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Date: 12th January 2021

# The underlying neural mechanisms of Neurofeedback

University: Birkbeck, University of London

Programme: Master of Science, Cognition and Computation

Module: MSc Research Dissertation, PSYC078D7

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# The underlying neural mechanisms of Neurofeedback

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**Abstract**

Neurofeedback offers a non-invasive approach to treat psychiatric disorders such as depression, AD/HD, autism and epilepsy. It also has been studied amongst healthy individuals to enhance performance in cognitive areas such as attention, working memory, rational thinking, creativity, musical performance and general well-being. However, although some accounts have been done at a theoretical level on the brain areas involved in successful regulating brain dynamics via Neurofeedback, how the different brain regions interact at a neural level during Neurofeedback is still not fully understood. This work addressed this question and explored the underlying brain mechanisms behind successful Neurofeedback. To do so, we have investigated the neural mechanisms via a computational model using a dataset from a Neurofeedback study done by Davelaar and Jilek (2020). The computational model implemented is a mean-field model of cortico-thalamic electrodynamics. We have applied the model to the EEG phenomena of 15 participants that received Neurofeedback training to upregulate sensorimotor rhythm (SMR). We have seen evidence for the role played by the intra-thalamic loop responsible to promote inhibition via GABA inhibitory projections from the thalamic reticular nucleus (TRN) to the ventrobasal thalamus (secondary relay nuclei) in suppressing sensorimotor input to the cortex and in producing SMR bursts. This, together with less excitatory projections being sent from the cortex to the relay nuclei of the thalamus (SRN), seems to be key for successful SMR regulation.

Keywords: Neurofeedback neural mechanisms, mean-field cortico-thalamic model

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**List of acronyms**

AD/HD: Attention deficit hyperactivity disorder

A/T: Alpha/Theta training protocol

EEG: Electroencephalogram

FIR: Finite impulse response

fMRI: Functional magnetic resonance imaging

GABA: Gamma-Aminobutyric acid

ICA: Independent Component Analysis

QEEG: Quantitative electroencephalogram

MLE: Maximum likelihood

NFB: Neurofeedback

NFT: Neurofeedback training

NIRS: Near-infrared spectroscopy

SMR: Sensorimotor rhythm

SNR: Secondary relay nuclei of the Thalamus

TRN: Thalamic reticular nucleus

# 1. Introduction

The control over brain dynamics is an exciting field, with its roots dating back to the 1940's with the work of Jasper and Shagass (1941a) demonstrating the possibility of the human alpha brainwave oscillation (8-12Hz) to be modulated through conditioning. These authors ran several studies successfully demonstrating classical Pavlovian conditioning effects when applied to alpha blocking in the human electroencephalogram (EEG; Jasper & Shagass, 1941a, 1941b; Shagass, 1942; Shagass & Johnson, 1943).

The 1960's saw the proliferation of studies paving the way to start adopting these techniques and their benefits in a clinical context. One of the first studies was conducted by Sterman (Sterman, 1970; Wyrwicka & Sterman, 1968) demonstrating that the sensorimotor rhythm (SMR) could be upregulated in the cat via operant conditioning. Sterman (1970) demonstrated that training this brain wave in the cat would result in increased sleep spindles and in the reduction of motor movement.

Since then, the field has grown, and is currently referred to as Neurofeedback. Neurofeedback has been studied predominantly in a clinical setting to treat certain psychiatric conditions, being the first scientific research of electroencephalogram (EEG) clinical operant conditioning done by Sterman in 1972 to treat epilepsy using the SMR protocol (Sterman & Friar, 1972; Sterman, 2000). More on the SMR protocol specifically will be discussed in section 1.1.1.

## 1.1. Neurofeedback

Neurofeedback (NFB) is the process of learning how to gain voluntary control over one's brain dynamics via real-time feedback of a specific neural state (Berger & Davelaar, 2018; Davelaar, 2018; Egner & Gruzelier, 2001; Peeters et al., 2014). During the training sessions, feedback is given to the trainee via an auditory, visual or gamified stimulus when the target frequency is above or below a threshold level, which is determined following a

baseline measurement (Davelaar, 2017). Although several forms of Neurofeedback exist, e.g., EEG, real-time fMRI, NIRS (Gruzelier et al., 2014), the most widely used form continues to be electroencephalography (EEG) Neurofeedback (Coben et al., 2010).

NFB learning leverages principles of operant conditioning, where certain brain states are reinforced or suppressed to the trainee via positive or negative feedback (Birbaumer et al., 2013). Within EEG NFB, the overall objective is to enhance poor brain wave rhythms (Coben et al., 2010).

The Neurofeedback literature lists several examples of successfully using this approach as a non-invasive treatment in psychiatry as an alternative to drugs. The most frequent NFB clinical uses have been in treating depression (Linden et al., 2012), attention deficit disorder (Arns et al., 2014; Lévesque et al., 2006; Lubar & Lubar, 1984), autism (Coben et al., 2010) and epilepsy (Sterman & Friar, 1972; Tan et al., 2009).

More recently, research efforts have focused on understanding the role of Neurofeedback in boosting cognitive performance amongst healthy participants (Berger & Davelaar, 2018; Gruzelier, 2014). Neurofeedback in this context has been used to enhance cognition in areas such as attention (Egner & Gruzelier, 2001; Vernon et al., 2003), rational thinking (Davelaar & Jilek, 2020), creativity (Gruzelier, 2014b), musical performance (Egner & Gruzelier, 2003; Gruzelier et al., 2014; Gruzelier, 2014b) and general well-being (Gruzelier, 2014c; Peeters et al., 2014).

### 1.1.1. Neurofeedback protocols

Most of the current Neurofeedback protocols used have their origins in a clinical setting. Two of the most widely used protocols are a) training to increase the amplitude of the sensorimotor rhythm (SMR) whilst supressing other frequency bands (Davelaar & Jilek, 2020; Gruzelier et al., 2014) and b) raising the Theta-Alpha (A/T) crossover (Gruzelier, 2009; Gruzelier, 2014a). More NFB protocols exist but for the purpose of this review and as a way

to provide background to Neurofeedback, a brief discussion will be provided on the two most widely used, SMR and Theta-Alpha crossover.

The SMR is in the range of 11-15Hz and has been widely studied in clinical settings and in animal studies. The standard SMR training protocol involves upregulating its spectral amplitude, whilst supressing other brain waves in the EEG spectrum (Davelaar & Jilek, 2020; Gruzelier, 2014a).

Sterman and Friar (1972) studied this frequency in animals and humans and found SMR to be present in the central sulcus and blocked when subjects were engaged in motor or sensory activities (Mann et al., 1996). They also demonstrated its benefits in a clinical setting with patients suffering from epilepsy, where successfully upregulating their SMR frequency range via operant conditioning helped these patients in suppressing seizures as well as in regulating sleep cycles.

Because SMR is associated with the inhibition of somatosensory stimuli to the cortex, it is believed to be also linked with improvements in areas such as attention, performance and other cognitive functions (Davelaar & Jilek, 2020).

In the case of healthy individuals, SMR upregulation has shown positive results in enhancing performance in complex tasks. In a NFB study conducted by Ros et al. (2009) amongst trainee ophthalmic microsurgeons performing a cataract operations in a simulated environment, training the SMR proved to significantly improve both surgical technique and surgery time. Surgical technique was measured by a suture task in the cornea which had an improvement of four percentage points from 80% before NFB training to 84% after training. Furthermore, participants showed a reduction of 26% in overall surgery time. This study demonstrated regulating SMR enhances attention and contributed to task performance improvements.

Vernon et al. (2003) demonstrated that SMR is believed to contribute to improvements in semantic working memory. In their study, participants who were successful in upregulating SMR had higher recall levels in the conceptual span task which involved recalling a set of words belonging to specific categories. Participants in the SMR group displayed higher recall scores suggesting working memory was improved via regulating SMR.

Clinical studies have also demonstrated that raising the amplitude of Theta over Alpha would have benefits in treating patients with addiction. Peniston and Kulkosky (1989,1990) were the first to demonstrate the efficacy of Theta-Alpha training in the case of alcoholics (Gruzelier, 2014a). Amongst this community those that went through training and showed an increased percentage of alpha and theta brainwaves versus control group, had fewer symptoms of anxiety and depression (Saxby & Peniston, 1995).

In one of the first Theta-Alpha (A/T) studies done outside of a clinical context (Egner & Gruzelier, 2003), NFB has been successful in helping conservatoire musicians in improving their performance. This study trained music students in several NFB protocols and tested their performance on a 15-minute piece assessed by a panel of music experts. Out of the NFB protocols students were trained, the A/T protocol was the one contributing to a better performance specifically on measures of accuracy, musical understanding, interpretation and overall quality of performance. In a subsequent study amongst 11-year old school children, Gruzelier et al. (2014) confirmed A/T had benefits in both improving musical technique and communication amongst children.

Beyond the above examples of application in healthy participants, interventions in dance (Gruzelier, 2009), acting and creativity (Gruzelier, 2014b) have been found to produce effective results when using the A/T protocol.

### 1.1.2. The neural mechanism of Neurofeedback

Sterman and Friar (1972) and Wyrwicka and Sterman (1968) argued that the SMR rhythm originates within neurons in the ventrobasal thalamus through inhibition of somatosensory inputs within a thalamo-cortical inhibitory discharge communication network. These authors extensively studied this rhythm in cats. Through operant conditioning, cats learned to produce SMR bursts by standing still and inhibit motor movement (Egner & Sterman, 2006). After receiving a food reward, the cats would return to adopt the posture that produced the increase in SMR.

The authors advanced that when connections between the ventrobasal thalamus and sensorimotor cortex are impaired, this synchronised rhythm in sensorimotor cortex disappears (Egner & Sterman, 2006; Sterman, 2000; Wyrwicka & Sterman, 1968). Sterman (1996, 2000) defends that SMR EEG dynamics are relayed to the sensorimotor cortex via the thalamic somatosensory relay nuclei (ventrobasal thalamus) when these cells are hyperpolarised, i.e., when their resting state potential is increased. Neurons in the ventrobasal thalamus when hyperpolarised show a different behaviour from their typical inhibition state. This makes it more difficult for the cell to depolarise as the threshold for depolarisation increases. A slower depolarisation in this instance is mediated by a slow calcium influx to ventrobasal neurons leading to a sodium spike that originates a unique synchronised rhythm when discharging (Egner & Sterman, 2006; Mann et al., 1996; Sterman, 1996; Wyrwicka & Sterman, 1968).

The bursts of this discharge go simultaneously to the cortex and to the thalamic reticular nucleus (TRN). When the TRN cells are excited by this discharge, they respond in a synchronous rhythm, communicating again with the ventrobasal thalamus and release the inhibitory GABA neurotransmitter to the relay cells of the thalamus (Egner & Sterman, 2006; Wyrwicka & Sterman, 1968). This causes hyperpolarisation again in the thalamic somatosensory relay nuclei (ventro-basal thalamus) and the same cycle is reinforced. When

the ventrobasal thalamus becomes hyperpolarised, the discharged EEG rhythms appear in the sensorimotor cortex (Egner & Sterman, 2006; Wyrwicka & Sterman, 1968) and afferent excitatory input from sensory motor cortex is reduced.

Other accounts in the literature complement the above view on the Neurofeedback mechanisms involved in conditioning brain frequencies. For example, Birbaumer et al. (2013) postulated that Neurofeedback is driven by implicit learning with a predominant role of the basal ganglia in a close loop with the frontal cortex. The authors argued in favour of an unconscious learning process, mainly driven by procedural learning.

The literature indeed corroborates that learning new physical skills involves changes at the sub-cortical level, especially in the striatum, an area of the basal ganglia (Jenkins et al, 1994; Doyon et al., 1996). This has been shown to be true for procedural learning, in activities such as learning how to ride a bicycle. Yin et al. (2009) conducted one of the first studies to look into this specific pathway in mice and concluded that long term plasticity in the acquisition and consolidation of new skills occurs in the striatum. Koralek et al. (2012) looked into whether the cortico-striatal circuit would also apply when learning new abstract skills, i.e., skills not involving motor learning and procedural memory. They validated this hypothesis by showing that mice could modulate neural activity in M1 even when not executing any motor movement. They demonstrated that the striatum-cortical circuit was key in enabling this learning. The authors also argued that disruption to this circuit plasticity would disrupt learning.

Brickwedde et al. (2019) undertook a Neurofeedback study on up-regulating and down-regulating alpha power and linked higher alpha power to enhanced learning. The authors argue that higher alpha power helps with focused attention and this in turn can be modulated by Neurofeedback training. They argue that higher alpha levels involve greater inhibition of irrelevant information to the cortex, helping information processing. The authors

suggest that the neural mechanisms underlying the regulation of the human alpha brainwave oscillation can be compared to the ones involved in the SMR rhythm in cats explained by Sterman (1996), where a thalamocortical loop involving GABA inhibition promotes the SMR rhythm in the sensorimotor cortex. The authors defend that intracortical inhibition is key to control learning.

Hinterberger et al. (2005) also stressed the important role of sub-cortical areas such as the basal ganglia, thalamus, anterior putamen/pallidium with inhibitory functions in learning how to regulate slow cortical potentials that allow to control brain-computer interfaces. In their experiment, participants were trained to achieve self-regulation of slow cortical potentials and their EEG was recorded via fMRI. Successful self-regulation of slow cortical potentials was linked to the cortico-basal ganglia-thalamic circuit.

In a study by Halder et al. (2011), where participants were instructed to mentally perform a specific motor movement as well as observe some movements, those with a higher success in mental motor imagery had a higher SMR amplitude at rest. This reinforces the thalamocortical inhibition pathway of motor and sensory inputs in enabling skill learning as well as the role of the cortico-striatal loop (Birbaumer et al., 1990, 2013; Hinterberger et al., 2005; Koralek et al., 2012).

On SMR specific rhythms, Egner and Sterman (2006), argue that beyond the traditional thalamocortical loop described in the literature, changes at the striatum are key in modulating the SMR frequency in humans. Lévesque et al. (2006) in their SMR Neurofeedback study on children suffering from attention deficit disorder (AD/HD) came to the same conclusion. In this study, children suffering from AD/HD were scanned using fMRI while performing a Counting Stroop task one week before and one week after NFB training. This study confirmed that the striatum of these children showed significant increases in activity when the SMR rhythm occurred.

It is known that the putamen (part of the striatum) receives its main input from the sensorimotor cortex, and in turn exerts inhibition to the global pallidus (Egner & Sterman, 2006; Lévesque et al., 2006). The globus pallidus modulates the activity of the ventral thalamus, which closes the loop to the sensorimotor cortex. When the global pallidus is excited, it will exert inhibition on the motor and premotor cortex via the ventral thalamus. This is a loop that further enhances inhibition via the thalamus to and from the sensorimotor cortex.

A new theory from Davelaar (2018) suggests a multi-stage framework underpinning EEG brain NFB training. This theory brings together several of the previous elements discussed. The theory specifically addresses the role of the striatum and the thalamus in successfully controlling brain dynamics. At a first stage, Davelaar (2018) advocates the importance of the frontal cortex in defining goals and a number of behaviours/strategies to achieve a specific brain state. In this stage, a close link exists between the frontal cortex and the striatum through a feedback loop between the goal and the reward achieved (a positive reward reinforcing the specific strategy). The focus of the learning at this stage is in the frontal-striatal connectivity, here the striatum explores the positive rewards and reinforces the behaviour.

When this loop is driven mainly by positive feedback, reinforcement learning occurs, and a consolidation phase materialises in a Hebbian like learning rule between the striatum and the thalamus. This second stage of the model is one of neural plasticity between the striatum and the thalamus promoting stabilisation of the frontal representation that elicits a positive feedback. The last stage of the model involves being aware of the distinctiveness of the bodily subjective experiences that originates a specific brain state (i.e., feeling relaxed) and have this as a second reinforcer for the synaptic changes occurring between the striatum, thalamus and cortex.

In summary, the reported studies reveal a critical role for the thalamus, cortical structures and striatum in Neurofeedback learning and successful regulation of brain dynamics.

### 1.2. Research question

Although there is increasing evidence for the role of Neurofeedback in treating psychiatric conditions as well as in boosting cognitive performance, critics abound in the literature for its efficacy. Arguments have been focused on small sample sizes of studies (Gruzelier, 2014c), lack of standardised method to report the results (Davelaar, 2018; Gruzelier, 2014c; Tan et al., 2009), difference in NFB protocols implementation (Davelaar & Jilek, 2020; Tan et al., 2009), incoherence of threshold settings for positive or negative reinforcement, failure of some participants to achieve regulation (Sitaram et al., 2017) and variance in duration of NFB sessions to treat similar disorders (Gruzelier, 2014c; Sitaram et al., 2017).

Moreover, in spite of the brain areas involved in Neurofeedback to be known at a theoretical level, how the different brain regions interact at neural level to promote feedback-based learning is still not fully understood (Davelaar, 2018; Davelaar et al., 2018; Robinson et al., 2003, 2004). In order to address some of the above challenges of Neurofeedback, one field that can help in offering explanations for what is happening at a neurophysiological level as a result of Neurofeedback training is computational neuroscience.

Neurofeedback is still in early days from a clinical perspective. A new initiative from the European Commission, BRAINTRAIN, offers potential for larger scale trials and standardised procedures for the mapping of brain networks that could be targeted by Neurofeedback in clinical settings (Sitaram et al., 2017). With the challenges posed by Covid-19 during 2020 in terms of mental health, advances in understanding how EEG

Neurofeedback works at a neural level are key in as far as this form of treatment offers a non-invasive method to boost cognition and treating mental disorders.

Therefore, the research question we aim to explore is: **What are the Neurophysiological changes underlying successful Neurofeedback?**

The focus here is specifically on this paradigm, i.e., investigating the neural mechanisms behind successful Neurofeedback via a computational model, with the aim to further advance the theory and offer explanations for what is happening at a neural level when learning to modulate a specific EEG frequency. Our view is that by further explaining some of the changes occurring at a neural level, insights can then be then translated into a clinical setting.

To achieve our objective, the focus will be on applying a computational model to EEG Neurofeedback experimental data to understand the neurophysiology behind successful Neurofeedback learning. The dataset to be used will allow to explore the neural mechanisms involved when upregulating the SMR rhythm. Given that this is one of the most studied and used Neurofeedback protocols (Davelaar & Jilek, 2020; Gruzelier, 2014a), we believe exploring this circuit via computational neuroscience offers opportunities for further advances in the field.

## 2. Mean-field corticothalamic model

The computational model used to explore the underlying neural mechanisms of Neurofeedback, is a mean-field model of cortico-thalamic electrodynamics. Mean-field models allow for modelling the EEG dynamics by averaging the behaviour of neural populations in a specific time and space (Robinson et al., 2001, 2003, 2004, 2005; Rowe et al., 2004).

These models resemble the organisation of neural populations in the cortex and include neurophysiological attributes such as: neural synaptic and dendrite dynamics, fire

response dynamics, axonal propagation, inhibitory/excitatory neural populations, cortico-cortical, cortico-thalamic and intra-thalamic loops (Robinson et al., 2001, 2002, 2003, 2004, 2005; Rowe et al., 2004; Wright et al., 2001). It is a unique methodology in as far as it allows through a non-invasive approach to infer underlying physiological EEG parameters, by fitting the model to experimental EEG data (Robinson et al., 2005).

The specific neurophysiological mean-field model to be explored dates back to the early 2000's (Rennie et al., 2000, 2002; Robinson et al., 2001, 2002, 2003, 2004, 2005; Wright et al., 2001) and has been used extensively in the literature to fit real world EEG data to explore underlying neural physiological parameter changes. The corticothalamic model focuses on analysing the neural dynamics in the cortex and between the cortex and sub-cortical areas.

The neural structure used in the model has the aim to capture several features of the EEG. It has been successfully applied in psychiatric and neuroscience contexts such as Parkinson disease (Kerr et al., 2013; van Albada & Robinson, 2009), depression (Kerr et al., 2011), spindle oscillation (Wu & Robinson, 2007), neurophysiological changes arising from age (van Albada et al., 2010), spectral peaks across frequency bands (van Albada & Robinson, 2013), age and gender differences of Alpha peaks (Chiang et al., 2011), emergence of gamma activity (Rennie et al., 2000), epilepsy (Robinson et al., 2002), EEG spectra in seizures (Zhao & Robinson, 2015) by looking into parameter changes across subjects and exposures. It has previously been proven to offer good fits in reproducing the EEG features discussed in these studies, by using a set number of parameters that are a proxy for physiological neural changes.

Given that the model involves the key circuits believed to be responsible for modulating Neurofeedback, it presents itself as a great candidate to the current work. Fitting the model to EEG Neurofeedback experimental data can help advance the field by estimating

the parameters associated with specific physiological mechanisms contributing to EEG changes in the context of Neurofeedback.

The model (figure 1 below) incorporates local inhibitory and excitatory connections at an intracortical level, direct excitatory cortical projections to the secondary relay nuclei of the Thalamus (SRN) and from here back to the cortex allowing for a direct excitatory corticothalamic loop (Rowe et al., 2004). The model also includes an indirect inhibitory projection from the cortex to the thalamic reticular nucleus (TRN), to the SRN and back to the cortex. There is also a pathway of intra-thalamic communication with inhibitory projections from the thalamic reticular nucleus (TRN) to the secondary relay nuclei. In the model, the relay nuclei of the thalamus (SRN) also caters for projections from other sub-cortical areas such as afferent sensory stimuli (Rowe et al., 2004).

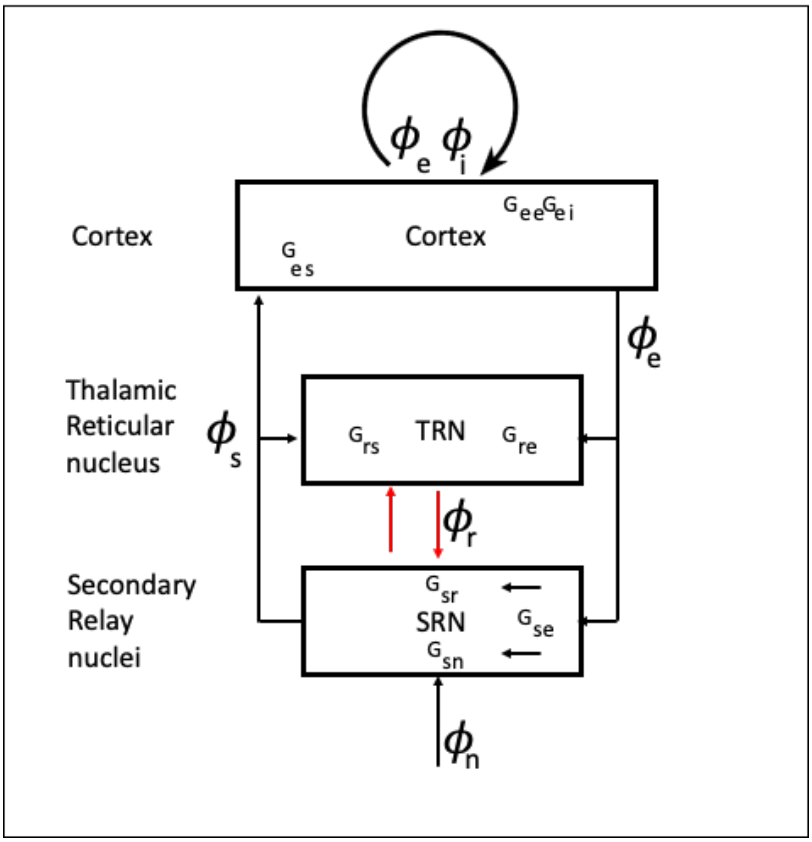


***Figure 1*:** Overview of the mean field cortico-thalamic model. Adapted from "Estimation of neurophysiological parameters from the waking EEG using a biophysical model of brain dynamics" by D. Rowe, P. Robinson and C. Rennie, 2004, Journal of Theoretical Biology, 231, p. 413–433. Copyright 2004 by Elsevier Ltd.

### 2.1. Model parameters

As previously discussed, the model includes three different feedback loops. An excitatory one, which consists of excitatory projections, with afferent action potentials given by $\phi e$, from the cortex to the dorsal relay nuclei of the thalamus (giving origin to gain $G_{se}$), and from here back to the cortex with action potential projections $\phi s$ (gain $G_{es}$). The relay nuclei feedback loop to the cortex and TRN also includes projections $\phi n$ afferents from external stimuli. Overall, the cortico-thalamic-cortical loop has positive gains given all involved neural regions are made of excitatory afferents mainly via glutamatergic projections (Robinson et al., 2004; Rowe et al., 2004). Total gain being $G_{ese} = G_{es}*G_{se}$.

The second feedback loop involves $\phi e$ projections from the cortex to the thalamic reticular nucleus (with gain Gre), and from here to the SRN with inhibitory afferents $\phi r$ (Gsr), simulating GABAergic projections (Robinson et al., 2004; Rowe et al., 2004). This projection then continues from the SRN to the cortex (Ges). The total process forms a negative feedback pathway with parameter Gesre = Ges*Gsr*Gre.

The third pathway consists of an intra-thalamic loop between the TRN-SRN-TRN with gains of Gsr and Grs respectively, giving origin to a negative feedback loop of $G_{srs} = G_{rs}*G_{sr}$.

Finally, the cortex itself is considered to be a continuum with populations of excitatory and inhibitory neurons interacting with each other, with gains Gee and Gei (Robinson et al., 2004; Rowe et al., 2004).

The parameters that govern the model have been chosen based on previous implementations of the model (Robinson et al., 2004; Rowe et al., 2004). We take this in consideration and use the same *initial* parameter values when fitting the model to experimental data. A total of 14 physiological parameters are therefore considered. Detail of the parameters and initial values can be found in table 1.

**Table 1**

*Parameters of cortico-thalamic mean-field model as per used in the literature. Initial values based on Rowe et al. (2004) work. * are fixed parameters.*

| Parameter | Description | Initial values |
|---|---|---|
| $Ye$ | Cortical damping (ve/re) | 140 $s^{-1}$ |
| $\alpha$ | Dendritic decay rate | 75 $s^{-1}$ |
| $\beta$ | Dendritic rise rate | 3.8 $\alpha$ * |
| $t0$ | Conduction delay via thalamic nuclei and projections | 0.084 s |
| $Gee$ | Excitatory gain-pyramidal cells | 5.8 |
| $Gei$ | Local intra-cortical gain-stellate cells | -7.5 |
| $Gese$ | Cortico-thalamocortical gain via SRN | 5.4 |
| $Gesre$ | Cortico-thalamocortical gain via TRN | -3.3 |
| $Gsrs$ | Intra-thalamic gain | -0.5 |
| $lx, ly$ | Linear dimensions of the cortex | 0.5 m* |
| $k0re$ | Volume Conduction filter | 3.0* |
| $re$ | Pyramidal axon length | 0.08 m* |
| $P0$ | Overall power normalization | $\phi$ =0.005 (to use in $P0$ calculation) |
| $A_{EMG}$ | Power normalization | 0.5 $\mu V^2$ $Hz^{-1}$ |

Adapted from "Estimation of neurophysiological parameters from the waking EEG using a biophysical model of brain dynamics" by D. Rowe, P. Robinson and C. Rennie, 2004, Journal of Theoretical Biology, 231, p. 413–433. Copyright 2004 by Elsevier Ltd

## 2.2. Equations running the Model

The following formulae govern the corticothalamic model and are taken from previous implementations of the model (Rowe et al., 2004) . Below, an overview is provided of the key equations used in the implemented version of the model.

### 2.2.1. Neural activity

Action potentials arriving at the dendritic tree in the cortex come in the form of $\phi$e (excitatory), $\phi$i (inhibitory) and $\phi$s (excitatory thalamic) pulses. Their total action potential impact is governed by:

$$\mathrm{Pa} = \mathrm{Vae}\phi\mathrm{e} + \mathrm{Vai}\phi\mathrm{i} + \mathrm{Vas}\phi\mathrm{s}. \quad (1)$$

The average response of cortical neurons is given by the sum of: $\mathrm{Vab}\phi\mathrm{b}$, meaning of pulses arising from neurons of type b (b = e, i or s) to neurons of type a. The term $\mathrm{Vab} = \mathrm{Nab}\ \mathrm{Sb}$ includes the average number of synapses (Nab) and the strength of the synapse (Sb).

### 2.2.2. Synaptic membrane potential

To calculate the membrane potential Va at the cell body, the temporal spread and conduction delay follows a convolution. The equation from the paper of Rowe et al. (2004) is as follows:

$$\mathrm{Va}\ (\mathbf{r},\mathrm{t}) = \int_{-\infty}^{\mathrm{t}} \mathrm{L}(\mathrm{t}-\mathrm{t}')\ \mathrm{Pa}(\mathbf{r},\mathrm{t}')\mathrm{d}\,\mathrm{t}', \quad (2)$$

$\mathrm{L}(\mathrm{u})$ is the normalized dendritic response function. The constant parameters α (initial value = 75 $s^{-1}$) and β (3.8*$\alpha$) in table 1 mediate the decay and rise rate of the impulse response, corresponding to the dendritic filtering

$$\mathrm{L}(\mathrm{u}) = \frac{\alpha\beta}{\beta-\alpha}\,(\mathrm{e}^{-\alpha\mathrm{u}} - \mathrm{e}^{-\beta\mathrm{u}}), \quad (3)$$

The final equation used in the model for the Fourier transformation of the dendritic filtering $\mathrm{L}(\mathrm{u})$ is:

$$\mathrm{L}(\omega) = (1 - \frac{\mathrm{i}\omega}{\alpha})^{-1}\,(1 - \frac{\mathrm{i}\omega}{\beta})^{-1}, \quad (4)$$

$\omega = 2\pi f$ is the angular frequency and f is the Hz equivalent.

### 2.2.3. Neural impulse firing rate

Next, the mean firing rate Qa at the cell body is given by the sigmoid function increasing from 0 to Qmax as Va increases from - ∞ to ∞ (Robinson et al., 2002, 2004; Rowe et al., 2004):

$$S[Va(\mathbf{r},t)] = \frac{Qmax}{1+\exp\{-\frac{[Va(\mathbf{r},t)-\theta]}{\sigma'}\}}, \quad (5)$$

θ is the mean firing threshold and $\sigma' \pi/\sqrt{3}$ its standard deviation and Qmax the maximum firing rate.

### 2.2.4. Spreading activation

After cell body firing, the action potentials will travel along the axon forming neural fields $\phi$ (these can be $\phi$e = excitatory, $\phi$i = inhibitory, $\phi$s = excitatory thalamic, $\phi$r = inhibitory intra-thalamic and $\phi$n = sensory afferents). Propagation is approximated by a damped wave equation (Robinson et al., 2002, 2004; Rowe et al., 2004):

$$(\frac{1}{Ya^2}\frac{\partial^2}{\partial t^2} + \frac{2}{Ya}\frac{\partial}{\partial t} + 1 - r_a^2\nabla^2)\,\phi a(\mathbf{r},t) = S[Va(\mathbf{r},t)], \quad (6)$$

$\gamma a = \frac{Va}{ra}$ is the damping rate and ra is the mean range of axons of type a.

### 2.2.5. Corticocortical and corticothalamic connectivity

We have seen before that the signals arriving to the cortex from sub-cortical thalamic areas $\phi$s are a mixture of sensory signals ($\phi$n) and signals arriving from the corticothalamic loop ($\phi$e).

$$\phi s = T\phi n + S\phi e, \quad (7)$$

where

$$T = \frac{LGsn\, e^{i\omega t0/2}}{1-LGsr\, LGrs} \quad (8)$$

$$S = \frac{(LGse+LGsrLGre)e^{i\omega t0/2}}{1-LGsr\, LGrs} \quad (9)$$

T is the thalamic transfer function, with sensory signals given by LGsn, i.e., signals $\phi$n from sensory afferents arriving at SRN adjusted for the intra-thalamic signals between the TRN and SRN given by LGsr*LGrs, i.e., signals $\phi$r from the TRN arriving at the SRN and signals $\phi$s from SRN arriving at the TRN. S is the corticothalamic transfer function, covering a) the direct excitatory path from the cortex to the SRN with signals $\phi$e from the cortex arriving at the SRN and sent back to the cortex via signals $\phi$s, given by LGse; b) the inhibitory cortico-thalamic loop given by LGsr*LGre with signals $\phi$e going from the cortex to the TRN, from here to the SRN with signals $\phi$r and back to the cortex and TRN with signals $\phi$s. This path is adjusted for the intra-thalamic signals between the TRN and SRN given by LGsr*LGrs. L in the equation is the dendritic response function (equation 4) seen before, and t0 is the delay parameter in the corticothalamic loop.

### 2.2.6. Theoretical EEG spectra calculated by the model

The spectral power density formula is a combination of linearization of equation 5 and the Fourier transformation of the following equations.

$$\mathrm{Peeg}(\omega) = \mathrm{P0}\left[\frac{\mathrm{L}(\omega)\mathrm{T}/\mathrm{Gsn}}{1-\mathrm{Gei}\,\mathrm{L}(\omega)}\right] 2\,\frac{(2\pi)^2}{\mathrm{lx}\,\mathrm{ly}} \quad (10)$$

Where

$$q^2(\omega)r_e^2 = (1-\frac{i\omega}{\gamma e})^2 - \frac{\mathrm{Gee}\,\mathrm{L}(\omega)+\mathrm{Ges}\,\mathrm{L}(\omega)\mathrm{S}}{1-\mathrm{Gei}\,\mathrm{L}(\omega)}, \quad (11)$$

$$\mathrm{P0} = \frac{\pi\,|\phi n|^2}{r_e^2}\,\mathrm{Ges}\,\mathrm{Gsn}, \quad (12)$$

$$K_{m,n}^2\,r_e^2 = (2\pi m r_e/l_x)^2 + (2\pi n r_e/l_y)^2 \quad (13)$$

When fitting the model to experimental data, P0 is adjusted according to the amplitude of the experimental data. To adjust for potential EMG artefacts (i.e., muscle movements) an additional parameter is included to compensate for this, parameter $A_{EMG}$ (table 1), and implemented in the model following the $P_{EMG}$ formula from Rowe et al. (2004).

### 2.3. Model fitting routine

To fit the model to experimental data the maximum likelihood estimation (MLE) method was used. The MLE fitting routine includes Gaussian density functions for each parameter with means taken from Rowe et al. (2004) and standard deviation set at |mean|. The chi-squared formula to derive $X^2 errors$ was adopted as per implementation from the same authors:

$$X^2 = \sum_{i=0}^{n} \frac{[log_e (P_{exp} (fi)) \ log_e (P_{est} (fi))]^2}{\sigma_i^2} \quad (14)$$

### 2.4. Hypotheses to be tested via the model

The following six hypotheses will be tested when fitting the model:

**Hypothesis 1:** We have seen in the literature review several authors (Egner & Sterman, 2006; Lévesque et al., 2006; Sterman, 1996; Sterman & Friar, 1972) associating the production of SMR rhythm with the inhibition of somatosensory input to the cortex. One current hypothesis of the study is that the inhibitory parameter Gesre will be significantly different before and after Neurofeedback. This parameter is linked to the indirect inhibitory pathway from the cortex to the relay nuclei of the thalamus via the thalamic reticular nucleus. It is therefore hypothesised that this parameter will see increases of negative values after NFB training.

**Hypothesis 2:** As the conditioned SMR activity relies on the activity of the intra-thalamic pathway (i.e. of the TRN in conjunction with SRN), to achieve a synchronous SMR bursting activity (Egner & Sterman, 2006), the hypothesis is that the Gsrs parameter will be significantly different between the two sessions as the inhibitory $\phi$r pulses between TRN and SRN would help in regulating the SMR rhythm. In biological terms this mimics the GABA inhibitory neurotransmitter mediating this hyperpolarisation. This would suggest the blockage of sensorimotor $\phi$n afferents to the cortex allowing for greater inhibition.

**Hypothesis 3:** In the multi-stage framework underpinning EEG Neurofeedback training, Davelaar (2018) advocates the importance of the frontal cortex in regulating the desired brain frequency. The hypothesis is that the gamma parameter (γe) associated with faster cortical transmission will have different values between sessions. This is believed to help with modulation of the inhibitory neural thalamocortical loop (Gesre).

**Hypothesis 4:** Gese is believed to be reducing between sessions as $\phi$e excitatory afferents give place to inhibitory $\phi$i $\phi$r gains.

**Hypothesis 5:** Dendritic decay rate ($\alpha$ = alpha) will increase between sessions due to hyperpolarisation of cells, as opposed to staying in a stable inhibited state.

**Hypothesis 6:** Gei will increase in negative values to promote a steady corticothalamic inhibition state promoting the inhibition of sensorimotor afferents to the cortex and as a consequence enabling the rhythmic SMR bursts to be maintained.

## 3. Methods

### 3.1. Overview of modelling dataset

To test our hypotheses, a dataset from a Neurofeedback study done by Davelaar and Jilek (2020) was used. The original study had been approved by the Birkbeck ethics committee. The dataset includes a total of thirty Czech participants, with 10 females and 20 males (mean age = 30.6; SD = 9.4). No significant age differences between the two genders exists (males: mean = 30.9; SD = 2.2; females: mean = 30.1; SD = 2.8), the same applying between the SMR and the control group (SMR: mean = 29.3; SD = 2.6; control: mean = 31.9; SD = 2.3). A total of six females were in the SMR group and four in the control group.

The objective of this study was to understand the impact of upregulating SMR rhythm (SMR; 12-15Hz) while simultaneously suppressing theta (4-7Hz) and beta2 (25-29Hz) on cognitive performance measures such as attention, working memory, reinforcement learning and rational thinking. Davelaar and Jilek (2020) found a significant effect of raising

the amplitude of SMR over the sensorimotor cortex for measures of reinforcement learning and to a lesser extent for rational thinking.

Out of the 30 participants in the study, a total of 15 participants went through training, whilst the other 15 participants served as the control group and did not receive Neurofeedback training. Participants on the training group went through 15 sessions of NFB training over seven weeks, each session lasting approximately 50 minutes (see figure 2 for full details of procedure).

Both participants in the training and control groups undertook a number of cognitive tests (pre and post NFB training sessions) to assess the measures of the study (i.e., attention, working memory, reinforcement learning and rational thinking) and also had quantitative EEG (QEEG) being recorded (before and after training).

For the interest of the research question and hypotheses to test, the focus will be exclusively in modelling the resting-state QEEG data collected as part of the Neurofeedback study, more specifically for the 15 participants that went through NFB training. The resting state QEEG data consisted of five minutes of eyes closed (EC) and five minutes of eyes open (EO) before and after Neurofeedback training. Participants were tested at similar times of day, being the maximum time difference one hour.


***Figure 2:*** Neurofeedback experiment design. Adapted from "Sensorimotor Rhythm is

Associated with Reinforcement Learning and Cognitive Impulsivity: A Neurofeedback Study' by E.J. Davelaar and J. Jilek, Current Neurobiology, 11(2), p.27-36.

Both the pre- and post- data were recorded with a 19-channel Deymed Truscan EEG (with a sampling rate: 256 Hz). Activity from 19 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2) were registered and referenced to the auricles (A1, A2).

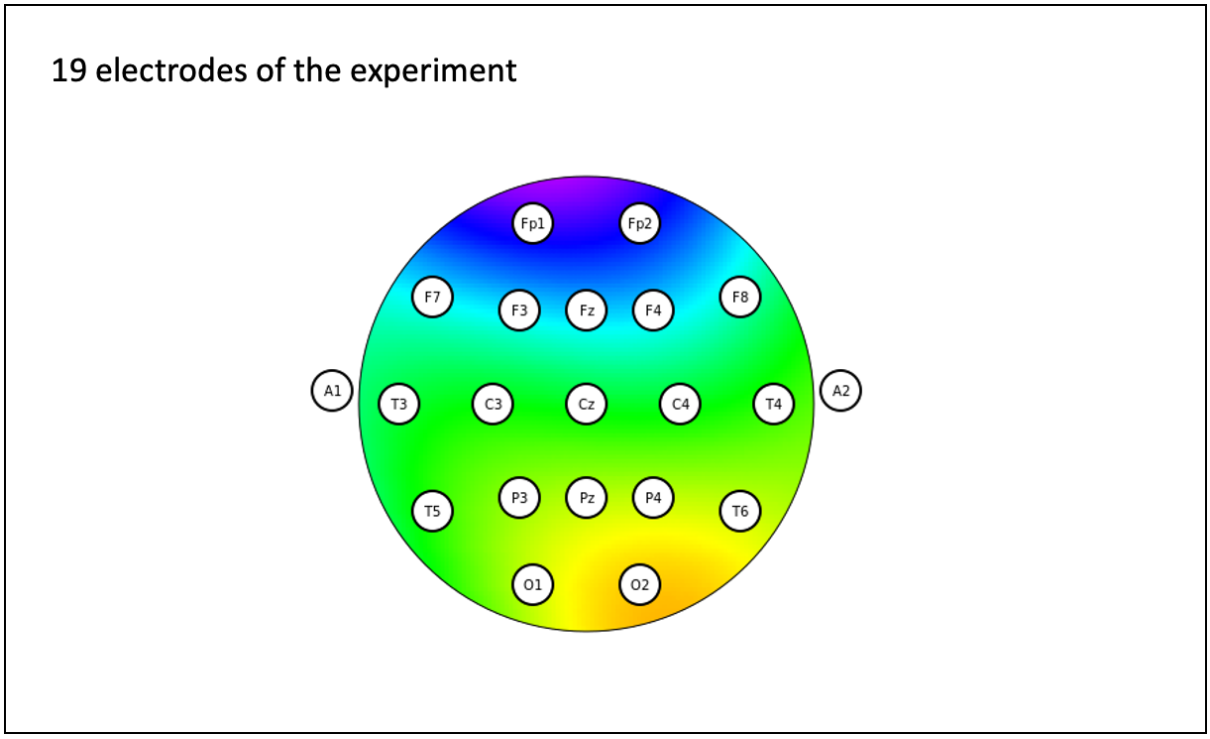


***Figure 3:*** Overview of the 19 electrodes (plus 2 reference electrodes) of the experiment.

### 3.2. Pre-processing of resting state QEEG data

The software used to do data pre-processing was EEGLAB in MATLAB. The resting state QEEG data had originally been re-referenced offline by Davelaar and Jilek (2020) when running their experiment to the auricles [(A1 + A2) / 2]. However, as part of the data pre-processing stage, the data was also re-referenced to the channel average following best practices for this stage of data preparation (Cohen, 2014). The epoch baseline (mean amplitude of each channel) was removed, and channel locations uploaded during pre-processing.

A Finite Impulse Response (FIR) band-pass filter was applied with a high-pass cut-off set at 0.25Hz and a low-pass cut-off at 40Hz. The first and last 14 seconds of each participant's resting state data (eyes closed and eyes open for both conditions: before and after Neurofeedback training) were removed due to noise in the data. Large ocular movements and muscle movement were rejected from the data as per Mike Cohen's tutorial on data cleaning[1].

Artefacts were removed with the Independent Component Analysis (ICA; runica algorithm). Components were identified via the DipFit plugin and automatically removed via EEGLAB. After the pre-processing, powers were computed at 0.25Hz resolution. Welch's method was used for calculating power spectrums (Welch, 1967). Relative power of each frequency band was calculated as the ratio of their absolute power and the absolute total power (0.25Hz to 40Hz).

### 3.3. Analysis after calculating power spectra

Before fitting the model, statistical analysis was performed on the dataset. A paired sample t-test (two-tailed) across the eyes open and eyes closed conditions was done on the 15 participants who received NFB training. Electrode location for this analysis was restricted to Cz to understand the regulation effect on SMR. After this analysis, it was observed that 7 participants had a significant increase of SMR after NFB training. These were the participants chosen to fit the model and make observations on parameter changes before and after training. More to be discussed in the results section.

### 3.4. Model fitting routine

The model was developed in the Matlab programming language. The formulas described in section 2 were translated into Matlab code. When fitting the model to experimental data, the maximum likelihood (MLE) fitting routing was adopted as per

[1] http://mikexcohen.com/lectures.html

previously discussed in section 2. The MLE fitting routine includes Gaussian density functions for each parameter with means taken from Rowe et al. (2004) and standard deviation set at |mean|. This provided sufficiently flat priors on the parameters. The objective function minimised the loglikelihood using Matlab's native fminsearch. When fitting the model, the estimated spectra from the model was compared with the experimental data spectrum. A chi-square per participant was calculated to provide an overall fit to the model (full details in table 7 of appendix I).

After fitting the model to the experimental data, the model was tested for goodness of fit by running an independent sample t-test (two-tailed) where the experimental spectra power was compared to the theoretical spectra power. Different QEEG bands were analysed and full details of the analyses is available in section 4 of the results.

**3.5. Parameter analysis**

Once the model was fitted, parameter values were analysed for the seven participants (N=7) who successfully upregulated SMR using a paired sampled t-test (two-tailed) across all 19 electrode locations. A normality of distribution test was done via plotting histograms of the relevant parameters. We focused the analysis on the specific parameters that helped in investigating and answering the study research question and hypotheses. Correlations were also performed amongst the parameters to understand the relationship between them and how they change before and after NFB training. Full results discussed ahead.

**3.6. Dataset limitations**

We only had access to the NFB participant raw data, hence the analysis will be within these subjects and not between NFB group and control group. Although the ideal methodology would be to compare SMR upregulation between the group receiving treatment and the control group, this is one of the limitations of the present study, as we did not have access to the raw data for the control group. Due to covid-19 and limitations in face-to-face

contact to run an EEG experiment to collect raw data specifically for modelling, this is one of the limitations of the current work. However, in order to mitigate this and when fitting the model, the focus will be exclusively on those participants who successfully upregulated their SMR rhythm.

## 4. Results

In order to analyse the effect of NFB training, a comparison was done to look into QEEG resting state SMR power at location Cz before and after the training sessions amongst the 15 participants. There was a statistically significant difference for SMR upregulation across the entire 15 subject population (eyes open and eyes closed). On average before NFB training the group had a mean SMR power of 0.23 $\mu V^2$(M = 0.23, SD = 0.066) and after training the SMR power increased to 0.29 $\mu V^2$(M =0.29, SD = 0.098). This difference -.0601 $\mu V^2$, 95% CI [-.103, -.016] is significant, t(51) = -2.77, *p* =.007.

**Table 2**

*SMR power (* $\mu V^2$*) before and after Neurofeedback training at location Cz.*

| Condition | N | Mean | SD | t-value | p-value (two-tailed) |
|---|---|---|---|---|---|
| Before training | 30 | .23 | .066 | | |
| After training | 30 | .29 | .098 | -2.77 | 0.007 |

N=30 (eyes open (N=15) and eyes closed (N=15) analysed together)

A closer look into the experimental data, revealed that out of the 15 participants 7 participants showed an SMR growth above average when compared to the other 8 participants. These 7 participants showed across both conditions (Eyes Open and Eyes Closed) a significant increase in SMR rhythm from the session prior training (M = 0.22, SD = 0.06) to the session after training (M = 0.34, SD = 0.09). The difference -.12 $\mu V^2$, 95% CI [-.18, -.06] is significant, t(24) = -4.18, p < .001.

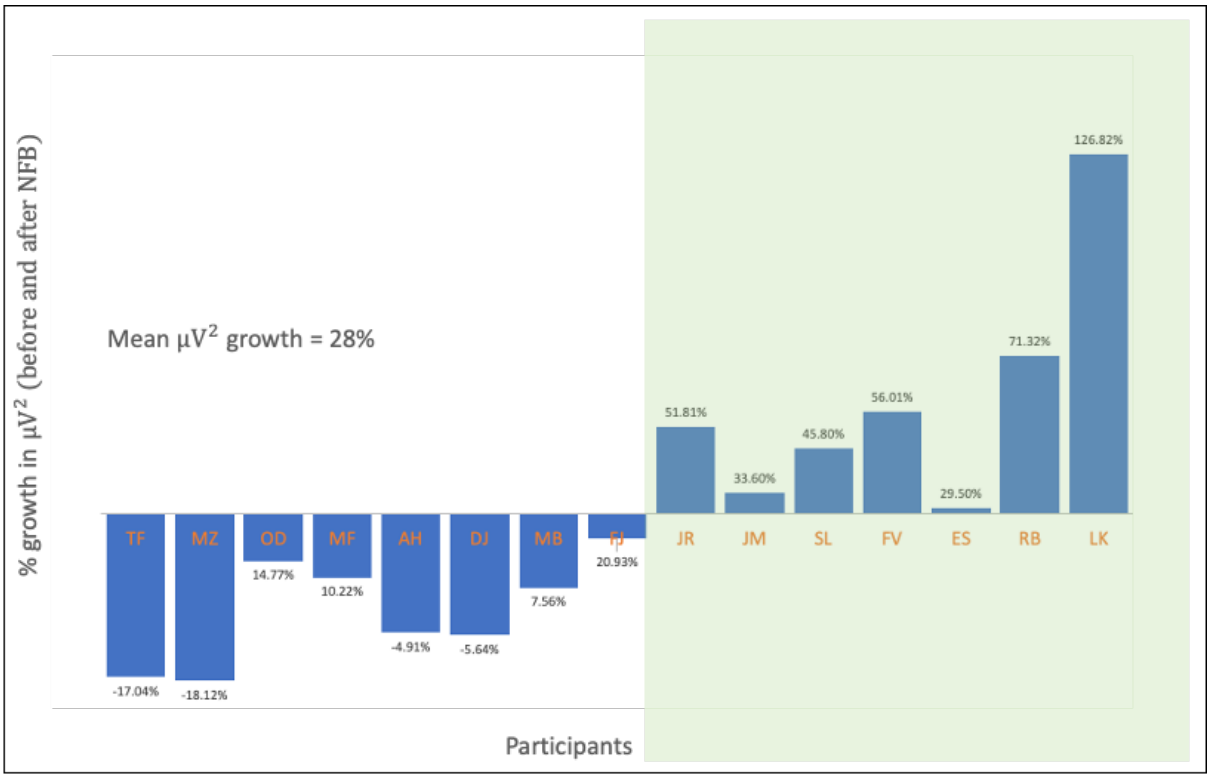


***Figure 4:*** QEEG SMR power $\mu V^2$ growth (%) over Cz channel before and after training (eyes open and eyes closed conditions). X axis (participants) crosses at mean growth percentage of y axis (28%).

These seven participants (coded as: JR, JM, SL, FV, ES, RB and LK) will be the focus of fitting the model to analyse the underlying neural mechanisms that gave origin to the successful conditioning of upregulating SMR.

### 4.1. Model fitting

**Model goodness of fit.** The model was fitted to the QEEG resting data of the seven participants that showed an uplift in SMR regulation. A sample of the fitted data is given in figure 5. There is a good fit of the model to the experimental data being shown by the red line in the graphs that closely simulate the experimental spectrum of participants (blue line). The $\chi^2$ error for goodness of fit includes values ranging from 164 to 2153, with a mean of 722 (SD = 603) in the eyes closed condition and of 569 (SD= 428) for the eyes open condition. Full $\chi^2$ results per participant can be found in table 7 of appendix I.

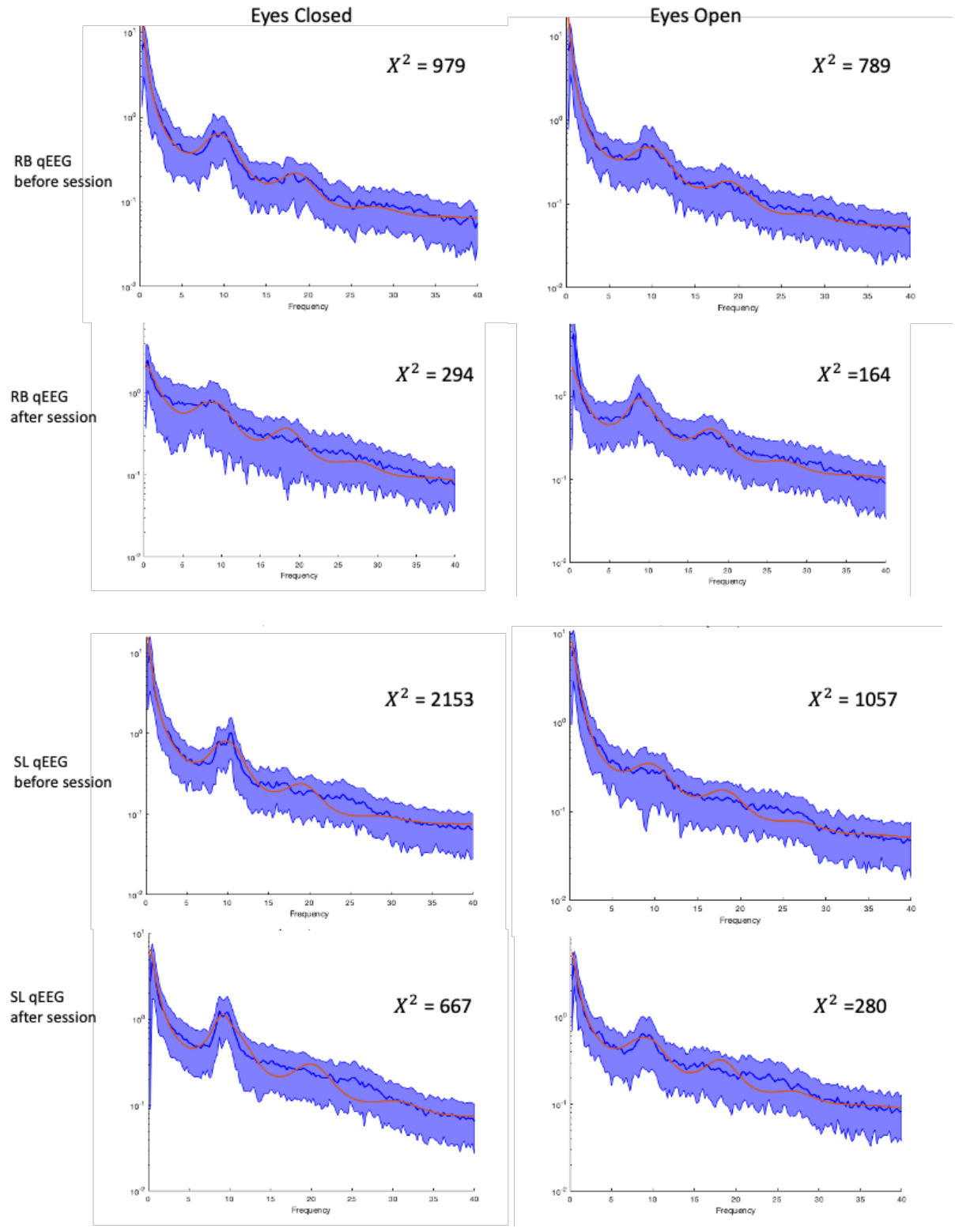


***Figure 5:*** Sample of model fits for 2 subjects at channel Cz (eyes open and eyes closed before and after Neurofeedback). Red line indicates power spectra estimate from model; blue line = experimental data; shaded blue swoosh = standard deviation.

In order to assess the $\chi^2$ value, an independent sample t-test was done comparing the frequency band power of the theoretical spectrum given by the model versus the experimental data across all 19 channel locations and all 15 participants. The following frequencies have been analysed: delta wave (0.25 – 4 Hz), theta (4.25-7.75 Hz), alpha (8-11.75 Hz), SMR (12 - 15 Hz), beta (15.25-30 Hz) and gamma (30.25-40 Hz). As per table 3 below, the model shows a good fit to the data across the spectra as there is no significant difference between the theoretical spectra and the experimental spectra for the frequency bands analysed. With the exception for the beta frequency which shows a significant difference in both the eyes closed ($p$=0.01) and eyes open ($p$=0.02) conditions between the experimental and theoretical model data, all other band power frequencies are not significantly different. We conclude therefore that the chi-square results for the model offer a good fit to the experimental data.

**Table 3**

*Comparison of experimental spectra power and theoretical spectra power across all subjects per frequency QEEG band (two-tailed t-test). N=15. All 19 electrodes.*

| | QEEG bands | | Experimental data | Theoretical spectra | t-value | p value (two-tailed) |
|---|---|---|---|---|---|---|
| | Delta | mean | 1.28 | 1.36 | -1.50 | **0.13** |
| | (0.25 – 4 Hz) | SD | (0.32) | (0.40) | | |
| | Theta | mean | 0.44 | 0.41 | -1.79 | **0.07** |
| | (4.25-7.75 Hz) | SD | (0.22) | (0.22) | | |
| **Eyes** | Alpha | mean | 0.50 | 0.51 | -0.62 | **0.53** |
| **Closed** | (8-11.75 Hz) | SD | (0.27) | (0.27) | | |
| | SMR | mean | 0.32 | 0.32 | -0.13 | **0.84** |
| | (12 -15 Hz) | SD | (0.14) | (0.14) | | |
| | Beta | mean | 0.17 | 0.16 | 2.38 | 0.01 |
| | (15.25-30 Hz) | SD | (0.06) | (0.06) | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Gamma | mean | 0.08 | | | |
| | (30.25-40 Hz) | SD | | | | |
| | Delta | mean | 1.24 | 1.31 | -1.39 | **0.16** |
| | (0.25 – 4 Hz) | SD | (0.58) | (0.71) | | |
| | Theta | mean | 0.44 | 0.41 | 1.12 | **0.25** |
| | (4.25-7.75 Hz) | SD | (0.33) | (0.33) | | |
| | Alpha | mean | 0.41 | 0.43 | -0.77 | **0.43** |
| **Eyes** | (8-11.75 Hz) | SD | (0.26) | (0.25) | | |
| **Open** | SMR | mean | 0.27 | 0.27 | 0.70 | **0.48** |
| | (12 -15 Hz) | SD | (0.10) | (0.10) | | |
| | Beta | mean | 0.17 | 0.16 | 2.28 | 0.02 |
| | (15.25-30 Hz) | SD | (0.06) | (0.06) | | |
| | Gamma | mean | 0.09 | 0.09 | -0.42 | **0.67** |
| | (30.25-40 Hz) | SD | (0.04) | (0.04) | | |

*Note:* p-values in bold show no significance between experimental and theoretical spectra

### 4.2. Model parameters

Fitting the model to experimental data allows to understand which model parameters have significant changes between sessions. By observing changes in parameters this allows to infer physiological changes happening at a neural population level, that would be correlated with SMR upregulation. Looking into the parameter distribution in figure 6 we can see that, with the exception of a few outliers (especially for parameters gamma (γe) and Gsrs), the majority of parameter values are within a normal distribution.

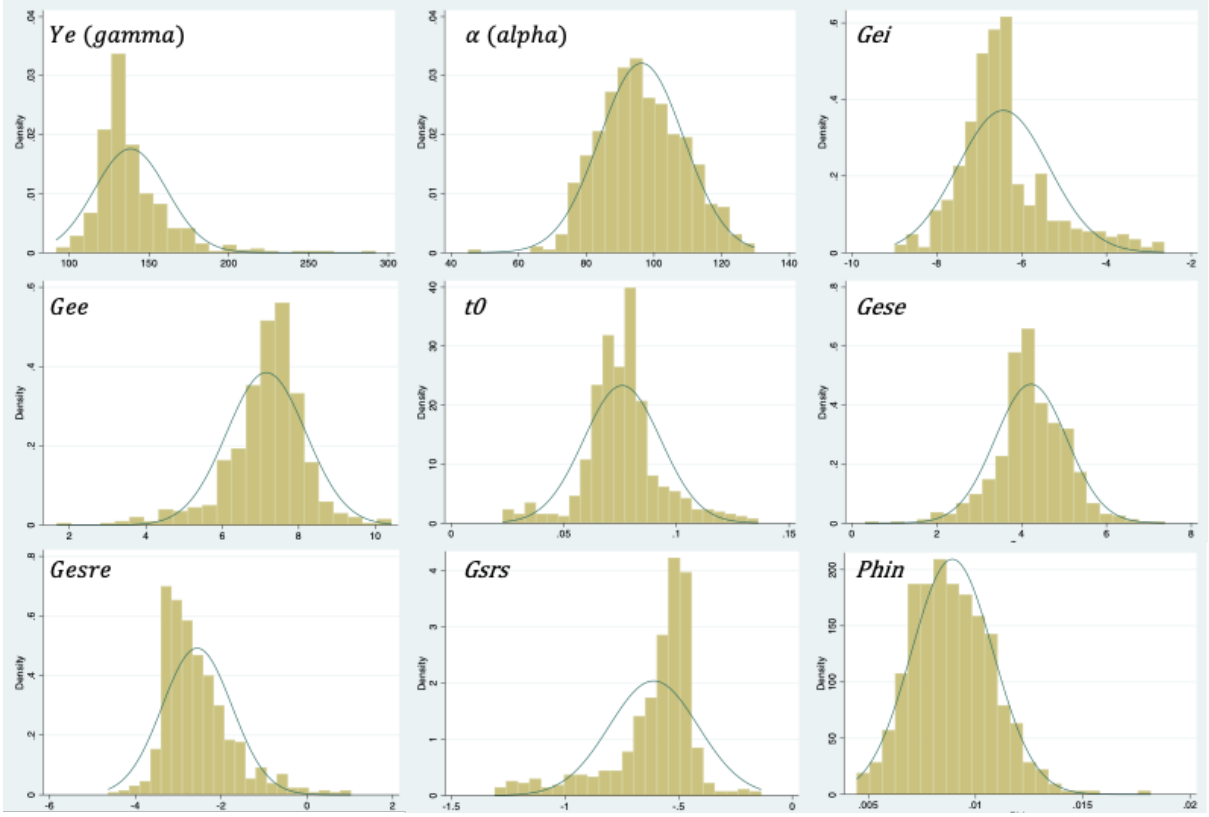


***Figure 6:*** Parameter distribution of the 7 participants (eyes open and eyes closed combined)

After checking for normality of distribution, a paired sample t-test (two-tailed) was done on the parameter values of the 7 participants who had larger improvements on SMR power spectra between sessions. This analysis was done across all 19 electrodes.

As per table 4, the analysis revealed some parameters to have values significantly different between the two sessions. The increase of the gamma (γe) parameter (before training: M = 132, SD = 15; after training: M = 143, SD = 27) for the eyes open condition is significant ($p$<.001), suggesting a faster dissipation of cortical damping pulses. The literature links this parameter to enabling a higher spectra power overall due to cortico-thalamic feedback loop (Rowe et al., 2004).

Looking into correlation tables 5 and 6, parameter gamma (γe) was significantly correlated with parameters Gese (r=-0.39, N=7, p<.001) and Gesre (r =0.30, N=7, p<.001), after Neurofeedback training. We have observed a change in correlation of this parameter before and after NFB training. Whilst before training no significance was observed between

this parameter and parameter Gese ($p>0.05$), after training a significance was observed. The observed correlations are of interest. Gese is of a negative nature and Gesre of a positive one. This suggest that after Neurofeedback faster cortical dissipation pulses are contributing more to inhibitory gains of Gesre.

Table 4 shows a significant increase ($p = 0.03$) in the alpha (α) and (β) parameters related with dendritic decay rate for the eyes closed condition (before training: M = 94, SD = 12; after training: M = 97, SD = 12). This reflects an increase in the low pass filter in neurons enhancing the lower frequency spectra (Rowe et al., 2004).

The significant change in parameter Gei for eyes closed ($p = 0.01$) and eyes open ($p<.0.001$) condition related with local intra-cortical gain from stellate cells, indicates a stronger effect on lower frequencies and on alpha and beta (Rowe et al., 2004). For this specific analysis we are interested in exploring this further as internal inhibition is believed to be highly correlated with SMR brain rhythm. In this experiment we saw an increase of Gei between sessions (i.e., less negative values between sessions) suggesting there was less inhibition from stellate cells and therefore an increase in the overall power of lower frequencies as well as alpha and beta. However, a closer look into correlation tables 5 and 6 reveals a significant negative correlation between this parameter and parameter Gee after Neurofeedback. Whilst before Neurofeedback (table 5) no significant correlation existed between these two parameters ($r=0.09$, $N=7$, $p>0.05$), after Neurofeedback (table 6) a significant negative correlation exists between these two parameters ($r=-0.40$, $N=7$, $p<.001$), suggesting higher inhibition from stellate cells is occurring.

Indeed, table 4 reveals parameter Gee did not show any significant change between sessions in both conditions (eyes open: $p=0.65$; eyes closed: $p =0.58$). If a change in parameter values was to occur for Gee the expectation would be to have been a decrease as stellate cells would exert more inhibition.

The positive cortico-thalamic gain via thalamic secondary relay nuclei (SRN) given by parameter Gese showed a significant decrease between sessions ($p<.001$) for the eyes closed condition (before training: M = 4.44, SD = 0.85; after training: M = 4.05, SD = 0.99). This parameter when increasing between sessions is associated with increases in the alpha and beta band frequencies (Rowe et al., 2004). This parameter is linked with excitatory fields Øe coming from the cortex directly to the relay nuclei of the thalamus (SRN) and from here thalamic Øs afferents are sent again back to the cortex. This pathway also brings Øn afferents gains coming from sensorimotor pathways via the SRN to the cortex.

The parameter Gesre related to cortico-thalamic gain via thalamic relay nuclei (TRN), showed between session significant decreases of negative values ($p<.001$) for both eyes closed (before training: M = -2.80, SD = 0.70; after training: M = -2.08, SD = 0.99) and eyes open conditions (before training: M = -2.93, SD = 0.42; after training: M = -2.43, SD = 0.74). This parameter is linked with enhances in delta and theta and decreases in alpha frequency band. Correlation tables 5 and 6 reveal an interesting finding for the correlation between parameters Gesre and Gese. Whilst before Neurofeedback training (table 5) no significance in correlation existed between these two parameters ($p>0.05$), after Neurofeedback training (table 6) these two parameters were significantly correlated (r=-0.54, N=7, p<.001). This suggests a modulation was being done by the inhibitory loop of the corticothalamic when SMR was being regulated.

As per table 4, a significant increase of negative values in Gsrs ($p = 0.01$) was observed for the eyes open condition between sessions (before training: M = -0.55, SD = 0.12; after training: M = -0.61, SD = 0.61). The eyes closed condition also presented a negative increase but not significant ($p = 0.16$). As we have seen in the introduction section, this is a critical parameter promoting inhibition in the intra-thalamic pathway. More will be discussed about this parameter in the following section.

Figure 7 brings to life some of the results discussed. Although it relates to one participant only (coded RB in the dataset), it allows to visually observe some of the changes discussed for the physiological parameters before and after Neurofeedback training. More specifically, it can be observed the significant increase in values of the gamma (γe) parameter for the eyes open condition, the significant increase of parameter alpha (α) for the eyes closed condition, Gei significant changes across both conditions, a significant decrease in Gese values in the eyes closed condition, Gesre significance in both conditions and Gsrs significance in the eyes open condition.

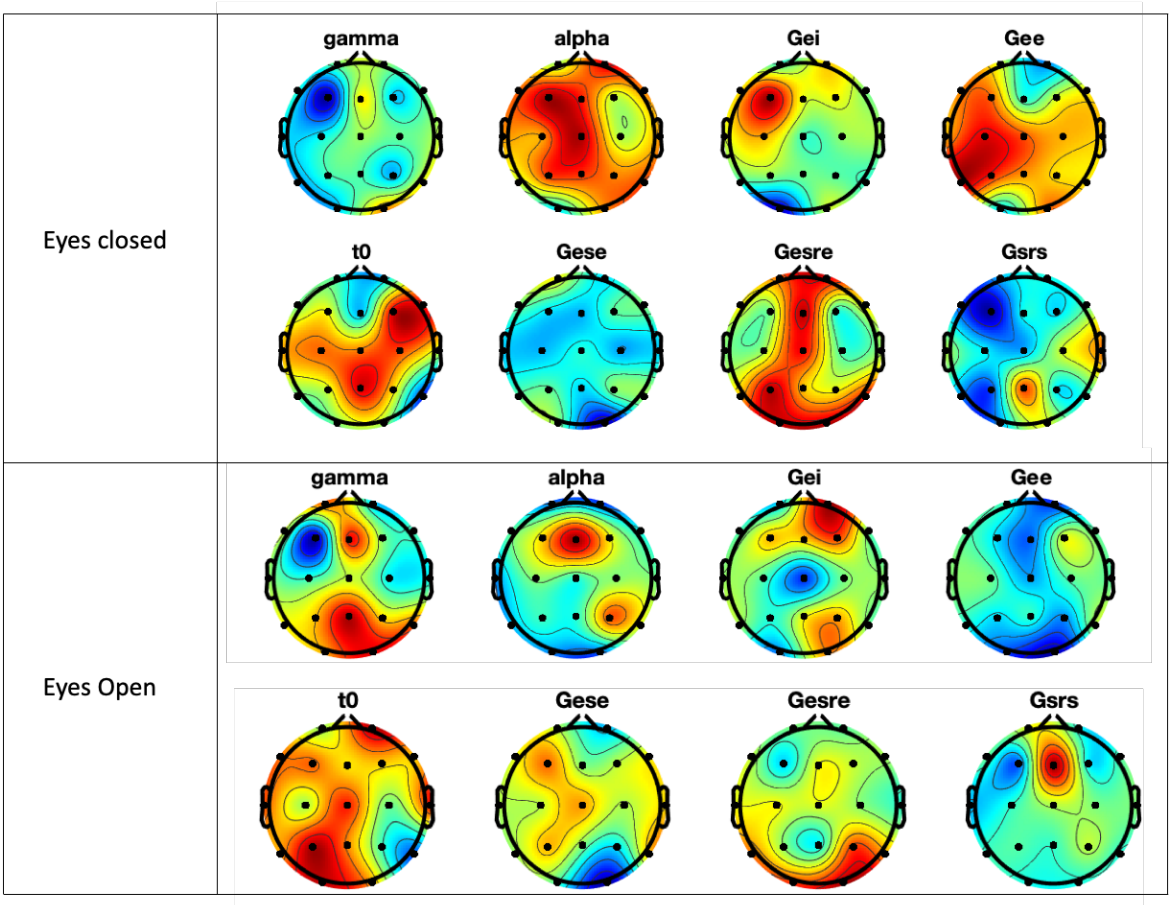


***Figure 7:*** Topographic maps of parameter changes post-training. Example of changes in parameter values before and after Neurofeedback (view for participant coded as RB).

**Table 4**

*Comparison of mean values of parameters before and after Neurofeedback across the 19 electrodes. N=7. EC = eyes closed. EO = eyes open. Significant values highlighted in bold.*

| Parameter | | Description | Before Training | | After Training | | t value |
|---|---|---|---|---|---|---|---|
| | | | Mean | SD | Mean | SD | |
| $Ye$ | (EC) | Cortical damping (ve/re) | 141 | 23 | 137 | 23 | 1.32 |
| | (EO) | | 132 | 15 | 143 | 27 | **-4.06*** ** |
| $\alpha$ | (EC) | Dendritic decay rate | 94 | 12 | 97 | 12 | **-2.07*** |
| | (EO) | | 96 | 13 | 97 | 13 | -0.83 |
| $t0$ | (EC) | Conduction delay via thalamic nuclei | 0.075 | 0.01 | 0.075 | 0.01 | -0.37 |
| | (EO) | | 0.075 | 0.01 | 0.077 | 0.017 | -1.09 |
| $Gei$ | (EC) | Local intra-cortical gain-stellate cells | -6.46 | 0.96 | -6.12 | 1.19 | -**2.57*** |
| | (EO) | | -6.77 | 0.78 | -6.36 | 1.20 | **-3.26**** |
| $Gee$ | (EC) | Excitatory gain-pyramidal cells | 7.13 | 1.05 | 7.06 | 1.20 | 0.45 |
| | (EO) | | 7.17 | 0.69 | 7.23 | 1.12 | -0.55 |
| $Gese$ | (EC) | Cortico-thalamocortical gain via SRN | 4.44 | 0.85 | 4.05 | 0.99 | **3.40*** ** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | (EO) | | 4.18 | 0.59 | 4.20 | 0.84 | -0.20 |
| $Gesre$ | (EC) | Cortico-thalamocortical gain via TRN | -2.80 | 0.70 | -2.08 | 0.98 | **-6.81***** |
| | (EO) | | -2.93 | 0.42 | -2.43 | 0.74 | **-6.67***** |
| $Gsrs$ | (EC) | Intra-thalamic gain | -0.62 | 0.20 | -0.65 | 0.23 | 1.40 |
| | (EO) | | -0.55 | 0.12 | -0.61 | 0.20 | **2.37*** |

*Note.* * indicates p < .05, ** indicates p < .01, *** indicates p < .001

**Table 5**. *Correlation matrix of model parameters gamma* (γe)*, Gei, Gee, Gese, Gesre and Gsrs before NFB session. N=7. All 19 channels fitted. Eyes open and eyes closed.*

| | $\gamma e$ | Gei | Gee | Gese | Gesre |
|---|---|---|---|---|---|
| Gei | 0.10 | | | | |
| Gee | **0.16 *** | 0.09 | | | |
| Gese | -0.11 | 0.06 | **-0.31 **** | | |
| Gesre | **0.20 **** | 0.06 | **0.21 **** | -0.02 | |
| Gsrs | **-0.35 **** | -0.10 | **-0.30 **** | 0.04 | **-0.21 **** |

*Note.* Numbers in bold are significant at * p<.01 **p<.001.

**Table 6**. *Correlation matrix of model parameters gamma* (γe)*, Gei, Gee, Gese, Gesre and Gsrs after Neurofeedback session. N=7. All 19 channels fitted. Eyes open and eyes closed.*

| | $\gamma e$ | Gei | Gee | Gese | Gesre |
|---|---|---|---|---|---|
| Gei | **0.17*** | | | | |
| Gee | **0.16**** | **-0.40**** | | | |
| Gese | **-0.39**** | **-0.35**** | 0.09 | | |
| Gesre | **0.30**** | **0.30**** | **-0.21**** | **-0.54**** | |
| Gsrs | **-0.25**** | 0.04 | **-0.20**** | **0.43**** | **-0.54**** |

*Note.* Numbers in bold are significant at * p<.01 **p<.001.

## 5. Discussion

We have seen in the results section that significant changes occurred for some of the model parameters. In this section the discussion will be organised according to the hypothesis we had before fitting the model. The results will also be compared with the existing literature and theory discussed in the introduction (section 1).

**Hypothesis 1: the inhibitory parameter Gesre will be significantly different before and after Neurofeedback**. The results show a significant increase ($p$<.001) for both eyes closed and eyes open of this parameter. Looking into the literature we would have expected this parameter to show a significance in the opposite direction, i.e., a negative increase of the parameter values after Neurofeedback. Gesre gains are mainly of an inhibitory nature given the neural fields involved in this pathway. As a recap, this loop goes from the cortex via the thalamic reticular nucleus (TRN: with gains Gre) to the relay nuclei (SRN: with gains Gsr) and then back to the cortex (with gains Ges). The total negative feedback pathway gives parameter Gesre = Ges*Gsr*Gre. Given this cycle forms an inhibitory pathway and SMR is considered to rely on an inhibition via the thalamus to prevent sensory input to go to the cortex, this would have been expected to increase in negative values. However, as per discussed previously in the results section, given that parameter Gese showed a significant decrease ($p$<.001) for the eyes closed condition, we hypothesize that although the physiological parameter Gesre did not show a significant increase in negative values, the fact that Gese saw a decrease seems to be enough to promote a more inhibitory thalamo-cortical dynamic. The significant negative correlation after Neurofeedback training previously discussed in the results section for these two parameters, Gesre and Gese (r=-0.54, N=7, p<.001), also provides support for this inference, although future work would be needed to validate this.

**Hypothesis 2: the Gsrs parameter will be significantly different between the two sessions as the inhibitory ∅r pulses between TRN and SRN would help in regulating the SMR rhythm.** The results indeed provide support for this hypothesis. In fact, as per previously discussed, a significant increase of negative values in Gsrs ($p = 0.01$) was observed for the eyes open condition between sessions. The eyes closed condition although not significant ($p = 0.16$) also presented a negative increase of this parameter. The changes seen in this physiological parameter for the eyes open condition reinforce the literature and provide support for the importance of the intra-thalamic network in promoting inhibition of sensory and motor stimuli to the cortex via the thalamus. In fact, Brickwedde et al. (2019) and Egner & Sterman (2006) argue that this network plays a key role in promoting this regulation. The parameter Gsrs of the computational model does seem to provide evidence for this insight.

**Hypothesis 3: the gamma parameter (γe) associated with faster cortical transmission will have different values between sessions**. A highly significant increase of the gamma (γe) parameter was seen for the eyes open condition. This suggests that a faster dissipation of neural pulses was seen amongst all regions of the corticothalamic model. Looking at table 6, a significant negative correlation between this parameter (γe) and Gese ($r = -0.39$, N=7, $p<.001$) can be observed after Neurofeedback, we hypothesise therefore that the gains of this parameter were mainly in the inhibitory feedback loop, Gesre, ($r = 0.30$, N=7, $p<.001$) as per observed in the correlation matrix (table 6).

This also provides support for the cortico-striatal loop theoretical account reviewed in the introduction for learning how to modulate brain dynamics. Several authors (Birbaumer et al., 1990, 2013; Davelaar, 2018; Hinterberger et al., 2005; Koralek et al., 2012) defend that a strong modulation between the cortex and the striatum has been found for successful Neurofeedback learning. Faster dissipation of neural pulses can also be interpreted (although

it is a hypothetical account at this stage given the model does not incorporate parameters for the striatum) to contribute to the first stage of conditioning between the cortex and the striatum (i.e., the striatum being reinforcing the behaviour for SMR rhythm).

**Hypothesis 4: Gese is believed to be reducing between sessions as ∅e excitatory afferents give place to inhibitory ∅i gains.** The model gives evidence to support this hypothesis. The results showed a significant decrease ($p$<.001) of Gese for the eyes closed condition. Although the eyes open condition did not show the same significant behaviour, it also did not show a significant increase ($p$=0.84). The Gese parameter forms the excitatory positive feedback corticothalamic loop gain via the SRN. When the gains are positive and the negative gains provided by Gesre (via the TRN) do not offset these, excitatory stimuli coming via the SRN will be relayed to the cortex. However, we have seen that the values for this parameter actually decreased significantly, from 4.44 before Neurofeedback to 4.05 after Neurofeedback ($p$<.001) in the eyes closed condition. This also suggests that the ∅n afferents gains coming from sensorimotor pathways via the SRN to the cortex are being attenuated.

On SMR conditioning specifically, Egner and Sterman (2006) and Lévesque et al. (2006) provide insights for the critical role of the striatum to exert control over SMR. It is believed that less excitatory inputs from the sensorimotor cortex to the striatum are responsible to exert more inhibition via the thalamus to the motor and premotor cortex.

**Hypothesis 5: Dendritic decay rate ((**α), **alpha) will increase between sessions due to hyperpolarisation of cells, as opposed to staying in a stable inhibited state**. The literature review in the introduction section, highlighted that cells in the relay nuclei of the thalamus show an atypical behaviour when producing SMR bursts (Egner & Sterman, 2006; Sterman, 1996). As opposed to being in a general inhibition state, they become hyperpolarised, meaning it is more difficult for these cells to achieve a threshold to fire and

depolarise. In the literature it is mentioned that the threshold for the cells to fire increases, and given that the results of fitting the model to the experimental data revealed a significant increase ($p = 0.03$) in the alpha parameter (α), related with dendritic decay rate for the eyes closed condition, this suggests that alongside a higher threshold for the cell to depolarise, a dendritic decay rate is higher when these cells are conditioned as there is an increase in the low pass filter of these neurons. This suggests Øn are being inhibited.

**Hypothesis 6: Gei will increase in negative values to promote a steady corticothalamic inhibition state promoting blockage of sensorimotor afferents to the cortex**. The results showed parameter Gei to have a significant decrease in negative values between session both for eyes closed ($p = 0.01$) and eyes open ($p = 0.001$) condition. The expectation would have been for Gei to have increased in negative values between sessions in order to promote further internal inhibition. However, we have seen that the parameter Gee (intracortical excitatory gain) although not significant for either eyes closed and eyes opened, did show a decrease for the eyes closed condition (from 7.13 to 7.06, p = 0.65) and a marginal increase for the eyes open condition (from 7.17 to 7.23, p = 058). This may suggest that the negative gains of the Gei parameter (although not as high in negative values as we expected) offset the gains of the Gee parameter, contributing to further reinforce the inhibitory loop, and promoting the SMR bursts to happen. The negative significant correlation previously discussed between parameters Gei and Gee after Neurofeedback (r=-0.40, N=7, p<.001) also provide reinforcement for this argument. This is further validated by hypothesis four where the excitatory cortical loop (Gese) decreases.

**Advances to the field by applying the cortico-thalamic model.** The results obtained by fitting the model to experimental data, generally support what has been discussed in the literature review for the neural mechanisms involved in regulating brain dynamics. As the dataset used to fit the model focused specifically on SMR upregulation, specific insights were

obtained for this protocol. Given this is one of the most widely used protocols, we feel these insights will help in corroborating the neural areas specifically involved in SMR upregulation. Although some of the results obtained were contrary to initial expectation and hypotheses, clear findings can be derived from having applied the model.

It was expected as per hypothesis 1, an increase of negative values in parameter Gesre, suggesting more inhibition in the cortico-thalamic loop, this however was not found when fitting the model. Parameter Gei as per hypothesis 6, was also expected to have increase in negative values. However, this was not observed. In spite of this, there are clear findings that help in further understanding what is happening at a neural level. Specific neural areas seem to interact to promote SMR regulation, more specifically:

i) evidence was found for the role of the inhibitory thalamo-cortical network in modulating SMR rhythm (Egner & Sterman, 2006; Sterman, 1996; Sterman & Friar, 1972; Wyrwicka & Sterman, 1968). Sub-cortical areas such as the thalamic inhibitory pathway between the reticular nucleus and ventrobasal thalamus/secondary relay nuclei (explained by negative increases in parameter Gsrs) as well as inhibitory cortical networks (explained by a decrease of parameter Gese) appear to be crucial in upregulating SMR.

ii) we have seen that the intra-thalamic pathway (between the TRN and SRN) accounted by parameter Gsrs to be highly significant ($p = 0.01$) for the eyes open condition. This loop is critical in promoting the inhibition of sensory afferents to the ventrobasal thalamus (SRN) and in blocking their transmission to the cortex. Biologically, when ventrobasal cells are hyperpolarised, the slow depolarisation is mediated by a calcium influx leading to sodium spikes to the TRN and the cortex (Egner & Sterman, 2006; Sterman, 1996; Wyrwicka & Sterman, 1968). As discussed previously, this burst originates a unique synchronised rhythm when discharging to the sensorimotor cortex. The TRN when receiving these bursts from SRN releases the GABA neurotransmitter that further promotes the

inhibition of the SRN and mediates the production of more synchronised SMR rhythms whilst blocking sensory and motor stimuli. This behaviour was corroborated by the observed changes in Gsrs with significant increases in negative values of this parameter from -0.55 and -0.61 in the eyes open condition. This mechanism is therefore considered to be a critical one for SMR production.

iii) The above was reinforced by parameter Gese seeing a significant decrease in the eyes closed condition ($p<.001$). In spite of not having seen a significant increase of negative Gesre values, we believe the significant decrease of Gese in the eyes closed condition played a role in promoting the intra-cortical inhibition of sensory inputs to the cortex and exerting more inhibition in the thalamic loop as less excitatory action potentials were being sent to the thalamus. This can be corroborated by looking into parameter gamma (γe) having a significant increase which suggests a faster cortical dissipation of the inhibitory network and reinforcement of the negative gains to the cortex, as per significant correlations (table 6) of parameter gamma (γe) and parameter Gesre ($r = 0.30$, $N=7$, $p<.001$) after Neurofeedback training. The same can be derived from the highly significant negative correlation between parameter Gesre and Gese after training ($r = -0.54$, $N=7$, $p<.001$). This correlation saw an increase of 52 points from non-significant before training ($r = -0.02$, $N=7$, $p>0.05$) to highly significant after training ($r = -0.54$, $N=7$, $p<.001$).

iv) although not covered by the model, the striatum is believed to also mediate the generation of SMR bursts. As per discussed in the literature (Egner & Sterman, 2006; Lévesque et al., 2006), the global pallidus of the striatum exerts inhibition of the motor and premotor cortex via the thalamus. When the global pallidus receives less input from the sensorimotor cortex (which would be the case given parameter Gese to drop significantly in the eyes closed condition and not have significant increases in the eyes open condition), more

activation happens at the global pallidus and more inhibition is targeted at the thalamus and motor cortex.

Further enhancements of this physiological model to incorporate the striatum and validate the observation deducted in this work based on the literature review would allow to further validate this hypothesis.

## 6. Conclusion

As far as we are aware this work has been one of the first attempts in the literature to apply the cortico-thalamic model to explore Neurofeedback. The model presents itself as a non-intrusive method to explain the underlying neural mechanisms involved in Neurofeedback. Applying the model to experimental data allowed to demonstrate some of the underlying brain physiological mechanisms of successful Neurofeedback. We have seen the intra-thalamic loop explained by parameter Gsrs to be key in promoting inhibition via GABA inhibitory projections. These inhibitory projections would further contribute to hyperpolarise the ventrobasal thalamus and send inhibitory projections back to the TRN and cortex resulting in SMR rhythm and suppression of sensorimotor input to the cortex.

We have also seen this cycle being reinforced at the cortex via inhibitory intra-cortical Gei gains that reduce sensorimotor projections to the striatum. This has been confirmed by the Gese parameter significantly decreasing its projections in the cortico-thalamic loop in the eyes closed condition, as well as by the significant negative correlation between parameters Gei and Gee ($r=-0.40$, $N=7$, $p<.001$) after Neurofeedback training, suggesting higher inhibition from these cells was occurring. One of the advances to the literature of this research is in explaining that a Gsr significant increase of negative values in the eyes open condition (intra-thalamic inhibition) together with a significant Gese decrease in the eyes closed condition (less excitatory projections from the cortex directly to the relay nuclei of the thalamus) seem to be key in enabling successful SMR upregulation.

It is our point of view that a direct influence of the striatum in the relay nuclei of the thalamus is also mediating the observed hyperpolarisation. As an extension to this work, future research on SMR specific regulation would benefit from incorporating the striatum in the model. This would allow to offer a validation of the assumption that the striatum plays a key role both in learning consolidation (Birbaumer et al., 2013) and in regulating the thalamus with inhibiting sensory stimuli (Davelaar, 2017, 2018; Egner & Sterman, 2006; Lévesque et al., 2006).

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## Appendix I: Model goodness of fit

**Table 7.** *Model goodness of fit* $\chi^2$

*Results per participant (N=7) before and after Neurofeedback across all 19 electrodes (eyes closed and eyes open).*

| Participant | | | $X^2$ mean | $X^2$ SD |
|---|---|---|---|---|
| ES | Before NFB | Eyes closed | 536 | 266 |
| | | Eyes open | 738 | 520 |
| | After NFB | Eyes closed | 204 | 104 |
| | | Eyes open | 536 | 320 |
| FV | Before NFB | Eyes closed | 829 | 866 |
| | | Eyes open | 762 | 966 |
| | After NFB | Eyes closed | 354 | 142 |
| | | Eyes open | 235 | 97 |
| JM | Before NFB | Eyes closed | 274 | 123 |
| | | Eyes open | 275 | 142 |
| | After NFB | Eyes closed | 228 | 128 |
| | | Eyes open | 207 | 90 |
| JR | Before NFB | Eyes closed | 1847 | 1001 |
| | | Eyes open | 1693 | 1097 |
| | After NFB | Eyes closed | 927 | 566 |
| | | Eyes open | 666 | 325 |
| LK | Before NFB | Eyes closed | 515 | 266 |
| | | Eyes open | 329 | 264 |
| | After NFB | Eyes closed | 294 | 118 |
| | | Eyes open | 228 | 149 |

| | | | | |
|---|---|---|---|---|
| RB | Before NFB | Eyes closed | 979 | 556 |
| | | Eyes open | 789 | 383 |
| | After NFB | Eyes closed | 294 | 98 |
| | | Eyes open | 164 | 79 |
| SL | Before NFB | Eyes closed | 2153 | 1140 |
| | | Eyes open | 1057 | 466 |
| | After NFB | Eyes closed | 667 | 306 |
| | | Eyes open | 280 | 126 |