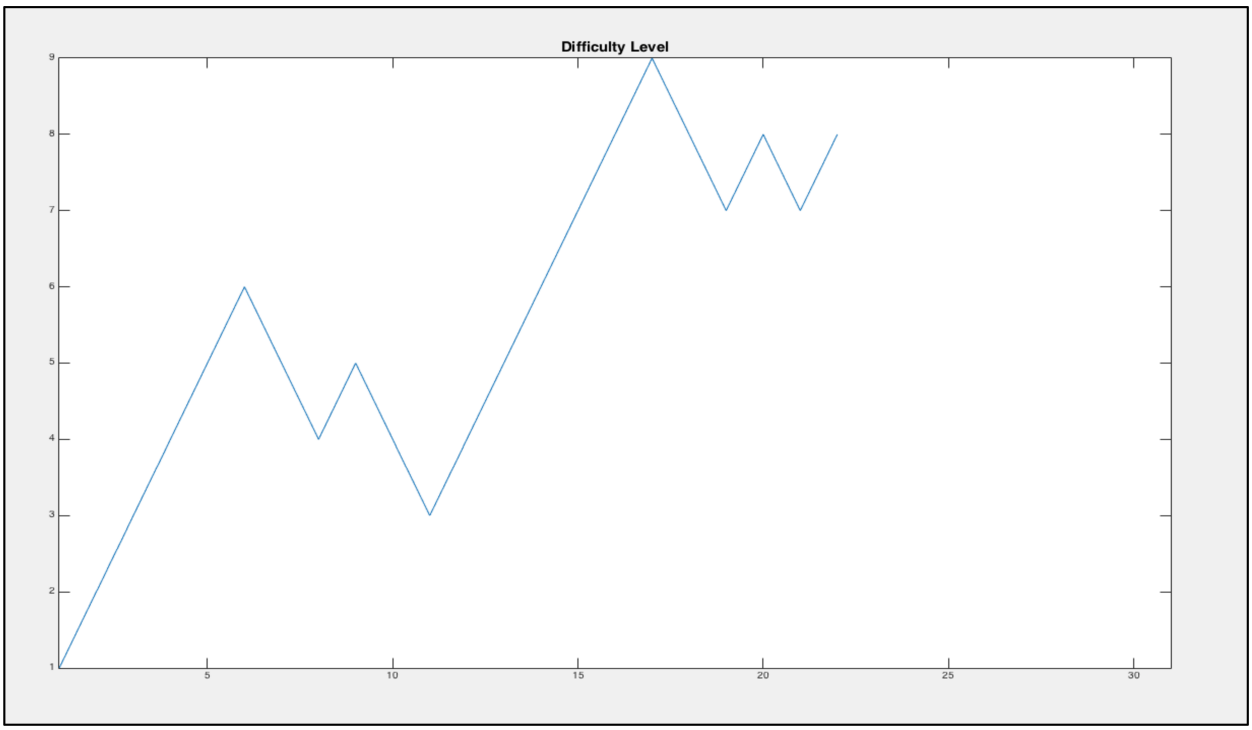

Figure 7 *Feedback screen displayed during 8s rest blocks. Trial (1-30) is plotted on the x-axis, and difficulty level is plotted on the y-axis.*

To ensure the ERD/ERS values used to generate the NFB signal were not generated by overt movement, online analysis of the EMG signal was performed. Specifically, every 500ms the amplitude of the full-wave rectified EMG signal from the flexor and extensor musculature of the right arm was compared to the corresponding average obtained during the baseline period (i.e., the 15s block obtained immediately prior to the first II- NFB block). In the real-time II-NFB system, if the amplitude of the current 500ms sample of EMG was 2 SD greater than the baseline amplitude values, EMG activity was considered excessive, and the Video Score was reset to 1.

4.6.2 *Provision of Sham Neurofeedback*

All individuals in the sham group were yoked to an individual in the NFB group. The

color-levels and difficulty-levels experienced by the sham subjects during their 4 sessions were identical to those of the NFB subject they were yoked to. This was achieved by recording the Video Score and Difficulty Level values for the entirety of the NFB group's sessions as text files, then having the MATLAB code reference these text files when communicating with Presentation.

4.7 Data Analysis

4.7.1 Offline Preprocessing

Given that online preprocessing procedures in Curry7 do not alter the raw data file[244], pre-processing procedures were conducted offline in Curry 7. A high-pass filter at 0.5 Hz, a notch filter at 60 Hz, and baseline correction (using the first 3s of data acquired) were applied to all continuous data files. A PCA was also performed, using a threshold of ±200mV at both vertical and horizontal ocular electrodes to identify eye blinks and movements, with the first component in the time window -200 - 500ms relative to the peak of the artifact being removed.

Pre-processed continuous EEG data were then epoched using event markers placed in the continuous data file by the II-NFB Presentation script (with unique event markers identifying the beginning and end of each block). For each session, there were 30, 50s epochs of II-NFB, and 30, 10s epochs of rest; and for the MI condition there were 10, 25s epochs of MI, and 10, 8s epochs of rest. All epochs from the NFB and MI task were concatenated into

two continuous data files, and these new files (one for each task, for each session, for each subject) were exported to MATLAB for subsequent analysis. Consistent with the online approach described above, EMG from both real and sham NFB groups were evaluated for the presence of EMG activity in the right arm. Specifically, data from II-NFB blocks where the EMG signal from the flexor and extensor musculature of the right arm was >2 SD from the baseline period were discarded from subsequent analysis.

4.7.2 *Preparation for Statistical Analysis*

Both alpha (7.5-14.5) and beta (15-30 Hz) power from all continuous EEG data, from all remaining II-NFB trials were calculated. The power in these bands was calculated (using a fast Fourier transform) in 750 ms segments, and the power at each segment was divided by the mean baseline power in their respective frequency band (i.e., the mean power during the 15s that preceded II-NFB). The ERD/ERS values from each 750 ms segment were concatenated with the following independent variables: subject, group (i.e., NFB or sham), task (i.e., NFB vs. MI), experimental session, trial, difficulty level, time (ms), hemisphere, sensor (i.e., C3, C4, CP3, CP4), frequency band (i.e., alpha and beta), session start time, session schedule (i.e., the spacing of the four experimental sessions, within the maximum one-week they are conducted), sex, age, handedness, (i.e., Edinburgh Handedness Inventory score), and imagery ability (i.e., KVIQ scores for visual and kinesthetic imagery modules respectively). The resulting matrix was then exported to rstudio[245] for analysis.

4.7.3 Conditional Inference Random Forest Modeling

We used conditional inference random forest modeling[246,247] (CForest) to investigate the differences in motor activity between the NFB and sham groups. CForest is a recursive machine learning algorithm, well-suited to modeling data with a non-normal distribution[248,249]. This method is advantageous for the study of longitudinal NFB data, given the variability in the types of effects found in the NFB literature. CForest (1) randomly selects a subset of a full data set (bootstrap aggregation or *bagging*[247,249,250]), (2) randomly selects a subset of independent variables (the number of which is chosen ahead of time), testing (using a permutation testing method[251]) each to detect an omnibus relationship with the dependent variable[249]. The variable whose omnibus test renders the smallest p-value is then tested in the same way at every possible split-point of the independent variable, and the data is partitioned again at the split point that renders the smallest p-value. This results in two new subsets of data, that are each tested using the same number of randomly selected variables in the same manner. The process continues until the 'best split point' of a variable renders a p-value <0.05 (Bonferroni corrected for multiple comparisons). The conclusion of this process produces a single decision tree, and after a pre-selected number of trees have been grown, they are averaged,[252,253] resulting in a single predictive model which can be explored using A priori hypotheses about the relationship between the independent and dependent variable.

The CForest method is a uniquely efficacious solution to the bias/variance tradeoff—the desire to avoid false-negatives (i.e., type II errors) while endeavoring to not over fit the

model (and thus commit type I error). Crucially, the elements of randomization (bagging and variable pre-selection) included in the CForest algorithm led to the creation of decision trees that are sufficiently de-correlated that the classifier will increase in accuracy monotonically as (A) more trees are grown and (B) a large number of independent variables are included in the model, reducing the potential for overfitting[254,255]. The fact that a unique, random training set is being created with each iteration of the bagging procedure means that each decision tree utilizes a random, unique training set. The result of this is that the entirety of one's dataset can be used provided to the CForest algorithm, without a fear of overfitting by 'information bleed'[249,256]. Furthermore, given that the CForest algorithm randomly selects which independent variable to test at each node of each decision tree, a large number independent variables can be included in the model, without a fear of overfitting—as long as (A) the final model is explored a priori, and (B) the number of trees grown is sufficient.

4.7.4 *CForest Analysis*

In keeping with best practices,[257] 2,500 CForest decision trees were grown[256], using bags (i.e., initial partitions) encompassing 23.3% of the entire dataset, and testing each node with 1 randomly selected independent variable. The dependent variable in the model will be event-related power with respect to baseline. The independent variables were all subject specific variables listed in section 4.7.3.

Because of its recursive partitioning nature, CForest is highly sensitive to small effects,

however such algorithms have a tendency to over-fit—i.e., to model noise as well as reliable, systemic effects present in the data. The use of the bagging procedure described previously attenuates the effect of noise on the final model, while also attenuating random effects[248]. For these reasons it is advantageous to include as many independent variables as possible in the model, then to explore this model in an a priori manner.

CHAPTER 5 RESULTS

5.1 Subjects

As indicated previously, the NFB and Sham groups consisted of 17 and 15 subjects respectively. Two subjects in the NFB group only completed 2 of the 4 sessions, however the data from these two sessions was included in the final analysis. The visual and kinesthetic sub-scores on the KVIQ were within a normal range[217] for both groups (NFB: 19.29 $\pm$ 2.85 for visual, and 19.88 $\pm$ 3.18 for kinesthetic; Sham: 20.53 $\pm$ 3.42 for visual, and 20.8 $\pm$ 3.99 for kinesthetic).

5.2 EMG Rejection

In total 31.9% of the II-NFB blocks in the NFB group, and 36.9% of the II-NFB blocks in the sham group were discarded due to excess EMG activity in the right flexor and extensor muscles of the digits.

5.3 Neurofeedback Results

5.3.1 Contralateral Hemisphere

To investigate our hypothesis that subjects in the NFB group will produce more contralateral sensorimotor activity than the sham group in the II-NFB task, the significant partitions of the data, as defined by the CForest procedure, were explored in order to determine the effect of group (NFB vs. Sham) and session (1-4) on the activity of the contralateral (left) alpha ERD/S data.

The bar graph in Figure 8 plots the mean log2 values of both the sham and NFB groups during the II-NFB task. While subjects in the sham group have a lower log2 value in sessions 1-2, this trend reverses in sessions 3-4. The fact that no mean alpha or beta log2 ERD/ERS values were <0 (i.e., decreases from baseline or ERD) is likely due to the extended length of time over which these values were averaged (50s worth of 750ms segments) compared to other studies using alpha/beta ERD as a proxy for increased sensorimotor activity. To demonstrate that this finding represents a smoothing effect, as opposed to no ERD taking place at all, Figure 9 shows the percentage of all data segments used in the CForest analysis that represented a power decrease from baseline.

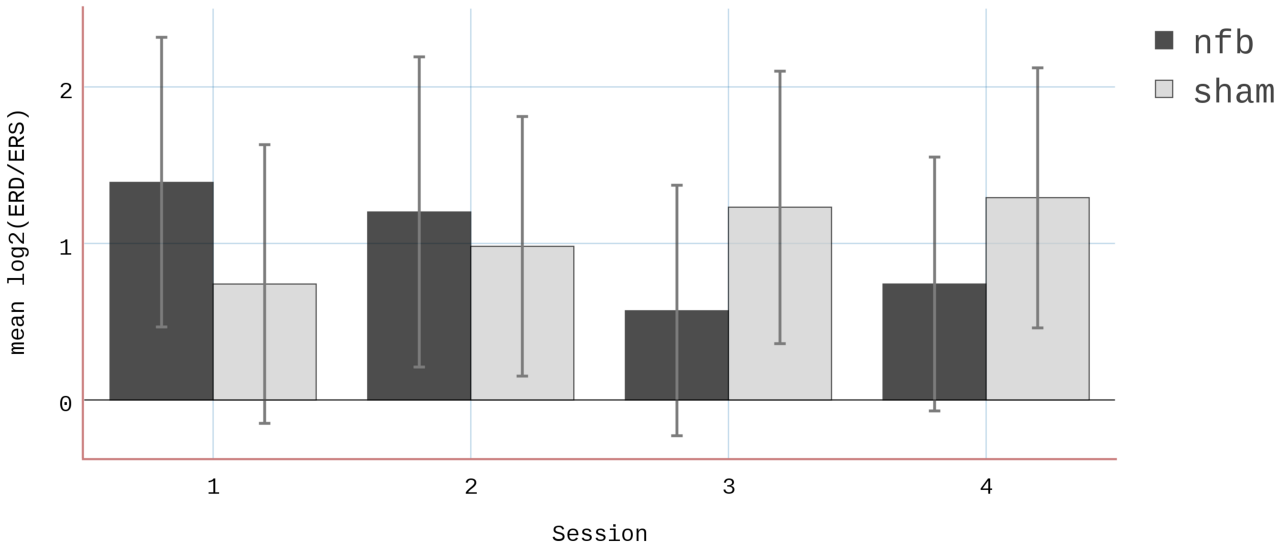

Figure 8 *Results from the average of the contra-lateral (left) EEG sensors during NFB at all 4 sessions are plotted. Note that a lower Log2(ERD) value represents greater sensorimotor activity. The log2 of the ERD/S values*

in the alpha band have an inverse relationship to sensorimotor activity—i.e., lower values representing a greater ERD, and therefore more sensorimotor activation. Error bars represent the standard deviation.

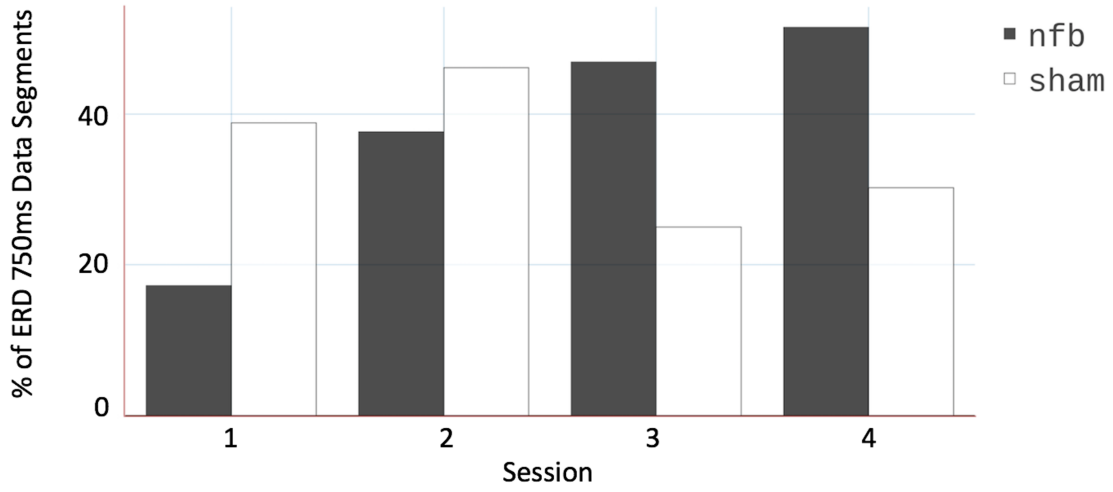

Figure 9 Alpha power was measured offline in 750ms segments. This plot shows the percentage of these segments that represented an ERD (i.e., a decrease in power from baseline).

The decision tree for the group by session effect on Alpha ERD/S during the II-NFB task in the contralateral electrodes is displayed in Figure 10. The results of the CForest analysis indicate that there was an interaction effect of group by session in the manner specified by our hypotheses. Specifically, at the third level of the decision tree we see a significant effect of group on the partitions of data containing sessions 2-3 and 4 respectively.

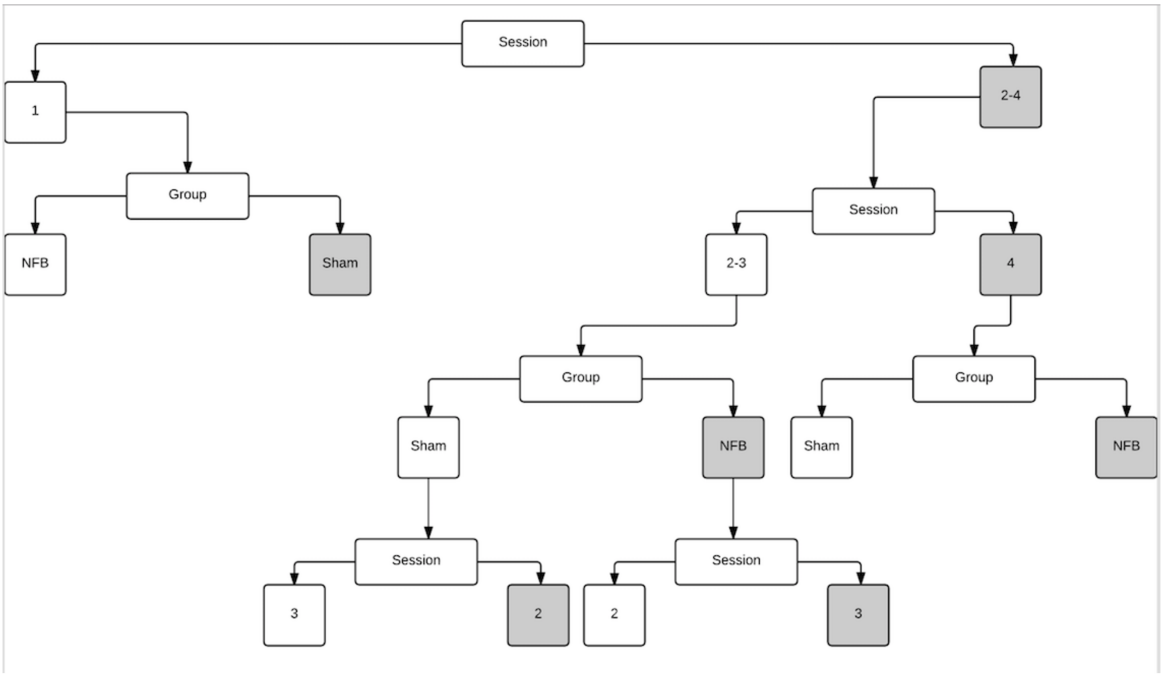

Figure 10 *CForest results from the contralateral (left) EEG sensors during the NFB task. Rectangles indicate a significant split point at the independent variable contained in the rectangle. Splits to the right (gray squares emanating from the right of a significant effect) indicate the data partition with significantly lower mean ERD/ERS value (i.e., more sensorimotor activity), while splits to the left (white squares emanating from the left of a significant effect) indicate data partitions with significantly higher mean ERD/ERS values.*

5.3.2 Ipsilateral Hemisphere

To investigate the hypothesis that subjects in the NFB group will produce less contralateral sensorimotor activity than the sham group in the II-NFB task, the significant partitions of the data, as defined by the CForest procedure, were explored in order to determine the effect of group (NFB vs. Sham) and session (1-4) on the activity of the ipsilateral (right) alpha ERD/S data.

The bar plot in Figure 11 shows the results from the II-NFB task in both groups across all 4 sessions. Similar to the bar plot for the contralateral hemisphere (Figure 8), the bar plot for

ipsilateral hemisphere shows that the NFB group showed a higher mean log2 value (i.e., less sensorimotor activity) in sessions 1-2, with this trend reversing in sessions 3-4.

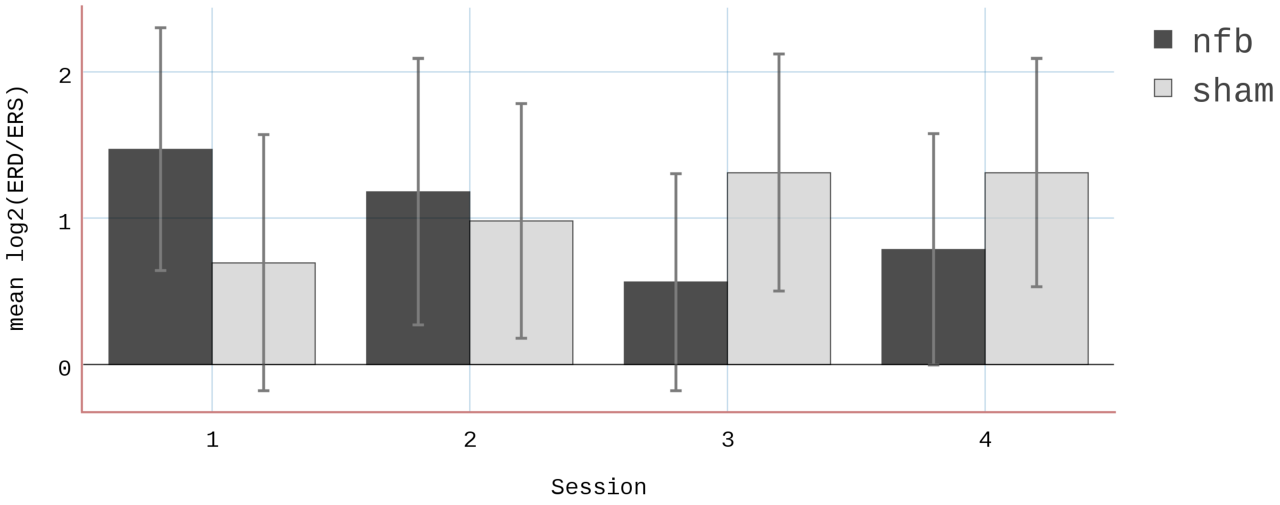

Figure 11 *Results from the average of the ipsilateral (right) EEG sensors during NFB at all 4 sessions are plotted. Note that a lower Log2(ERD) value represents greater sensorimotor activity. The Log2 of the ERD/S values in the alpha band have an inverse relationship to sensorimotor activity—i.e., lower values representing a greater ERD, and therefore more sensorimotor activation. Error bars represent the standard deviation.*

The decision tree for the group by session effect during the II-NFB task in the ipsilateral electrodes is displayed in Figure 12. While this decision tree partitions the sessions in a slightly different manner, the group by interaction effect seen in the contralateral hemisphere is also seen in the ipsilateral hemisphere. After the initial partition, between sessions 1 and 2-4 respectively, the splits at the group variable show that in sessions 1-2 the NFB group had a larger ERD/ERS value (indicating significantly lower ERD/ERS values for the 750ms data segments that made up the whole of the 50s trial) in sessions 1, and that this

effect reverses in sessions 2-4. While the direction of this effect aligned with our hypothesis in the contralateral hemisphere, the fact that this same pattern is found in the ipsilateral hemisphere is the inverse of our hypothesis that there would be a group by session effect, with more ipsilateral ERS seen in the NFB as opposed to the sham group.

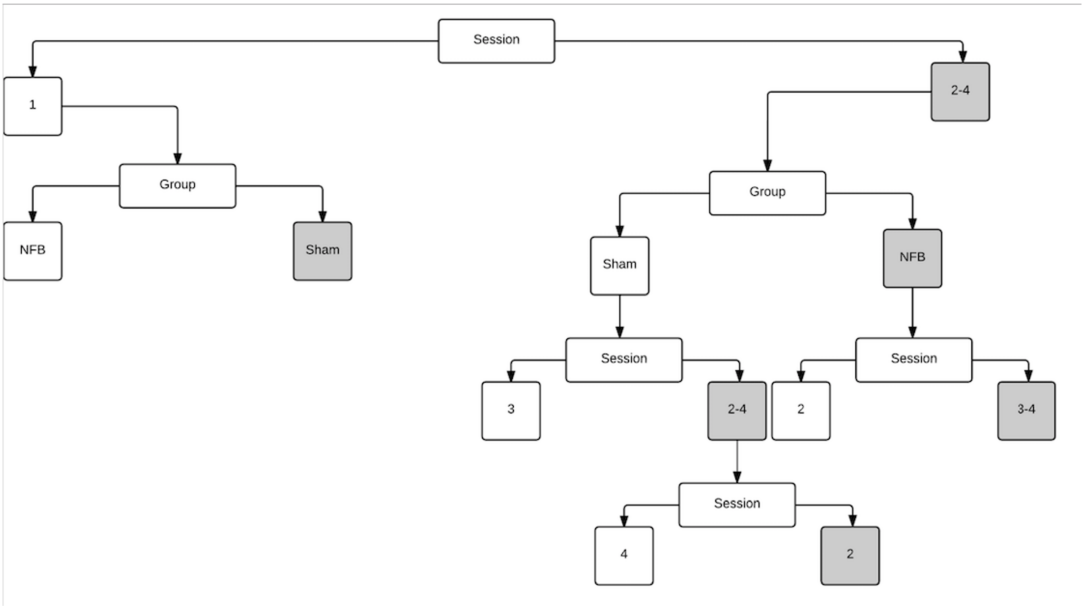

Figure 12 *CForest results from the ipsilateral (right) EEG sensors during the NFB task. Splits to the right (gray squares emanating from the right of a significant effect) indicate the data partition with significantly lower mean ERD/ERS value (i.e., more sensorimotor activity), while splits to the left (white squares emanating from the left of a significant effect) indicate data partitions with significantly higher mean ERD/ERS values.*

5.4 Motor Imagery Results

5.4.1 Contralateral Hemisphere

To explore the hypothesis that any effects of II-NFB on subjects' sensorimotor activity in the contralateral electrodes during II transfer to subsequent MI, subjects' ERD/ERS values from the MI block were explored in the same manner as the II-NFB task.

The results for the sham and NFB groups' contralateral sensorimotor activity during the MI task are plotted in Figure 13. In line with our hypothesis that the NFB group would produce more sensorimotor activity in the MI task during the sessions >1, the NFB group's mean log2 value was larger than the sham group in session 1, and virtually the same in session 2, slightly less than sham in session 3 and considerably less than the sham group in session 4.

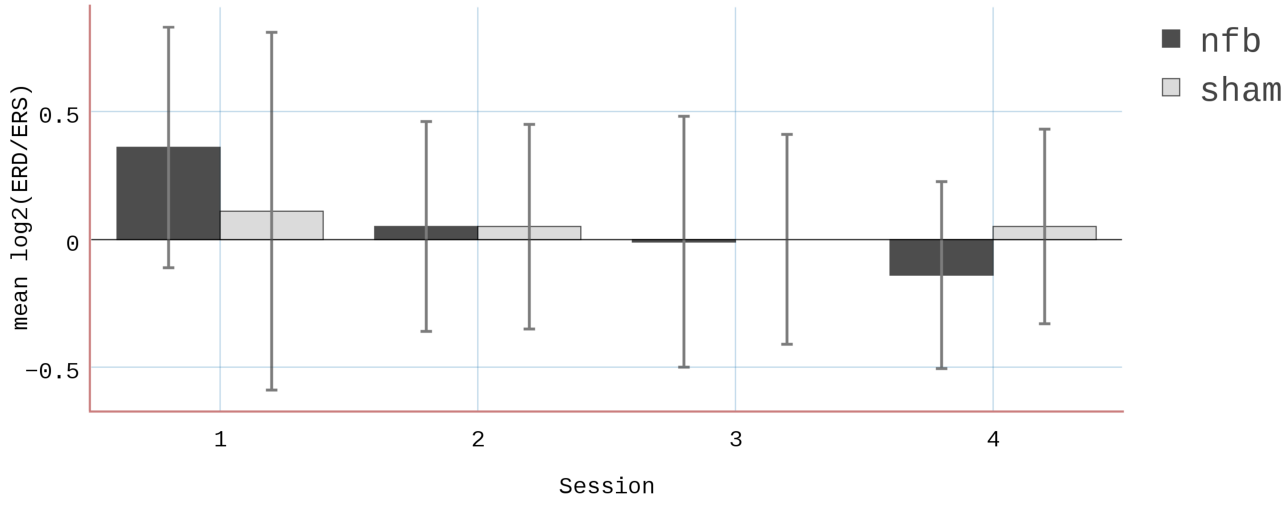

Figure 13 *Results from the average of the contra-lateral (left) EEG sensors during MI at all 4 sessions are plotted. Note that a lower log2(ERD) value represents greater sensorimotor activity. Error bars represent the standard deviation.*

This decision tree is similar to that found for the NFB task in the contralateral hemisphere (Figure 14). The left branch shows that during the first session, subjects in the sham group had significantly lower ERD/ERS values during MI. While the split at the third

level of the decision tree indicates a significant effect for group in the partition containing sessions 2-4.

For the MI task, the effect of group is present at the third level down, indicating that subjects in the NFB group produced significantly lower ERD/ERS values during sessions 2-4 than sham subjects.

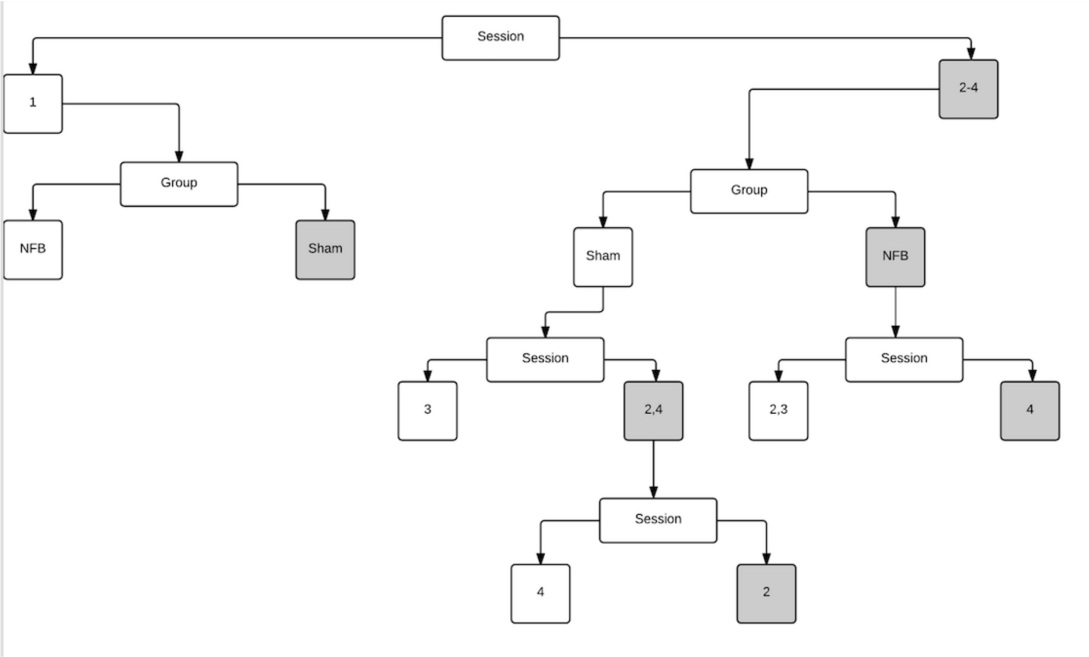

Figure 14 *CForest results from the contra-lateral (left) EEG sensors during the MI task. Splits to the right (gray squares emanating from the right of a significant effect) indicate the data partition with significantly lower mean ERD/ERS value (i.e., more sensorimotor activity), while splits to the left (white squares emanating from the left of a significant effect) indicate data partitions with significantly higher mean ERD/ERS values.*

5.4.2 Ipsilateral Hemisphere

The results from the ipsilateral hemisphere, for both the NFB and sham groups during the MI task is plotted in Figure 15. The NFB group shows a larger mean log2 value (i.e., less sensorimotor activity) than the sham group in sessions 1 and 3, but a lower value in session 4.

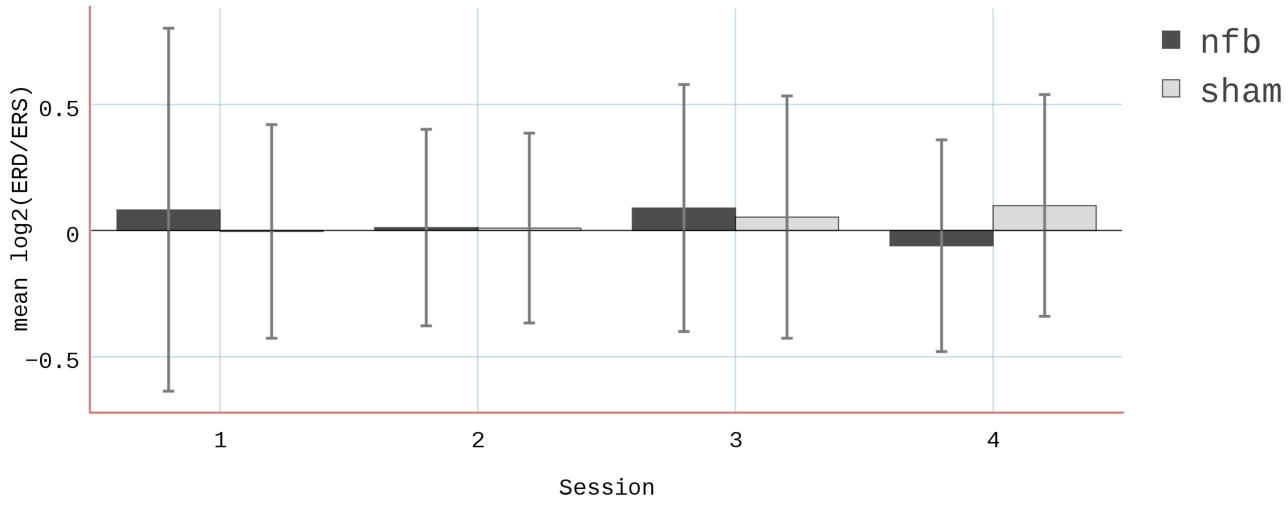

Figure 15 *Results from the average of the ipsi-lateral (right) EEG sensors during MI at all 4 sessions are plotted. Note that a lower Log2(ERD) value represents greater sensorimotor activity. Error bars represent the standard deviation.*

The decision tree for the group by session effect in the ipsilateral hemisphere during the MI task is displayed in Figure 16. Interestingly, while the results from the ipsilateral hemisphere in the NFB task were an inverse of our hypothesis, this inversion was not seen in the exact same manner in the MI task. The split at the third level of the decision tree indicates that the third session was characterized by significantly higher ERD/ERS value than sessions 2-4, which differs from the findings for the NFB task in the ipsilateral hemisphere, which found lower ERD/ERS values in sessions 3-4 compared with 1-2.

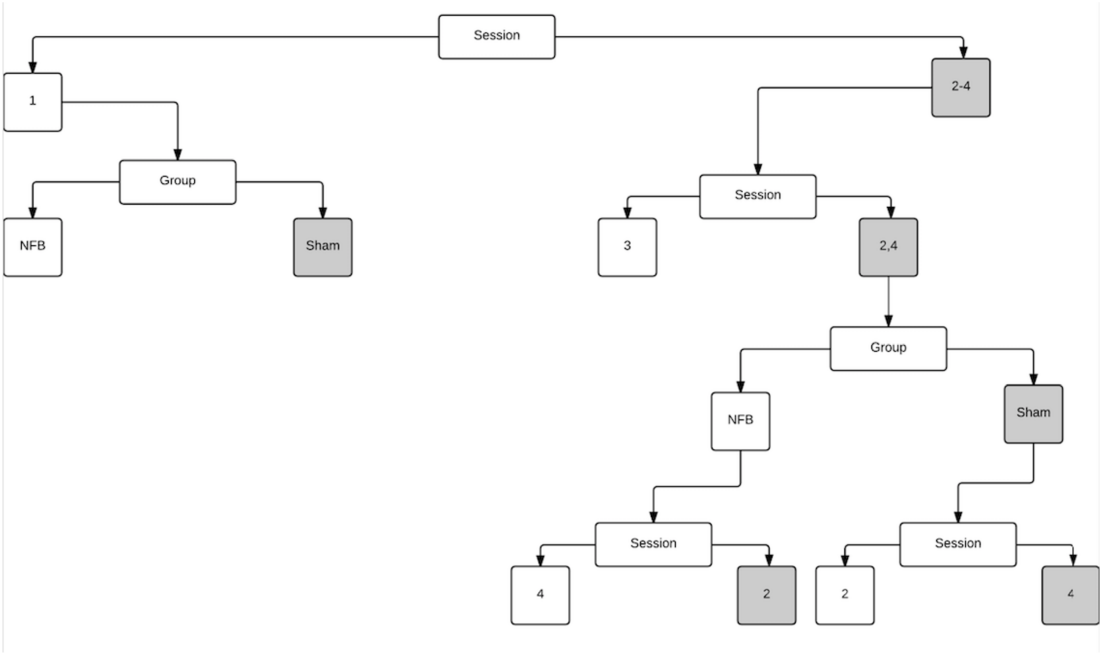

Figure 16 *CForest results from the ipsilateral (right) EEG sensors during the MI task. Splits to the right (gray squares emanating from the right of a significant effect) indicate the data partition with significantly lower mean ERD/ERS value (i.e., more sensorimotor activity), while splits to the left (white squares emanating from the left of a significant effect) indicate data partitions with significantly higher mean ERD/ERS values.*

5.5 Supplemental Results

5.5.1 II NFB Performance Results

The average difficulty level achieved by subjects in the NFB and sham groups for all 4 sessions (Figure 17) reveal a pattern similar to that of the EEG data in the contralateral hemisphere (Figure 8). The finding that subjects in the NFB group produced greater contralateral sensorimotor activity in sessions 3-4 is mirrored by the finding that these same subjects achieved the highest average difficulty levels in sessions 3-4. The notable exception to this is the fact that the NFB group achieved a higher difficulty level than the sham group

during session 1, despite producing significantly less contralateral sensorimotor activity during session 1.

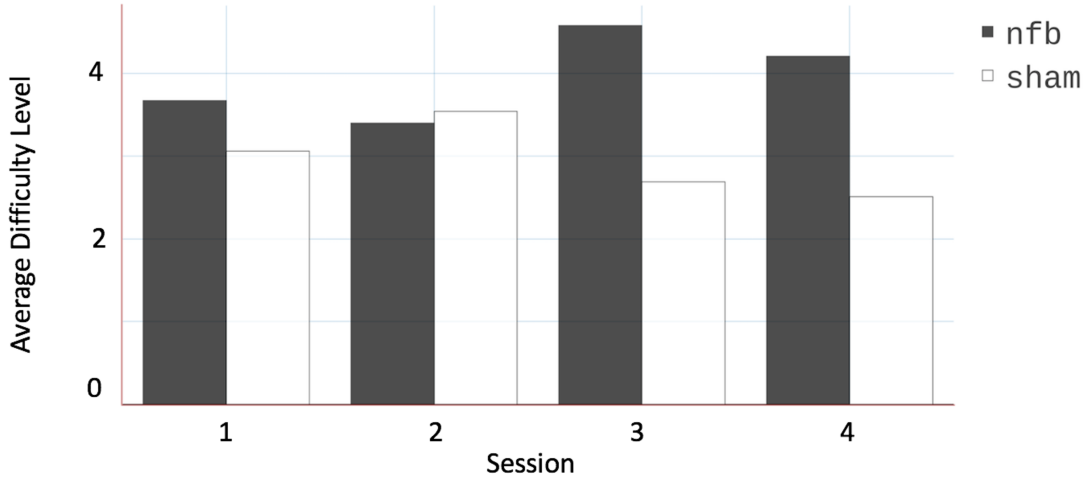

Figure 17 *The average difficulty level achieved by subjects in both the NFB and Sham groups are plotted. Note that there were two difficulty levels below 1 (i.e., 0 and -1).*

The differences between the average difficulty level achieved by each group were not measured in the CForest analysis, as the difficulty level encoded for each sham subject was the difficulty level that they were yoked to at that time. Moreover, it should be noted that since the primary purpose of the present study was to characterize the effect of II-NFB on sensorimotor activity, the difficulty level achieved (a proxy for this)

5.5.2 Beta Band Effects

Given that both alpha and beta ERD have been used as a proxy for sensorimotor activity in ME and MI[258-261], it is of note whether this II-NFB system, which utilized alpha ERD as a NFB metric, sees its effects using beta ERD as well. Exploring the CForest results for the contralateral beta ERD/ERS, we see identical results—decreased ERS in sessions 3-4. In

addition, in the ipsilateral hemisphere, we see the same null results found when exploring the CForest results for the alpha band.

Moreover, the transfer of NFB learning to subsequent MI seen in the alpha band (as discussed in section 4.4.1) was observed in the beta band as well. NFB subjects showed less contralateral ERD in sessions 1-2 compared with sham subjects, with this trend reversing in sessions 3-4. And finally, the null findings in the ipsilateral hemisphere (discussed in section 4.4.2) were also replicated in the beta band.

CHAPTER 6 DISCUSSION

The present work sought to determine the feasibility of providing NFB during II—specifically, to test subjects' ability to modulate sensorimotor cortex activity during the performance of II. Our results show that subjects receiving real NFB during II were able to learn to up-regulate contralateral sensorimotor cortex activity to a greater degree than subjects receiving sham NFB, and that this effect occurred over several experimental sessions. Moreover, this study showed that the learning that took place during II-NFB in the NFB group generalized to performance of a subsequent block of MI. Specifically, we observed a group by session effect, with increased contralateral sensorimotor cortex activity during subsequent MI in later (2-4) sessions in the NFB, but not the sham group. Given that the yoked-pairs of subjects in the NFB and sham groups were presented identical audio-visual stimuli throughout the II-NFB task, we conclude that the enhanced contralateral sensorimotor cortex activity seen in the NFB group during the II-NFB task as well as subsequent MI was a result of the provision of NFB. While previous studies have demonstrated that the provision of NFB allows individuals to modulate sensorimotor activity during MI[17,27-31], this study is the first to show NFB learning during II. Despite only achieving partial success, our findings suggest that II-NFB is feasible.

Moreover, the present work also ventured to test whether any effects of NFB learning generalized to subsequent MI. Since we found that NFB subjects demonstrated more sensorimotor activity during II-NFB compared to sham subjects during sessions 3-4, we would expect to find that subjects in the NFB group showed more sensorimotor activity

during MI during sessions 3-4. Our results showed that NFB subjects did indeed produce more contralateral sensorimotor activity during MI following II-NFB in sessions 2-4 (Figures 13-14), suggesting that the NFB learning effects imparted by provision of NFB generalized to MI of the motor task used for II. These findings, together with the limitations of the present study, and the future of NFB for mental simulation, will be discussed in detail in the following sections.

6.1 Contralateral Sensorimotor Activity is Increased with II-NFB Training

In line with the first objective of the present work, we hypothesized that subjects in the NFB group would demonstrate a lateralized pattern of brain activity, namely increased contralateral and decreased ipsilateral sensorimotor activation during II compared to the group receiving sham NFB. This hypothesis was partially confirmed, as subjects in the NFB group demonstrated greater sensorimotor activation in the contralateral hemisphere in sessions 3-4, but did not show a similar effect for down-regulation of (i.e., decreased) sensorimotor activity in the ipsilateral hemisphere.

6.1.1 Contralateral Sensorimotor NFB Effect

The finding that subjects in the NFB group produced more sensorimotor activity during sessions 3-4 than subjects in the sham group suggests that the provision of NFB during II is in fact feasible. As discussed in section 2.1.2, in order to regain the functions previously accomplished by the cortical region damaged in a stroke, the area surrounding an infarct must change, in a process akin to motor learning[27], in order to bring the pre-existing motor functions back into the behavioral repertoire of the patient. However, accomplishing the

motor learning necessary to bring about recovery is an uphill battle, as studies have shown that stroke patients produce less motor activity during ME and MI[262-264]. This depression of neural activity is caused by a combination of acute damage to motor regions[265]; an inhibition of the ipsilesional and disinhibition of the contralesional hemisphere[266,267], resulting from a reduction in inhibitory GABA-A[190,191]; changes in intracellular signaling[267,268], as well as a permanent reduction in cortical volume[269,270] resulting from the infarction.

This 'Catch 22', that the state of a patients' brain post-stroke makes the learning necessary for recovery more difficult than it would normally be, makes it critical that the scientific community leave no stone unturned to inventing new ways to allow patients to engage their motor system. While other researchers have investigated the feasibility of using noninvasive brain stimulation to produce more neural activity in the motor regions of the ipsilesional hemisphere[194,195], the present study sought to take a novel type of motor simulation technique (i.e., II) and test whether the provision of NFB allowed healthy controls to more effectively modulate sensorimotor activity over several sessions.

The finding of the present study, that healthy individuals performing II are able to produce more sensorimotor activity in the contralateral hemisphere due to the provision of multiple sessions of NFB has implications for the development of mental simulation therapy adjuncts in the future. Considering II has been shown to produce more motor cortex activity [10-13] and cortico-spinal excitability [6-9] than either MI or AO alone, the finding that II with NFB could enable healthy individuals to produce more contra-lateral sensorimotor activity

than a sham group, suggests that II-NFB could be used to allow stroke patients to produce ipsilesional activity to a greater degree than other mental simulation techniques.

6.1.2 Ipsilateral Sensorimotor NFB Effect Results

The inability to show a significant group by session effect for down-regulation of ipsilateral sensorimotor activity in the NFB compared to the sham group is the greatest shortcoming of the present study. As discussed in section 2.8, mIHI and its negative effect on motor recovery from stroke is well documented. For this reason, the ability to down-regulate ipsilateral (or in a clinical setting, contralesional) sensorimotor activity via II-NFB would have been a finding of great interest.

Instead, the Sham group appears to demonstrate the group differences we hypothesized for the NFB. However, given that the Sham group demonstrated this same pattern in the contralateral hemisphere (group by session effect for down-regulation in sessions 2-4), we interpret these results as a bilateral sensorimotor down-regulation over subsequent sessions.

In the NFB group, we found that the ipsilateral sensorimotor activity during NFB exhibited a similar group by session effect as the contralateral hemisphere—with more sensorimotor activity produced in sessions 3-4. This finding is the inverse of our hypothesis, and given the fact that NFB subjects were exposed to markedly more NFB where ipsilateral activity was not meaningfully factored into the NFB metric (discussed in detail below), our interpretation of these results are that the individuals in the NFB group were learning to upregulate sensorimotor activity bilaterally over the course of NFB training. This

interpretation is consistent with previous research showing a degree of bilateral sensorimotor activation even in unilateral tasks[100,271-275].

This shortcoming is not unprecedented in NFB studies involving the lateralization of sensorimotor activity. Several other studies attempting to utilize MI-NFB to show that healthy controls could lateralize sensorimotor brain activity found that subjects were successfully able to up-regulate contralateral sensorimotor activity, though were not able to down-regulate ipsilateral sensorimotor activity[15,276]. Moreover, while the number of neuroimaging studies on II is too small to draw from with authority, several of the initial neuroimaging studies on II[10-12] found that the motor regions associated with greater activity in the II versus the MI or AO condition, showed a largely bilateral profile. Given this finding, it is worth drawing attention to work using TMS that found no laterality effect during AO of a unilateral arm movement[100]. However, another study using a similar design, found similar laterality effects for AO, MI, and II of a unilateral arm movement.

Concretely, the reason for this null finding in the present study can likely be attributed to one of three explanations (or a combination of two or three of these factors):

1. The attentional demands of II-NFB are such that down-regulating ipsilateral sensorimotor activity is too difficult.
2. Four sessions simply did not provide enough training time in order to see a NFB that would have emerged if the present study had subjects participating in >4 sessions.

3. The way the calculation of the NFB metric changed to facilitate difficulty titration resulted in subjects not having enough exposure to difficulty levels where ipsilateral down-regulation was being factored into the NFB metric calculation.

6.1.2.1 Potential Explanation 1: Ipsilateral Down-regulation During II is Too Difficult

Previous studies have found that healthy subjects were successfully able to up-regulate contralateral sensorimotor activity, though not able to down-regulate ipsilateral sensorimotor activity[15], suggesting that learning to down-regulate one's ipsilateral sensorimotor activation through NFB is more difficult than to up-regulate one's contralateral sensorimotor activation. The most apparent reason for this is that down-regulating ipsilateral activity during II of a unilateral motor movement requires an individual to reverse the normal pattern of activation, that takes place during a unilateral motor task (i.e., even during a unilateral task, the ipsilateral sensorimotor cortex exhibits activation[223,259] albeit to a lesser degree than the contralateral hemisphere). Conversely, promoting an increase in contralateral sensorimotor activity during II simply requires an individual to amplify a natural neurophysiological response.

Moreover, it is possible that the complexity of the unilateral motor task used as the basis of the II-NFB system could also have affected the ability of subjects' in the NFB group to inhibit ipsilateral sensorimotor activity, as complex movements, with more degrees of freedom, have been shown to elicit a more bilateral sensorimotor response-pattern than simple movements[277,278]. The use of short, simple, unilateral tasks is the norm in MI NFB

studies. For example, previous work in our lab[14]—where MI-NFB was shown to result in significantly more lateralized sensorimotor activity than MI with no NFB—used MI of a unilateral button pressing task.

6.1.2.2 Potential Explanation 2: >4 sessions required to demonstrate II-NFB learning for ipsilateral down-regulation

The number of sessions required in order to demonstrate successful NFB learning varies widely, given the considerable variability that exists between all NFB systems as well as the experimental protocols designed to test them. While several studies have shown NFB learning in a single session[16,150],[81], often >1 session of NFB training is required. While some NFB experiments have found that >4 sessions of NFB training is required in order to demonstrate NFB learning[276,279] (for a review see[175]) it is difficult to prescribe the exact number of sessions required to achieve NFB learning. A previous NFB study in our lab[14] showed NFB learning in session 3, the same session in which the current study showed NFB learning. While there are several differences between the present study and this past study by our lab (e.g., the previous study used MI, and the feedback was primarily utilized during rest intervals; the feedback signal was taken from a MEG source location acquired using median nerve stimulation), the NFB metric used is quite similar (despite the previous studies use of beta in lieu of alpha, as discussed in section 4.5.2, we found that these frequencies were modulated by NFB in an analogous fashion).

6.1.2.3 Potential Explanation 3: Design of NFB Difficulty Titration

In the present study the average difficulty level of subjects in the NFB group was 3.97, a difficulty level at which the contribution of ipsilateral down-regulation to the calculation of the NFB metric was not factored into the NFB metric calculation. For comparison, the contralateral up-regulation was the sole factor in determining the NFB metric at difficulty levels 1-4, meaning subjects in the NFB group were training the down-regulation of ipsilateral sensorimotor activity to a much lesser degree than the up-regulation of contralateral sensorimotor activity.

While not directly testable using data from the present study, the finding that the average difficulty level for NFB subjects contained no contribution from the ipsilateral hemisphere, suggests that the difficulty titration method used was in fact the reason for the lack of ipsilateral down-regulation in the NFB group.

6.2 NFB Learning Transfers to Subsequent MI

Our second hypothesis was that the NFB learning effects seen (Hypothesis 1) would generalize to MI (without NFB) performed subsequent to II-NFB training. Our results confirm this hypothesis, as the significant increase in contralateral sensorimotor activity seen during II-NFB in sessions 3-4 was also seen during subsequent MI performed without NFB. This finding, that individuals who learn to modulate brain activity through neurofeedback during mental simulation, show a transfer of this NFB learning to subsequent MI performed without NFB, replicates MI-based NFB studies that have shown successful transfer of MI-

NFB learning to subsequent MI[210,276]. This finding has two interesting implications for the implementation of NFB into mental simulation therapy for stroke recovery.

The first is simply that it buttresses the argument for integrating NFB into mental simulation therapy. Regardless of how user-friendly and portable any future consumer-grade neuroimaging device may be, a patient with personal access to NFB hardware and software (be it for use with MI or II) will undoubtedly perform MI without NFB in addition to their use of the NFB device, simply because of the seamless barrier between performing MI and everyday life. While MI without NFB has its pitfalls (discussed in detail in section 2.5), its principle advantage is that it can be performed anywhere, anytime. No matter how enamored a patient may be with their NFB device and software, there will be moments when it just makes sense to perform stand-alone MI. Be it on a short bus ride, while stuck in a line at a coffee shop, or during countless other short everyday intervals, there is no doubt that the provision of effective and user-friendly NFB will not mean that stand-alone MI becomes an extinct practice. Thus, our finding that II-NFB learning transfers to subsequent MI would be of note if II-NFB were to be implemented clinically. The transfer of NFB learning from II-NFB to MI could be used to encourage patients to engage in MI over and above the use of any prescribed II-NFB therapy. Specifically, the sense of reward patients' experience as they improve their performance on the NFB system may not only encourage them to continually engage in more MI- or II-based NFB—moreover, the knowledge that this improvement is generalizing to stand-alone MI may empower them to take the opportunities afforded them to perform stand-alone MI in addition to their MI- or II-based NFB as much as possible.

Secondly, this finding is encouraging in that it suggests that II-NFB training may also lead to a transfer to ME as well. Previous studies have shown that both MI and AO performed prior to ME result in greater activity from regions of the motor network during ME[83,84]. Moreover, it is thought that the ability of MI and AO to elicit changes in functional activation in subsequent ME is likely a critical reason why these motor simulation therapies have utility in neurorehabiltation[280,281], and this is in line with the theory that MI, AO, are both simulations of ME[88,89]. If II represents another type of motor simulation (as argued in section 2.5.2), we would expect any NFB learning that takes place during II-NFB training to transfer to subsequent MI and ME.

While at the moment we do not have any direct evidence that the NFB learning that took place in the present study would transfer to ME, the finding that it transferred to MI is an encouraging sign that a similar transfer to ME may also take place.

6.3 Limitations

In addition to the limitations discussed above, there are several other limitations to the present study that need to be addressed.

6.3.1 Wide Alpha-band

In the present study, sensorimotor activation was operationalized as a decrease in event-related power in the alpha band—specifically between 7.5-14.5 Hz. In its original conception, the II-NFB system presented here was to measure event-related power decreases in the beta band (15-30 Hz). Unfortunately during data collection a mistake was uncovered in the MATLAB script used to calculate the NFB metric—rather than calculating power in the beta

band, power in the alpha band was being calculated and used as the basis for the NFB metric instead. The primary author takes full responsibility for this mistake.

As discussed in section 5.4.2, power decreases in the alpha band have been used almost interchangeably with the beta band as a proxy for sensorimotor activation. Moreover, given the prominence of power decreases in the alpha band during AO[282], and the critical involvement of AO to the II-NFB system presented here, as well as the fact that the alpha and beta bands were modulated in tandem (discussed in section 5.4.2) this unfortunate accident does not dramatically affect the interpretation of the results.

However, if the alpha band had been selected apriori as the frequency band of interest for NFB metric calculation, it is likely a specific sub-component of the alpha band would have been used. Specifically, the sensorimotor rhythm[283] (12-15 Hz) or mu[218,284,285] (7-12.5) band would likely have been the best possible sub-components of the alpha band to use for NFB metric calculation. With that acknowledged, given that the present study did not include whole-head neuroimaging, it is unlikely that the lack of specificity associated with the use of the whole alpha band precluded us from answering any mechanistic questions (regarding the neural correlates underlying NFB learning in this particular study) we otherwise would have been able to address if either the sensorimotor rhythm or mu band had been used in isolation.

6.3.2 Visual Alpha During Rest Block

Furthermore, re-referencing to the bilateral mastoid electrodes may have increased the alpha power present in our reference signal. Given that the offline analysis conducted used alpha power during the preceding rest block as a baseline, it is a limitation of the present

study that the experimenter did not scrupulously investigate whether the sensors' detection of alpha ERD/S were affected by the increase in alpha power that has been documented to take place over the occipital lobe during visual attention[271,286].

6.3.3 Control Group

In order to determine whether the II-NFB system tested in the present study resulted in a pattern of sensorimotor activity distinct from II without NFB, a control group presented with yoked feedback was utilized. This type of control group was selected because it most closely resembles the NFB group used—the interactivity of the NFB task is simulated, and the audio-visual stimuli delivered to both groups is identical, making the claim that any differences between the groups was due to the provision of NFB as experimentally sound as possible.

However, since the purpose of the present work was to determine if the addition of NFB to II allowed healthy controls to more effectively modulate sensorimotor activity, it would have been optimal to include a third group that engaged in II without NFB. While a comparison between a NFB group and a group that engaged in II without NFB would invite its own distinct criticisms (i.e., the motivation and reward felt by participants in the NFB group would be entirely lacking from the group receiving no NFB), future work comparing the pattern of sensorimotor activity of subjects engaging in II with those engaging in II-NFB would be of great interest for the greater goal of validating II-NFB as a tool worthy of clinical testing for stroke rehabilitation.

6.4 Methodological Strengths

Despite the limitations discussed in the previous section, the present study possesses several noteworthy methodological strengths. The use of an active control, where the NFB and sham groups were exposed to indistinguishable audio-visual stimuli, is critical in order to determine that NFB itself is the crucial factor responsible for any between-group differences in sensorimotor activation in response to II-NFB training.

In addition, the use of strict EMG rejection criteria, both online and offline, is important to differentiate NFB learning associated with motor simulation from NFB learning associated with motor system activation generally.

And lastly, the design of the NFB system was undertaken with an eye on the potential to translate any possible findings to a real-world setting. Thus the present study endeavored to marry NFB mechanics and interface design with carefully considered user experience (UX) elements (e.g., attempting to reduce frustration through gradual onboarding, and striving to drive user motivation through titrating difficulty and simple feedback regarding the users overall progress). The marriage between NFB mechanics and interface design in the present study represents an emphasis on UX (a phrase curiously absent from the NFB literature) that is uncommon in the NFB literature.

6.5 Future Directions

6.5.1 *Immediate Future Work*

The most pressing immediate issue to resolve is the question of why the II-NFB system presented here did not allow subjects in the NFB group to down-regulate ipsilateral sensorimotor activity to a greater degree than sham subjects. As discussed in section 6.4.1, there are three potential reasons for this finding. However, the most likely reason for this shortcoming is that the NFB group spent a majority of their time engaging in II-NFB with ipsilateral sensorimotor activity not factored into the NFB metric at all. Therefore, the most pressing follow up to the current study would be determining if subjects can learn to down-regulate ipsilateral sensorimotor activity within 4 sessions, if the NFB metric factors in contralateral and ipsilateral hemisphere sensorimotor activity equally regardless of difficulty level. To this end, a third experimental group is currently being collected where the NFB metric—for all difficulty levels—is determined equally by the increase and decrease of sensorimotor activity in the contralateral and ipsilateral hemispheres respectively.

Beyond the collection of a third group, where the feedback at all difficulty levels is a product of bilateral sensorimotor activity, there are two other potentially fruitful areas of study that may be undertaken. *The first* is experimenting with alternative video delivery methods. While the group by session effect seen in the contralateral hemisphere for the II-NFB and MI tasks suggests that II-NFB is feasible, the fact that no average ERD/ERS value was in the ERD range (i.e., log2 of <0) may reflect the fact that subjects found it difficult to produce contralateral ERD for the duration of the video length (50s). A NFB interface where

the handshake is presented either one shake at a time (i.e., 7s videos), or one component at a time (i.e., ~1-2s videos) may result in more contralateral ERD. *The second* potential follow up, as noted above, would be to parse the effect of each individual UX design element (e.g., the inclusion of sound effects, of a feedback screen during rest blocks) on NFB learning.

6.5.2 *Towards a 'Digital Physiotherapy'*

As mentioned earlier, the present study included several UX design elements that limited experimental control over the variables of the NFB system. These design elements were included in the hope that they would make the NFB system more user-friendly, and thus enhance NFB learning. While there is no tangible, quantitative benefit of these choices to point to at the present moment, it is worth pointing out that the possibility space of NFB system design in the peer-reviewed sphere tends to limit itself to very simple systems (e.g., the manipulation of a single shape or tone); and while there are good reasons to use these simplistic interfaces (i.e., the affordance of precise experimental control over potentially confounding variables introduced by more complex UX elements), considering the large upper bound on the distribution/impact of NFB systems (in a world of increasingly-common consumer grade neuroimaging devices[206,207]), it is unlikely that the full potential of NFB technology exclusively involve perfecting simplistic-yet-controlled NFB systems within the confines of laboratories. While there are currently many NFB video games on the market[287], to date there are no examples of an attempt to test these games within the scientific community's peer-review system.

While the NFB system utilized in the present work is far from a video game, the emphasis placed on UX design represents at least a small step towards a future where a full exploration of the possibility space of NFB system design is conducted within the peer-reviewed system. The present study's emphasis on UX—while admittedly primitive relative to the commercial cutting-edge—is a notable demarcation from previous NFB studies where this factor is rarely mentioned. Academic researchers have been designing NFB systems—virtually in isolation of each other's design philosophies—for a relatively short period of time in comparison with commercial digital interactive system (video game) designers, who have been designing in a unified community for decades[288]. If NFB is ever to enter the clinical mainstream as a useful way to amplify the benefits of mental simulation therapy, the research community would be wise to (A) begin to factor UX elements into their experimental design, (B) share the details of the UX designs in their (ideally open-source) publications, and potentially (C) glean 'tricks of the trade' from the cutting-edge of video-game design.

6.6 Conclusion

The present work endeavored to achieve proof-of-concept in integrating NFB with II to allow healthy controls to lateralize sensorimotor activity, while emphasizing UX design, and aspiring to create an intuitive and user-friendly interface. Our findings, that healthy controls showed enhanced up-regulation of contralateral sensorimotor activation in sessions 3-4, represents a partial success, given that the corresponding lateralization results in the ipsilateral hemisphere (i.e., enhanced down-regulation) was not seen. Given this partial

success, subsequent studies are still needed to determine whether healthy controls are able to learn to lateralize sensorimotor activity via NFB during II. Specifically, it would be interesting to see if NFB subjects learn to lateralize brain activity if activity of the ipsilateral and contralateral activity contributed equally to the NFB metric throughout the during of the II-NFB training.

The present work also shows that this NFB learning, of enhanced up-regulation of contralateral sensorimotor activity in sessions 3-4, transferred to subsequent MI. This replicates previous studies utilizing MI-NFB systems[210,211], and bodes well for the potential of II-NFB for clinical application in motor recovery from stroke—though of course, at the moment the clinical utility of II-NFB remains undetermined.

However, for the time being, the present work suggests that integrating NFB with II is feasible. Further work is required to determine why the present study only achieved partial success in allowing healthy controls using NFB to modulate sensorimotor activity during II to a greater degree than those receiving sham NFB.

This first attempt at integrating NFB with II could provide a useful stepping-stone for others hoping to perfect this NFB modality for motor rehabilitation from stroke.

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Appendix I: Audio-Visual Script Presented Prior to Day One's Neurofeedback Session

During this study you are going to be imagining that you are doing a handshake that you will be simultaneously watching on the screen. This is called 'imagined imitation', and there will be alternating blocks of imagined imitation and rest.

The imagined imitation blocks will consist of a repeating video of the handshake. The amount of colour in the video is based on how well you are imagining doing the handshake yourself. At the beginning of each block the video will be black-and-white, but if your imagery is good, the video will gradually turn to full colour.

Here what the handshake looks like. *[16 second video plays—ie, 2 handshakes]*

After each imagined imitation block, your performance will be evaluated: if you did well (if the screen was colourful most of the time), you will move up a difficulty level. If you do poorly, you will move down a level. You will hear a sound at the beginning of each rest block if you moved up or down a level.

[Picture of graph onscreen] Here is a picture of the graph showing the results of the first two blocks of imagined imitation. In this instance, the participant first moved up to difficulty level two, and then in the next session dropped down to difficulty level one.

At the beginning of each day you will start at difficulty level one. If you remain at level one for several blocks, there are two easier difficulty levels below one to help you get a feel for the system.

While watching the videos and imagining, try to think about the sensations associated with all the movements. The tightening of your fingers into a fist, the snug feeling of having your hand lightly squeezed, or the feeling of hands clapping together. You also might want to pay attention to the timing of the shake—how one movement flows into another, and ***how it would feel*** to be doing this handshake yourself.

Feel free to use any strategy you like, however please do continue to stay concentrated on the handshake during imagined imitation blocks. And while imagining please try to keep your arms as still and relaxed as possible—if your muscles become tense, the video color settings will be automatically reset to black-and-white.

The first rest period is 20 seconds and will be used as a baseline of brain and muscle activity. During this block please stare at the fixation cross and count down from 100 by 3s in your head (eg, 100, 97, 94, …) while keeping your arms as relaxed as possible on the pillow.

Do you have any questions before we get started?

Appendix II: Standardized Responses to Participant Questions

Q – I'm imagining the handshake but it's not going into colour—are you sure the system is working?

Part of my responsibility is to watch the neurofeedback system to make sure it's working. Rest assured I will let you know if anything goes work at any time.

Q – I'm imagining the handshake but it's not going into colour—how can I make it go to colour?

Neurofeedback is a unique skill that can sometimes take time to learn. I'm sorry I'm not supposed to give any more advice than that.

Q – Is there a sham or placebo condition in the experiment?

I'm sorry I'm not allowed to discuss anything about the experimental design.

Q – What are the rules about what strategies I can use to try and make the screen go to colour?

You are supposed to keep your eyes on the video and actively imagine the handshake on the screen. Beyond that, you can utilize any strategy you like.