Universidade do Minho
Escola de Engenharia

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Self-regulation Learning in Neurofeedback Training: Effects of a Human-computer Framework to Prime Subjects with External Stimulation, like Mindfulness

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Self-regulation Learning in Neurofeedback Training: Effects of a Human-computer Framework to Prime Subjects with External Stimulation, like Mindfulness

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[EN] I envisioned a mechanistic approach to arrive at our flow state, scientifically known as transient hypofrontality (Csikszentmihalyi, 2014). Many authors contributed to this theme. Nowadays, the literature is more prosperous than ever before, enabling us to question: *"Presently, is it possible to mechanistically induce this mental state?"* Throughout this journey and the first steps undertaken in this Ph.D., I met people and authors that helped me in one way or another. These acknowledgements are a gentle reminder of their support along this path. [PT] Em primeiro lugar, os agradecimentos são dedicados aqueles que possibilitaram este momento, os meus pais. Aos meus irmãos, ver-vos crescer continua a ser uma das melhores experiências da minha vida. À minha companheira e melhor amiga, sem o seu amor incondicional, sem o seu carinho e sem a sua presença não teria ninguém para me apoiar quando magoa, para entender quando mói, para festejar aquando das vitórias. És minha, eu sou teu e juntos somos mais. No geral, para toda a minha família, todos os que me rodeiam e para os grandes que me ajudaram nesta conquista (vocês sabem quem são!), um grande obrigado. [EN] To my supervisors that agreed to aid me in this hard path and for the autonomy I was entrusted with. To my supervisor for hints on Neurofeedback learning and why it could be a tool for mechanistic control of mental states and support provided during this thesis. To my co-supervisor, I thank her for all her readiness to help. To everyone at MIT, ICVS, ALGORITMI, and 2AI that always had wise words to share. To all the authors used throughout the thesis, I commend you. Without you, this thesis, at this moment, would be impossible. Ideas have no authority, nor do they have time. They just have the right circumstance to be scientifically tested. To all the volunteers who were eager to participate in the study, there would be no results without them. Finally, I should congratulate my Self for always falling forward through all the dreams, the hard work, the joys, the hopes, the expectations, but also the gruelling pain of uncertainty, workload, the stress of deadlines, and the obsession. I agree with the popular saying, *"Your energy flows where your attention goes"*, for the better or the worse. Julio Verne summarizes this beautifully, *"There are no impossible obstacles, there are just stronger and weaker wills, that is all!"*.

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STATEMENT OF INTEGRITY

I hereby declare having conducted this academic work with integrity. I confirm that I have not used plagiarism or any form of undue use of information or falsification of results along the process leading to its elaboration.

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Aprendizagem de Auto-regulação no Treino de Neurofeedback: Efeitos de uma Framework Homem-máquina para Preparar Sujeitos com Estimulações Externas, tal como o Mindfulness.

RESUMO

A capacidade de autorregulação dos processos sociais e individuais é necessária na adaptação aos desafios ambientais (stress, procrastinação, relaxamento, atenção, subir escadas, escalar montanhas, etc.) e desafios sociais (comunicação, apresentação, exposição nas redes sociais, gestão de conflitos etc.), tornando-se indispensável na atual sociedade hiper-tecnonológica e hiper-estimulante. Em termos neurofisiológicos, o processo de adaptação aos desafios depende da capacidade do cérebro de controlar cuidadosamente o tempo nos diferentes estados mentais e nas transições entre os mesmos. O treino de neurofeedback (NFT) é uma das técnicas usadas para ensinar este tipo de controlo. Nos protocolos atuais, os benefícios do NFT diferem bastante entre indivíduos, existindo uma percentagem elevada de sujeitos que não apresentam desempenho satisfatório no controlo voluntário dos processos eletrofisiológicos e hemodinâmicos (ineficácia até ≈ 50%). Assim sendo, compreender auxiliar a autorregulação do neurofeedback tem elevada importância. A literatura propõe que o estado *"ideal"* de aprendizagem, de autorregulação do neurofeedback, é alcançado quando são evitadas associações irrelevantes entre estados internos e recompensas externas (e.g., *"Será que estou a conseguir?"*, *"Sou mesmo eu a controlar o feedback?"*) e quando o sujeito permanece envolvido, focado e sem distrações durante o treino. Como tal, questionamos se a preparação dos estados mentais dos participantes (usando estimulos pre-NFT) pode aumentar o desempenho de autorregulação do neurofeedback. Como resposta, sintetizamos uma nova framework open-source. Começando pelos fundamentos teóricos, depois pelo design, seguido pelo software e as aplicações da Framework. Finalmente, nos últimos capítulos, discutimos os processos, problemas, soluções, métodos, resultados e possibilidades futuras. Destacando que a preparação dos sujeitos com neuroestimulação externa, usando técnicas de mindfulness, aumenta significativamente ($t(29) = 4.38$, $p < 0.001$) a performance durante o NFT em comparação com uma intervenção sem preparação ($t(29) = 1.18$, $p > 0.1$). Provavelmente explicado pelo efeito da preparação em sujeitos com pouca capacidade de actuar com consciência, aumentando a presença e envolvimento nas tarefas. Estes resultados validam a nossa framework de preparação assistida e indicam a sua utilidade em estimular a capacidade de autorregular o neurofeedback.

PALAVRAS-CHAVE: APRENDIZAGEM DE AUTORREGULAÇÃO, ESTADOS MENTAIS, MINDFULNESS, TREINO DE NEUROFEEDBACK ASSISTIDO, OPEN-SOURCE BRAIN-COMPUTER INTERFACE.

Self-regulation Learning in Neurofeedback Training: Effects of a Human-computer Framework to Prime Subjects with External Stimulation, like Mindfulness.

ABSTRACT

Self-regulation (SR) of social and individual processes is a vital adaptation process to environmental (stress, procrastination, relaxation, attention, climbing a set of stairs or a mountain, among others) and social challenges (communication, presentation, social network exposure, conflict management, among others), becoming indispensable, in our growing hiper-technological and hiper-stimulative society. In neurophysiological terms, the adaptation process to challenges depends critically on the brain's ability to carefully control the time within and transitions among different brain states. Neurofeedback Training (NFT) is one of the techniques used to teach this kind of control. In the current protocols, the benefits from NFT significantly differ between subjects, i.e., a high percentage of subjects are missing a satisfactory performance in voluntary control of the electrophysiological and hemodynamic processes being trained (inefficacy up to ≈ 50%). As such, understanding how to assist SR in Neurofeedback protocols is of great importance. Some works in the literature hypothesize that the *"optimal"* state of SR learning using Neurofeedback is reached when irrelevant associations between internal states and external reward are avoided (e.g., *"Can I control my brain?"*, *"Is it me who is controlling the feedback?"*), and when the learner stays engaged, focused, and undistracted. As such, we hypothesize that priming the mental states of participants (with pre-NFT stimulation) can improve the performance of SR. To answer this, we developed a novel priming open-source framework. Starting from the theoretical foundations, then the design, followed by the open-source software and framework study applications. Finally, we discuss the process, problems, solutions, methods, results, and future possibilities throughout the last chapters. We highlight that priming subjects with external neurostimulation, based on mindfulness meditation techniques, significantly increased the NFT performance ($t(29) = 4.38$, $p < 0.001$) comparing to no-priming ($t(29) = 1.18$, $p > 0.1$) intervention. This is probably explained by the effect of priming in subjects with a lack of acting with awareness at pre-intervention, leading to increased task engagement and a relaxed non-judgemental attitude towards the NFT tasks. These results validate our assisted priming framework and indicate its usefulness in stimulating the capacity to self-regulate the neurofeedback.

KEYWORDS: ASSISTED NEUROFEEDBACK TRAINING, MENTAL STATES, MINDFULNESS, OPEN-SOURCE BRAIN-COMPUTER INTERFACE, SELF-REGULATION LEARNING.

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List of Abbreviations and Acronyms

A

ADHD: Attention deficit hyperactivity disorder

ADO: Adaptive Design Optimization approach

ANOVA: analysis of variance

APP: application

B

BCI: brain-computer interface

Bin: Block in

BM: breathing mindfulness

BMI: brain-machine interface

BOLD: blood oxygen level-dependent signal

Bout: Block out

BSDS: brain-state dependent stimulation

C

CG: control group

D

DASS: Depression Anxiety Stress Scale

DNFs: dynamic neural fields

E

E1: Experiment 1

E2: Experiment 2

EC: eyes closed

EEG: electrophysiological

EG: experimental group

EO: eyes open

EOG: Electrooculography

ERPs: event-related potentials

ERQ: Emotion Regulation Questionnaire

ES: eyes sequence

F

FFMQ: Five Facet Mindfulness Questionnaire

FFT: fast fourier transform

FIFO: First-In-First-Out Buffer

FIR: finite response filter

fMRI: functional Magnetic Resonance Imaging

G

GSR: Galvanic Skin Response

GUI: graphical user interface

H

HCI: Human-computer Interfaces

HRV: Heart Rate Variability

I

IAF: Individual Alpha Frequency

IM: imagery mindfulness

IRB: Internal Review Board

L

LOC: locus of control

LSL: Lab Streaming Layer

M

MANCOVA: multivariate analysis of covariance

MBAS: mindfulness breath attention score

min: minutes

MM: mindfulness meditation

MPS: mindfulness performance score

ms: millisecond

N

NF: neurofeedback

NFT: Neurofeedback Training

NFT_EC: NFT eyes closed

NFT_EO: NFT eyes open

O

OS: operating system

P

POMS: Profile of Mood States

PPG: Photoplethysmogram

PRIME: Pre-training Priming Protocol

PS: PRIME sequence

PSD: Power Spectral Density

R

RDA: remote data access

REST: rest state task

REST_EC: rest eyes closed task

REST_EO: rest eyes open task

RS: REST sequence

S

s: second

SA: Signal Acquisition

SCL: skin conductance level

SCR: skin conductance response

SD: Standard Deviation

SMR: Sensorimotor rhythm

SOC: sociodemographic questionnaire

SP: Signal Presentation

SPC: Signal Processing

SR: Self-regulation

S-R: Stimulus-Response

SS: stimuli sequence

T

tBAT: time in brain activity target

TMS: Toronto Mindfulness Scale

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THESIS LAYOUT

CHAPTER 1 comprises an introduction covering, from general to specific, the concepts, definitions, challenges, and the state of the art of self-regulation and Neurofeedback. Considering our specific challenge, it also covers the theoretical foundations of the framework developed to research self-regulation learning in neurofeedback training and the effects of priming subjects with external stimulation, like Mindfulness.

CHAPTER 2 builds upon the theoretical foundations to establish our framework: the design, measures, and ethical approval.

CHAPTER 3 details the concretization of the design from chapter 2 in an open-source Python framework by synthetizing and using the best parts of specific brain-computer interfaces (BCI) and EEG modules for signal acquisition, signal processing/classification, and signal presentation.

CHAPTER 4 presents the first experimental study of the framework (Experiment 1, E1). This pilot study enabled the refinement and establishment of the framework requirements. Through the study of 35 participants, divided into experimental priming (EG) and control no-priming (CG) groups, we subjected our experimental design conditions to the test (self-reports, session block and task design, priming protocol, neurofeedback protocol) and established what was needed to be adjusted.

CHAPTER 5 presents the improved experimental study (Experiment 2, E2). Sixty-two healthy naïve subjects (18 to 43 years) were divided into EG and CG. The EG results showed a significantly enhanced ability ($t(29) = 4.38$, $p < .001$) to control brain activity, compared to the CG ($t(29) = 1.18$, $p > .1$).

CHAPTER 6 has a general discussion of the results and future proposals that would help to explore further the findings obtained in this work. It also presents the advantages and limitations of the work presented in this thesis.

APPENDIX shows additional information referenced throughout the thesis.

NOTES section displays noteworthy endnotes and definitions. These endnotes located at the end of the thesis are referenced by a superscript number, e.g., endnotes[1].

CHAPTER 1

Introduction

1. CHAPTER 1 - INTRODUCTION

Neuroscience, the science exploring the unknown frontier of the brain, has become over the past three decades more accessible. The great interest in the neuronal system, allied with technological advancement, pushed brain research to the front line. Unlocking new knowledge in Neuroscience helps persons, directly or indirectly, with a significant impact on brain health, quality of life, or, in a broader sense, in homeostasis[2] (Damasio, 2010).

Concerning mental disorders, cognitive decline/impairment and cognitive training/rehabilitation various techniques have different degrees of effectiveness (Plassman et al., 2010). For example, techniques for self-regulation (SR, also defined as Self-control[3]) of mental states are widely used in clinical, professional, athletic, and gaming industries, whether for therapeutic, performance, or entertainment reasons. They include imagery training, music regulation, breathing, meditation, amongst others (Birbaumer et al., 2013; Damasio, 2010; John H. Gruzelier, 2014a, 2014d; Heatherton, 2011; Sitaram et al., 2017; Tang et al., 2015).

With the advancement of technologies, the research of possible mechanistic approaches[4] to behaviourism is increasing (by trying to invoke mechanical causality and reducing complex behavioural phenomena to less complex physical phenomena). Similarly, brain-machine interfaces (BCI) utilize our ability to learn how to self-regulate brain states when provided with corrective feedback training (Birbaumer et al., 2013; Enriquez-Geppert et al., 2017; Tomas Ros et al., 2014; Sitaram et al., 2017). Such training is known as Neurofeedback Training (NFT). Put simply, neurofeedback (NF) interface works as a virtual *"mirror"* for neuronal oscillations occurring within the brain (electromagnetic or haemodynamic), empowering a person to explicitly modify them (Birbaumer et al., 2013; Enriquez-Geppert et al., 2017; Tomas Ros et al., 2014; Sitaram et al., 2017). In this way, NFT acts as a technique to train brain SR.

In generic terms, SR is a vital adaptation process to environmental and social challenges. Moreover, SR deficits are linked to various behavioural problems and mental disorders such as depression, rumination, distraction, anxiety, stress, sleeping disorders, and attention control[5] (Heatherton, 2011; Moffitt et al., 2011; Posner et al., 2007; Rueda et al., 2011). In neurophysiological terms, the adaptation process depends critically on the brain's ability to carefully control the time within – and transitions among – different states (Gu et al., 2018).

NFT promising results (e.g., modulation of behaviourally relevant brain activity and self-administered therapy) attracted the attention and scrutiny of the scientific and medical community (Kamiya, 2011; Linden, 2014; Sitaram et al., 2017), and the technique of NF received criticism concerning the insufficient evaluation, reliability, and validation of its training effects (Tomas Ros et al., 2020; Sitaram et al., 2017; Thibault, Lifshitz, et al., 2018; Witte et al., 2018). With the current protocols, the benefits from NFT significantly differ between subjects, with a high percentage of inefficacy (up to 50% of non-responders/non-learners, or higher depending on the protocol used) (Alkoby et al., 2018; E. J. Davelaar et al., 2018; Enriquez-Geppert, Huster, & Herrmann, 2013; Kadosh & Staunton, 2019; Nan et al., 2018; Reichert et al., 2015; E. Weber et al., 2011; Zoefel et al., 2011). Leading to the frustration of potential users, economic costs, and discredit in NFT and its professionals (Alkoby et al., 2018; Enriquez-Geppert et al., 2017; John H. Gruzelier, 2014c, 2014d; Nan et al., 2018; Sitaram et al., 2017; Thibault, Veissière, et al., 2018; Zoefel et al., 2011; Zuberer et al., 2015).

Multiple mechanisms drive NF SR learning and experimental outcome (E. Davelaar, 2017; Tomas Ros et al., 2020). Nonetheless, it has been hypothesized that an "optimal" self-regulation state is necessary to achieve significant performance in voluntary modulating brainwaves (E. J. Davelaar et al., 2018; Manuel Ninaus, Kober, et al., 2013; Witte et al., 2013; Wood et al., 2014). In this state, the learner should be more engaged, focused (mental focus), undistracted, and mindful of the experiment. Conversely, the learner should avoid self-related thinking (self-monitoring), distracting and task-unrelated thoughts, ruminating and irrelevant associations between internal states and external reward (doubts, questioning, evaluation of progress), and mind wandering. Such state suggests a close relation to focused attention forms of mindfulness meditation (MM) that comprise training an individual to more efficiently sustain his/her attention toward an intended object (e.g., bodily sensations, like respiration, tingling in fingers) and away from external (e.g., sounds, visual cues) or internal (e.g., thoughts, mind wandering) sources of distraction (Chow et al., 2017; E. J. Davelaar et al., 2018; Kabat-Zinn, 2003; Tang, 2017; Tang et al., 2015). From a dynamical system perspective, the subject needs to *"walk"* (transition between states) in a trying-sensing continuum until it reaches the *"optimal"* sensing state (E. J. Davelaar et al., 2018; Gu et al., 2018; Tomas Ros et al., 2014). Therefore, brain SR practice seems closely related to MM, and they both seem to depend upon three core components: attention control[5], self-awareness[6] , and emotional regulation[7] (Silvia E. Kober et al., 2017; Lutz et al., 2008; Tang et al., 2015; Wood et al., 2014).

Current "big data" fMRI research investigates the influence of pre-training/priming[8] mechanisms associated with brain structures and NF success (Zhao et al., 2021) and activation levels on NF success (Haugg et al., 2020) to find possible predictors of NFT performance. Furthermore, this last group

investigated a wide range of subject- and study-specific factors on real-time fMRI NF success (Haugg et al., 2021), linking the significant positive effect of pre-training to the familiarization of the participants with the NF setup and mental imagery task before NFT runs. Other EEG studies focused on finding predictors from the resting state baseline (Diaz Hernandez et al., 2018; Nan et al., 2018; Reichert et al., 2015; Wan et al., 2014), psychological factors (Diaz Hernandez et al., 2018; Enriquez-Geppert, Huster, & Herrmann, 2013; Eva M. Hammer et al., 2014; Kadosh & Staunton, 2019; Silvia E. Kober et al., 2013), and neurophysiological factors (Halder et al., 2013; Nan et al., 2012, 2015; Wan et al., 2014).

Additionally, current electrophysiological (EEG) literature relates some of the *"optimal"* state behaviours (attention, relaxation, task-engagement) with electrophysiological up-regulation (synchronization) of the sensorimotor rhythm (SMR) and alpha rhythm (J. Gruzelier et al., 2010; J. H. Gruzelier et al., 2014; John H. Gruzelier, 2014c, 2014d; Hanslmayr et al., 2005; Klimesch et al., 2007; Silvia E. Kober et al., 2017; Silvia Erika Kober et al., 2015; van Lutterveld et al., 2017; Zoefel et al., 2011).

Summarizing, recent work on psychology and the philosophy of the mind has extended the conceptual legacy, while the development of neuroscience, neuroimaging, general biology and evolutionary biology has capitalized on the neural legacy. The evidence, conjectures, and hypotheses presented in this chapter are grounded on these developments (further detailed in the following sections). Using these developments as this thesis foundation, we propose an *"assisted neurofeedback self-regulation human-computer machine"* combining behavioural, psychological, emotional, and electrophysiological components of NFT, MM, and SR in a single framework[9].

The current thesis presents this framework in four parts: chapter 1, foundations of the framework; chapter 2, framework design for priming[8] subjects to *"optimal"* self-regulate in NF protocols; chapter 3, an open-source version of the framework in Python for utility, expandability, and reusability; chapters 4 and 5 with experiment applications to explore, test, evaluate and validate the framework. These steps aimed to answer the following questions: What can be gained by developing this framework? Does priming with external stimulation assist participants in self-regulating their NF? Are mindfulness stimuli more suitable SR primers compared with the standard rest baseline tasks used in NF? These questions can be further divided into four main questions:

- Targets: Which mental/brain states can be optimal for learning SR of brain activity?
- Stimulus: How can we non-invasively stimulate these *"optimal"* states?
- Measurements: How can we measure the target performance (learning and behavioural

outcomes) of each individual?

- Framework experimental temporal design: What is the best temporal design for the implementation of the framework?

In the near future, the value of these findings will be significant. They could prevent the potential frustration of users who do not benefit from NFT via personalizing the NFT intervention protocol - as a result, changing the susceptibility and affinity to NFT and reducing the inefficacy percentage (number of non-responders). Understand neural mechanisms underlying SR and improve the methodology of NFT protocols. Create an artificial intelligence framework to calibrate brain states tailored to each subject. Thus, providing a low cost, convenient, time-saving, and easy way to support NFT learning.

The previous paragraphs were intended to give a general introduction to the topics discussed throughout the thesis. In the following sections, we will detail these topics and define the foundations of this thesis framework.

1.1 The necessity of self-regulation for optimal homeostatic states

SR can be simplified as the capacity to regulate, alter or inhibit certain behaviours voluntarily. SR deficits are associated with diverse behavioural problems and mental disorders, such as the increased risk of school failure, attention deficit disorder, rumination, distraction, attention control, anxiety, stress, sleeping disorders, depression, and drug abuse (Birbaumer et al., 2013; Heatherton, 2011; Moffitt et al., 2011; Posner et al., 2007; Rueda et al., 2011). The world health organization reported that in 2001 an estimated 450 million people, 1 in 13 people, were affected by mental health disorders globally (Saraceno, 2002), and in 2007 4 in 5 people with mental health disorders were untreated (P. S. Wang et al., 2007). Furthermore, in 2018 an estimated 264 million people were affected by depression (S. L. James et al., 2018).

SR of brain activity is the central point of NFT (Birbaumer et al., 2013; Enriquez-Geppert et al., 2017; Sitaram et al., 2017). Therefore, understanding how to influence individual SR learning ability through training methods could be the key to unlock predictors and optimize the success of NFT and vice-versa.

As already introduced, SR is a vital adaptation process to environmental and social challenges. In neurophysiological terms, the adaptation process to challenges depends critically on the brain's ability to

carefully control the time within and transitions among different states (Gu et al., 2018). In this thesis, the term state may refer to neurophysiological and psychological patterns. Neurophysiological patterns refer to the electrical activity across neurons or brain regions, measured through EEG. Psychological patterns refer to emotional states measured through neurophenomenological[10] traits and states self-reports.

The literature points to meditation as a training technique that cultivates a better capacity to self-regulate (Aftanas & Golosheikin, 2003; Kabat-Zinn, 2003; Sierpina, 2005; Tang, 2017; Tang et al., 2015; Williams & Kabat-Zinn, 2011). This technique will be discussed further in section **2.2**.

NF closed-loop is an external vantage point that can be used to support the training of SR. It enables the development of hybrid human-computer operants to *"outsource"* sensory-feedback processing (brain activity feedback) by capitalizing on the computer's superior sensing accuracy and temporal resolution (Tomas Ros et al., 2014; Sitaram et al., 2017). This technique will be discussed further in the next section.

Finally, from another point of view, the Self and how it marks the mind stream with feelings/sensations can generate pathological (depression, anxiety) processes (Damasio, 2010; Man & Damasio, 2019) and a non-healthy mind-body connection (Kabat-Zinn, 2003; Tang, 2017). SR training has the aim to support a better mind-body connection, related to training the emotional detection system and enabling *"optimal"* homeostatic[2] states: *"Optimal workings of an organism, which result in efficient, harmonious states of life, constitute the very substrate of our primordial feelings of well-being and pleasure"* (Damasio, 2010). Additionally, it is essential to highlight that self-regulation is possible because the processes of the Self are dynamic, in constant change. The epistemology of the Self remains an open debate in other areas of knowledge outside the scope of the present Bioengineering dissertation. Thus, this topic will not be discussed in detail here.

1.2 Neurofeedback

NFT is a non-invasive neuromodulation technique that applies the principles of biofeedback to brain activity. Essentially, a subject is trained to self-regulate (volitionally control) a target variable of neuronal activity over a particular brain region or unspecific region. For that, the subject is asked to modify the target variable based on real-time feedback from his/her brain. This methodology provides a closed-loop, allowing the participant to *"learn how to control"* the neurophysiological target processes in the brain. For

these reasons, conceptually, the behaviour the subject is trying to learn is SR of neurophysiologic metrics, and the technique to achieve it is NFT (Fovet et al., 2015; Glannon, 2014; Krames et al., 2009).

1.2.1 Neuromodulation

Approximately 40 years ago, scientists believed the adult brain was *"hardwired"* — immutably fixed like electronic circuits. Now we know that the brain is flexible, adaptive, and resilient. Understanding the extent of this plasticity — the ability of neurons to form new connections (synaptogenesis), to strengthen or weaken existing connections and form new neurons in certain regions (neurogenesis) — is central for the understanding of how our brains grow, heal, and age (Tomas Ros et al., 2014).

Neuromodulation is the physiological process by which a given neuron uses one or more neurotransmitters (neuromodulators) to regulate diverse populations of neurons. Neurotransmitters secreted by a small group of neurons diffuse through large areas of the nervous system, affecting multiple neurons. Major neurotransmitters in the central nervous system include dopamine, serotonin, acetylcholine, histamine, and noradrenaline (Coben & Evans, 2011; Krames et al., 2009).

Brain plasticity assumptions underlying the practice of neuromodulation are as follows (Coben & Evans, 2011; Krames et al., 2009; Lubianiker et al., 2019; Tomas Ros et al., 2014): the brain is both structurally and functionally plastic, and conditioning and altering EEG rhythms facilitate changes in this plasticity of the neural circuitry; the ability to adapt, learn, and reinforce specific brain activity (EEG rhythms, blood oxygen level-dependent signal - BOLD, and event-related potentials - ERPs) under proper conditions can make lasting changes in the generation and regulation of selected brain neural circuits underlying the activity.

There are several ways to induce neuromodulation, aiming at psychological benefits. This modulation can be exogenous (external stimulation) or endogenous (internal stimulation). This thesis focuses on NFT, an endogenous neuromodulation technique[11] where the individual does inner stimulation using mental processes. There are also exogenous neuromodulation techniques that use external stimulation like Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation (McKinley et al., 2012).

1.2.2 The opportunity

An increasing body of studies demonstrated that NF has the potential for supportive treatment in abnormal patterns of cortical activity (S. W. Choi et al., 2010; Coben & Evans, 2011; Peeters et al., 2014) and has benefits on the enhancement of cognitive and behavioural performance (Enriquez-Geppert, Huster, & Herrmann, 2013; Nan et al., 2012; Reichert et al., 2015) increasing the capacity to self-regulate brain activity.

As introduced before, NF has begun to attract the attention and scrutiny of the scientific and medical mainstream (Kamiya, 2011; Linden, 2014; Tomas Ros et al., 2020; Sitaram et al., 2017), receiving criticism about its limitations. A big part of the studies in the last decades is from clinical setups with a shortage of robust research (absence or poor control groups, few randomized trials) and dubious evidence of NFT specific effects (cognitive and behavioural). Thus, crucial shortcomings remain, such as insufficient evaluation, reliability, reproducibility and validation of the distinct NFT protocol effects. Leading to the frustration of potential users, economic costs, and discredit in NFT and its professionals (Alkoby et al., 2018; Enriquez-Geppert et al., 2017; John H. Gruzelier, 2014c, 2014d; Nan et al., 2018; Sitaram et al., 2017; Thibault, Veissière, et al., 2018; Zoefel et al., 2011; Zuberer et al., 2015)

A good example is an interesting discussion about the cause and mechanisms that lead to the behavioural benefits of NFT: placebo processes or learning processes (Thibault et al., 2017)? Currently, a debate centres on the extent to which neurofeedback alters brain function, behaviour and the mechanisms through which neurofeedback operates (e.g., neurofeedback-specific versus non-specific) (Tomas Ros et al., 2020). A series of correspondence (Schabus, 2018; Thibault, Lifshitz, et al., 2018; Witte et al., 2018) discuss the theoretical arguments, pitfalls, and the empirical data backing the involvement of these two mechanisms. The controversy around this correspondence stems from the phenomenon that multiple components can drive the benefits of a treatment (Tomas Ros et al., 2020). The greater points of contention centre on, one, whether previous experiments provide sufficient evidence to identify specific factors as a key driver of neurofeedback outcomes and, two, how to best design an experiment to clearly dissociate the various mechanisms driving neurofeedback outcomes (Tomas Ros et al., 2020). As such, the research groups tried to reach a *"Consensus on the reporting and experimental design of clinical and cognitive-behavioural neurofeedback studies (CRED-nf checklist)"* (Tomas Ros et al., 2020).

Nonetheless, NFT creates multiple opportunities both at the scientific and clinical levels. An example of this, with interest to the thesis, is that NFT in its core serves as a technique to train SR, which presents advantages as a research tool compared to meditation techniques to train SR. As such, the NFT as a

research tool opens the path for the quantification of SR. It enables real-time control of brain oscillations using closed-loop feedback (Tomas Ros et al., 2014) and potentially provide safer interventions (e.g., EEG NF interventions are noninvasive and dangerous side effects are nonexistent), repeatability of the same intervention, and long-term persistent effects (J. Gruzelier, 2009; Renton et al., 2017; Tomas Ros et al., 2014; Strehl, 2014; Yoo et al., 2008). Also, it allows mental states to be decoded from brain activity (LaConte, 2011; Zotev et al., 2011, 2014). Additionally, SR is a crucial link to the effectiveness of the learning process and the outcome of NFT (John H. Gruzelier, 2014c).

1.2.3 The inefficacy problem

Contextually, designing optimal NFT paradigms remains elusive due to several technical, psychological, and neurophysiological factors/mechanisms (the following sections **1.2.4** and **1.3.2** further detail them) that influence the training outcome and are still uncharted (Eva Maria Hammer et al., 2012; Silvia E. Kober et al., 2013; Manuel Ninaus, Kober, et al., 2013; D. Vernon et al., 2009; Witte et al., 2013).

The training outcome directly depends on individual learning ability to self-regulate neurophysiologic metrics. However, learning ability differs vastly between individuals, with many studies reporting non-responders/non-learners (Nan et al., 2012, 2015; Reichert et al., 2015; Wan et al., 2014; E. Weber et al. As previously introduced, these subjects cannot successfully self-regulate their brain activity using NFT, representing up to 50% of the participants (E. J. Davelaar et al., 2018; Drechsler et al., 2007; Enriquez-Geppert, Huster, & Herrmann, 2013; Enriquez-Geppert, Huster, Scharfenort, et al., 2013; Kadosh & Staunton, 2019; Kotchoubey et al., 1999; Kouijzer et al., 2010; Nan et al., 2018; Reichert et al., 2015; Van Boxtel et al., 2012; E. Weber et al., 2011; Zoefel et al., 2011). This non-response leads participants to not benefit from this technique after several sessions. This limitation translates into concerns about the validity of the treatment paradigms and hinders further development of the NFT technique (Alkoby et al., 2018; Enriquez-Geppert et al., 2017; Rogala et al., 2016; Tomas Ros et al., 2020; Sitaram et al., 2017; Thibault et al., 2017; Thibault, Lifshitz, et al., 2018; Vollebregt et al., 2014; Witte et al., 2018; Zuberer et al., 2015).

For these reasons, it is critical to research NF learning ability, which indicates how well the training individuals learn to self-regulate their brain activity. Understanding its underlying mechanisms can help the NFT process (quantify cause and effect), enabling the prediction of *"which"* and *"how"* subjects benefit from NFT.

1.2.4 The big picture: comparing existing research lines in Neurofeedback learning ability

Different branches of research elaborate on three types of mechanisms that influence individual learning ability and susceptibility to NFT: neurophysiologic, psychologic, and technical/methodological (that can hardly be separated because they work in symbiosis). In the next paragraphs, we further describe these mechanisms by giving a brief overview of literature examples.

The neurophysiologic perspective focuses on implicit mechanisms and bottom-up processes. Current research argues that individual ability to learn NFT is dependent on structural properties of the brain - e.g., grey matter volume in some regions depending on the protocol (M. Ninaus et al., 2015). Other research points to the importance of targeting neuronal networks as a path for insight into the regional specificity of NFT effects (see section **1.3.7** for more detail in NFT specificity), dependent on new techniques of EEG that are inspired in functional Magnetic Resonance Imaging (fMRI). Such as reducing the need for fMRI scanning for probing specific subcortical regions such as the amygdala as the basis for brain-training procedures (MacInnes et al., 2016; Meir-Hasson et al., 2014, 2016; Manuel Ninaus, Kober, et al., 2013). Authors also raise concerns about the use of pre-defined targeting (choosing a region of interest offline[12], before the training) because spontaneous and deliberate control during online[12] training changes the areas of brain activation (K. Choi, 2013; Silvia E. Kober et al., 2013; Scharnowski et al., 2012). Also, because this targeting implies the necessity of an fMRI pre-session, it precludes widespread use at a low cost (George, 2016; Keynan et al., 2016). Concerning the inefficacy of non-responders, research also claims it may occur from neuronal systems needed for voluntary control that might not produce electrical activity detectable on the scalp (Silvia E. Kober et al., 2013). Indeed, neuropsychological tests show that part of the variations in NFT learning performance may be connected to memory and attentional networks (Witte et al., 2013). Additionally, features of resting baselines seem to predict the learning ability of NFT in healthy persons (Nan et al., 2015; Reichert et al., 2015; Wan et al., 2014), the following section **1.2.5** further describes these predictors.

The psychological perspective focuses on explicit mechanisms and top-down processes. Research on mental strategies is scarce, but some (e.g., kinesthetically/visual motor imagery, relaxation, positive thoughts, among others) seem to influence the NFT learning ability depending on the behavioural response target. Nonetheless, inner control of thoughts, perception, focus, discipline, attention, memory, among others, are all malleable, subjective, and very difficult to quantify (K. Choi, 2013; Curran & Stokes,

2003; Eva Maria Hammer et al., 2012; Silvia E. Kober et al., 2013; Nan et al., 2012; Neuper et al., 2005). The design of NFT task instructions can significantly impact learning but is usually poorly described in the literature. For example, concerning mental strategy instructions, the subject is often only invited to come up with its own best strategy (Hoedlmoser et al., 2008; Silvia E. Kober et al., 2013; Lacroix, 1986; Lacroix & Gowen, 1981; Lotte et al., 2013), section **1.3.6** discusses this topic in more detail. The emotional states (mood, motivation, and personal traits) and social states (empathy, habituation, and sensitization) of the subjects seem to play a moderate role (Eva Maria Hammer et al., 2012; Kleih et al., 2010; F. Nijboer et al., 2008; Femke Nijboer et al., 2010; Sherlin et al., 2011). Studies of cognitive states, such as meditation and mind wandering, show that the anterior part of the insula plays an important role in attention to and the awareness of internal cues - learning from NFT is probably dependent on substantial subjective control of self-referential processes[13] (attention and cognitive control of inner states), defined as explicit control mechanisms of learning (M. Ninaus et al., 2015; Manuel Ninaus, Kober, et al., 2013). Results also suggest that the overall cognitive resources dependent on lifestyle (physical activity, diet, education, job, sleep, stress levels and others) impact the level of control in NFT and brain-computer interface (BCI) tasks (Witte et al., 2013).

The technical/methodological perspective focus on different acquisition techniques (electrophysiological and hemodynamic) that provide different views of the problem and technical constraints – temporal/spatial detection resolution, regional specificity, feedback delay, muscle artefacts, signal-to-noise ratio (reinforcement speed), portability cost, and availability (Birbaumer et al., 2013; deCharms, 2008; George, 2016; Huster et al., 2012; Johnson et al., 2012; Keynan et al., 2016; Kropotov, 2009; Meir-Hasson et al., 2016; Ruiz et al., 2014; Scharnowski & Weiskopf, 2015; Sorger et al., 2018; Sulzer et al., 2013; Weiskopf et al., 2007). Likewise, the feedback interfaces cause distinct learning effects – feedback modality, sham feedback, interleaved/intermittent feedback, feedback delay, response latency, interface specificity, complexity, and immersion (Anguera et al., 2013; K. Choi, 2013; A. Cohen et al., 2016; Johnson et al., 2012; Maunsell & Gibson, 1992; McFarland & Wolpaw, 2011; Mishra et al., 2016; Sollfrank, 2015; Sollfrank et al., 2016; Stomrud et al., 2010). Protocol specificity remains inconclusive and should be further addressed by standardized, randomized controlled experimental designs and reported data (Drechsler et al., 2007; Egner & Gruzelier, 2001; Gevensleben et al., 2012; J. Gruzelier et al., 2006; Keizer et al., 2010; Kotchoubey et al., 1999; Nan et al., 2015; Rogala et al., 2016; Tomas Ros et al., 2020; David Vernon et al., 2003; Vollebregt et al., 2014; Zuberer et al., 2015).

From the NFT point of view, the three mechanisms are connected to the learner, the training setup, and the researcher/technician (see Figure 1), i.e., the learner and its individual factors (psychological and

neurophysiological), the training setup with all the technical and methodological factors, the researcher/technician and the social and instruction factors.

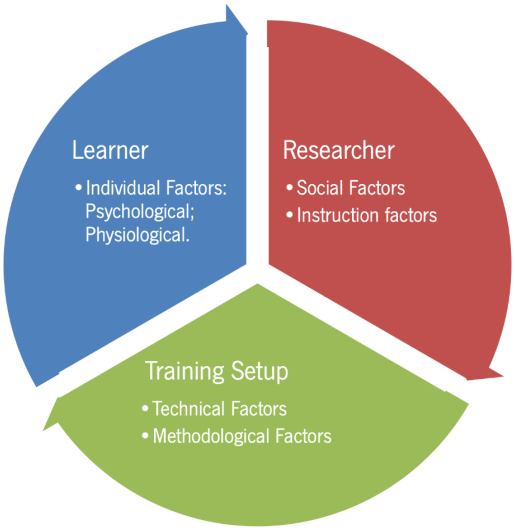


Figure 1 - Neurofeedback training mechanisms. The learner and its individual factors (psychological and neurophysiological). The training setup with all the technical and methodological factors. The researcher/technician and the social and instruction factors

These mechanisms were further divided by the current leading groups, trying to reach a *"Consensus on the reporting and experimental design of clinical and cognitive-behavioural neurofeedback studies (CRED-nf checklist)"* (Tomas Ros et al., 2020). They divided the mechanisms driving the effects of NFT into five bins: neurofeedback-specific (related to training a target neurophysiological variable), neurofeedback non-specific (dependent on the neurofeedback context, but independent from the act of controlling a particular brain signal), general non-specific (including the common benefits of cognitive training as well as psychosocial influences, such as placebo responding), repetition related (e.g., test-retest improvement), and natural (e.g., spontaneous remission, cognitive development). As such, an ideal demonstration of neurofeedback-specific effects would include evidence of online (i.e., intra-session) and offline (i.e., inter-session or post-treatment) changes in targeted brain activity, as well as a control group or condition to rule out non-specific effects (e.g., sensory stimulation, placebo) (Tomas Ros et al., 2020).

1.2.5 Predictors of NFT success

A new line of research has emerged focused on predictors of training success from parameters related to or factors affecting the learning ability - for a current systematic review on predictors, please go to (L. A. Weber et al., 2020). As an example, there are psychological factors of training success such as locus of control[14] (LOC), control beliefs, the degree of concentration/attention, personality, mood, mastery,

confidence, motivation, imagery abilities, visual-motor coordination abilities, intelligence, verbal and non-verbal learning abilities, psychological well-being, between others (Diaz Hernandez et al., 2018; Dickhaus et al., 2009; Egner & Gruzelier, 2001; Enriquez-Geppert, Huster, & Herrmann, 2013; Eva M. Hammer et al., 2014; Eva Maria Hammer et al., 2012; Hardman et al., 1997; Kadosh & Staunton, 2019; Kleih et al., 2010; Silvia E. Kober et al., 2013; F. Nijboer et al., 2008; Manuel Ninaus, Kober, et al., 2013; Ruiz et al., 2014; Witte et al., 2013). At the moment, neurophysiological predictors are the topic of interest because they are easier to quantify and find correlations. Such as pre-training EEG individual signatures (resting, initial EEG activity, baseline, and initial performance), the morphology of brain structures, memory span, among others (Blankertz et al., 2010; Enriquez-Geppert, Huster, Scharfenort, et al., 2013; Halder et al., 2013; Kotchoubey et al., 1999; Nan et al., 2012, 2015; Neumann & Birbaumer, 2003; Reichert et al., 2015; Wan et al., 2014; E. Weber et al., 2011; L. A. Weber et al., 2020). When reproduced and validated, these predictors will improve the success of NFT, as they enable during pre-training the detection of subjects that will benefit more from a specific protocol and enable personalization, thus preventing frustration for possible non-responders and reduce the cost of NF clinical applications.

Additionally, as we develop in section **1.3**, different attempts exist to explain how technical, psychological, and physiological mechanisms interact. For instance, the crossing of learning ability in NFT with theories like control theory, dynamical system theory, multi-stage learning theory, instructions design theories (E. Davelaar, 2017; Gu et al., 2018; Eva Maria Hammer et al., 2012; Kropotov, 2009; Lotte et al., 2013; Manuel Ninaus, Kober, et al., 2013; Tomas Ros et al., 2014; Sherlin et al., 2011; Wood et al., 2014). Also, other theories try to explain the phenomenon of BCI and NFT inefficacy (Dickhaus et al., 2009; Silvia E. Kober et al., 2013; Kübler et al., 2007), the assessment and measuring of SR learning ability in the context of NFT (Bauer & Gharabaghi, 2015; Wan et al., 2014; Zuberer et al., 2015) and theories that try to demystify self-control of brain ability (Silvia E. Kober et al., 2013; Manuel Ninaus, Kober, et al., 2013; Witte et al., 2013; Wood et al., 2014).

1.2.6 Our line of research

Framing the thesis, the final goal of the envisioned framework is to mechanistically train SR to achieve personalized *"optimal"* homeostatic states and possibly serve as groundwork to reach the most misleading and challenging state, the flow state. Which is scientifically known as transient hypofrontality, a state of concentration so focused on a present task that it amounts to absolute absorption in that activity, also known in the sports research as *"the zone"* (Csikszentmihalyi, 2014; J. Gruzelier et al.,

2010; Harris et al., 2017; Mladenović et al., 2017). Therefore, knowledge from systems of SR and what they can bring to NFT and brain SR performance are paramount. These SR systems might involve spiritual practice (Silvia E. Kober et al., 2017), MM (Tang et al., 2015), metacognition (Roebers, 2017), the flow state (Csikszentmihalyi, 2014; J. Gruzelier et al., 2010; Harris et al., 2017; Mladenović et al., 2017), binaural audio (Lavallee et al., 2011), and other senses stimulation. The vision is to use an adaptive design optimization approach (ADO), as suggested by Sanchez et al. (Sanchez et al., 2014) and further detailed in section **2.1.4**, to adapt the SR systems with artificial intelligence to create a framework of mental state training and priming/calibration of states of consciousness. Nonetheless, to bring this vision to fruition, the first step in this thesis was to develop a framework instrumental in researching SR priming with MM in an NFT setup.

From the previous sections' research lines, we choose a learner-centric approach, focused on the learner (psychological and neurophysiological), specifically in the capacity to self-regulate, and how we can develop training setups to stimulate (prime) this capacity implicitly.

Our framework took form using the Python language. Python is one of the most versatile open-source languages, has a great community behind it, and quality machine learning libraries are available. This framework was developed to simplify the use of advanced real-time closed-loop applications. The framework architecture is prepared for the personalized machine learning priming with an ADO approach. Chapter **3** describes in great detail the pythonic framework.

However, before proceeding with artificial intelligence, we first needed to demonstrate that priming can stimulate the learning of voluntary brain activity self-regulation and, consequently, increase NFT performance. The most straightforward path was to find in the literature a priming technique that leads the person closer to the hypothesized *"optimal"* state. From reports, as introduced before, the technique with similar priming targets is MM of focused attention forms (Chow et al., 2017; E. J. Davelaar et al., 2018; Silvia E. Kober et al., 2017; Navarro Gil et al., 2018; Tang et al., 2015; Wood et al., 2014). In fact, brain SR is closely related to mindfulness meditation, and they both seem to depend upon three core components: attention control, self-awareness, and emotional regulation (Silvia E. Kober et al., 2017; Lutz et al., 2008; Tang et al., 2015; Williams & Kabat-Zinn, 2011; Wood et al., 2014). Additionally, the *"optimal"* state definitions of learner versus non-learner have a close relationship to focused attention forms of MM. Involving training an individual to sustain their attention toward an intended object (e.g., the sensation of respiration) and away from external (e.g., sounds) or internal sources of distraction (e.g.,

thoughts, mind wandering) (Chow et al., 2017; E. J. Davelaar et al., 2018; Silvia E. Kober et al., 2017; Navarro Gil et al., 2018; Tang et al., 2015; Wood et al., 2014).

For these reasons, we choose to test the framework using two MM stimuli for priming the subject and assess the changes in NFT performance (this technique will be discussed further in section **2.2**).

1.3 Framework foundations

Before specifying the theoretical foundations of the framework[9], we start by defining the objectives and hypotheses that motivated its development.

The objectives for the framework are:

- Create an NFT intervention with subject priming.
- Prime subjects to calibrate their brain state, in this way producing benefits on SR of NF.
- Implicit design, the stimulus should scaffold the neuromodulation strategies used to self-regulate brain activity.
- Compare the priming with the standard baseline primers of resting (where the subject is only tasked to *"try to relax"*).
- Develop groundwork to create an artificial intelligence framework that should learn which sequence of stimuli leads the person to the *"optimal"* target.
- Preliminary steps in creating a framework to research the path to train SR to achieve personalized optimal states mechanistically, and ultimately the most elusive state, the flow state.

These objectives steamed from the following hypothesis:

- Brainwave calibration through exogenous priming stimuli will produce benefits on learning SR in protocols of EEG-NFT.
- Machine learning controlled stimulation can learn which sequence of stimuli 'storyboard' (or common factors in stimuli) leads to a specific behavioural target (mindful state).
- Stimulation (e.g., MM stimuli) can scaffold the desired mental task and initially minimize the cognitive demand and help users enter meta states (personalized *"optimal"* states of attention, emotional regulation, self-awareness, and others).

Additionally, one must be reminded about the definitions of mental and brain states as they will be used a lot in this chapter, even if they are intertwined. Mental State (psychological): pattern of behaviour activity (e.g., thinking, mind wandering, rumination). Brain State (neurophysiological): reliable pattern of activity or connectivity in multiple large–scale networks[15] (J. Gruzelier et al., 2010; Haynes & Rees, 2006; Lotte et al., 2013).

Concerning the theoretical foundations, first, from the vantage point of the learner, we want to give shape and chain the learning factors of NF SR. For that, we should use the theoretical constructs laid out throughout the years. Then, develop a model that establishes the first principles of our framework.

Additionally, one should expect that NFT entails several learning mechanisms. In the following sections, we specify them.

1.3.1 The basis, associative learning and information representation

Historically, NF self-regulation learning was first reduced to our linear and binary causal perception of external stimulus-response (S-R). As far as our perception goes, this causal perception seems to always occur between two separable forms, with life or no-life, from micro to macro, from electron-proton attraction to sun-earth attraction. Inherent in any definition of causality is the notion that the effect (response) cannot temporally precede the cause (stimuli). Such is the case of Pavlov applied psychology experiments (Pavlov, 2010). He showed us the classical operant conditioning as an open-loop of the same stimuli (e.g., simultaneous stimulating a dog with a bell and food), which is presented before obtaining the target behaviour response (e.g., the dog, after hearing the bell, responds with saliva).

Furthermore, John Watson, the father of behaviourism, emphasized the study of the external behaviour of people and their reactions to given stimuli (stimuli, including anything which may excite activity in a receptor) to the detriment of those people's internal mental state and consciousness. In his opinion, external behaviours and reactions were the only objective method to get insight into human behaviour (Watson, 1913). However, during NFT operant conditioning, the NF stimulus is presented to the participant based on the target behaviour response (brain activity target corresponding to the behaviour response).

Consequently, the stimuli cannot be defined as the sole cause of the behavioural outcome (Marken, 2009). As such, the open-loop S-R behaviourist model cannot convincingly account for the closed-loop S-R operant conditioning occurring during NFT, which inherently depends on internal mental states (Tomas

Ros et al., 2014). As a result, research in NFT is striving for a more robust learning theory, starting from the binary S-R dichotomy and how closed-loop operant conditioning steams from that dichotomy (E. Davelaar, 2017; Tomas Ros et al., 2014; Sulzer et al., 2013; Wood et al., 2014). Such is the case of associative learning theory and information representation theory.

According to the current view, associative learning forms input-output mappings between stimulus and response without representing the environment/state that makes the behaviour adaptive (Wilkes & Gallistel, 2017). For example, in the case of NFT, the NF of the participant is the stimulus, and the participant's objective is the target response. However, the environment/state in which the participant can effectively reach the target and conditionate its behaviour is unknown. The participant learning task is to find the state and loop through it until it gets conditioned (unlike classical and operant learning, e.g., the dog food and the bell is an explicit environment to adapt the behaviour of the dog). Also, most contemporary cognitive neuroscience theories of learning and memory are representational: learning mechanisms extract useful information from experience, while memory carries the acquired information forward in time in a computational form that could be retrieved and used by the subject (Gallistel & Matzel, 2013; Sulzer et al., 2013).

Representational and higher-order cognitive theories are centred on the concept of expectancy, defined as a future-oriented belief, as more than the activation of simple binary associations (like only S-R). In higher organisms like humans, behavioural flexibility requires greater complexity, forming associations via conditioning procedures and other sources of information. Recently, Koralek et al. demonstrated that controlling brain activity is a form of abstract skill (Koralek et al., 2012). In light of these results and earlier studies that show that learning an abstract skill involves cognitive or representational aspects (Beauchamp et al., 2003), we can surmise that learning may involve both methods discussed above, in different degrees (Sulzer et al., 2013).

1.3.2 Factors influencing neurofeedback learning. What don't we know?

Biofeedback literature and advances in NF point to significant factors affecting the learner: contingent feedback and reward, temporal contiguity, learner mental strategies, instructions, psychological variables, and shaping and chaining (Alkoby et al., 2018; Enriquez-Geppert et al., 2017; Silvia E. Kober et al., 2013,

2017; Lotte et al., 2013; M. Ninaus et al., 2015; Manuel Ninaus, Kober, et al., 2013; Tomas Ros et al., 2014; Sitaram et al., 2017; Sulzer et al., 2013; Witte et al., 2013).

Contingency refers to the conditional probability of reinforcement given a response or given a failure to respond (which relates to psychological and neurophysiological factors). In NF studies, the contingency of the feedback stimuli (relationships between response and the feedback) is often manipulated as a control condition, such as sham feedback (Sitaram et al., 2017; Sulzer et al., 2013).

Temporal contiguity refers to the technical factor of the time interval between response and reinforcement, i.e., the delay of technical constraints of measures. For example, the EEG is in the millisecond (ms) range, while real-time fMRI is in the second (s) range (Sulzer et al., 2013).

Mental strategies encompass the training strategies used by the learner to affect change in the NF voluntarily. For example, Kober and colleagues investigated the effects of different mental strategies on NF performance, training participants to use any mental strategy of choice to increase the sensorimotor rhythm (SMR) activity (brainwave activity between 12-15 Hz). Participants who reported no specific strategy showed better SMR control than participants who reported specific mental strategies. These results indicate that successful SMR control was not related to the use of explicit, verbalizable mental strategies (Silvia E. Kober et al., 2013; Sitaram et al., 2017).

Instructed reinforcement, data suggest that instructions are not at all neutral in influencing voluntary control. Subjects tend to report what instructions lead them to expect. Furthermore, tasks designed to test the effect of NFT must look for sensitive yet robust measures that control for the effects of placebo and instruction. Results suggest that contingent feedback (i.e., feedback stimuli that relate directly to the feedback signal) without explicit instructions on mental strategies enable more effective learning. Further comparison studies of this kind in different brain regions and about different brain functions would be necessary to establish the influence of feedback, reward, and instructions in learning brain SR (Lotte et al., 2013; Sitaram et al., 2017; Sulzer et al., 2013). Conflicts in EEG NF literature can be found regarding whether explicit instruction of mental strategies, no instruction of strategies, or only implicit feedback ('covert feedback', i.e., the subject performs non-NFT tasks that spontaneously target the same brain activity as the NFT, achieving similar results but without learning effects) lead to the most successful control of the feedback signal. It poses the question: *"If implicit learning can help regulate brain activation, is any explicit strategy needed at all?"*(Sitaram et al., 2017).

Psychological factors, such as the locus of control[14] and the sense of agency[16], could influence an individual's ability to learn to control brain activity. Studies found that the locus of control was negatively

correlated with the power of SMR self-regulation, leading to the conclusion that instructions should be given to individuals undergoing NFT to avoid forcing mastery over SR and aiming for a state of focused relaxation. The sense of agency for brain-machine interface (BMI) control decreased when the incongruence between the predicted and actual sensory feedback was high. Other factors that are likely to promote SR and require more investigation are concentration, mood, confidence in control, and motivation (Kadosh & Staunton, 2019; Sitaram et al., 2017).

Feedback shaping and chaining (**technical feedback factors)**, the nature of the feedback itself can be deconstructed into components that may individually or in concert affect learning: like feedback presentation, for example, controlling the feedback presentation to be affectively neutral, not intrusive, and not intrinsically rewarding, the type of modality, among others; feedback generation factors, like feedback delay and ensuring the feedback represents the underlying neural activity instead of physical or movement artefacts. How all these parameters may be tuned and to what extent remains one of many open questions for learning mechanisms (Sulzer et al., 2013).

These are significant factors affecting learning, but others can be pointed out, as already described in section **1.2.4**. In the following diagram, Figure 2, we try to shape and chain the research in NF closed-loop factors from the learner perspective to follow what we do not know.

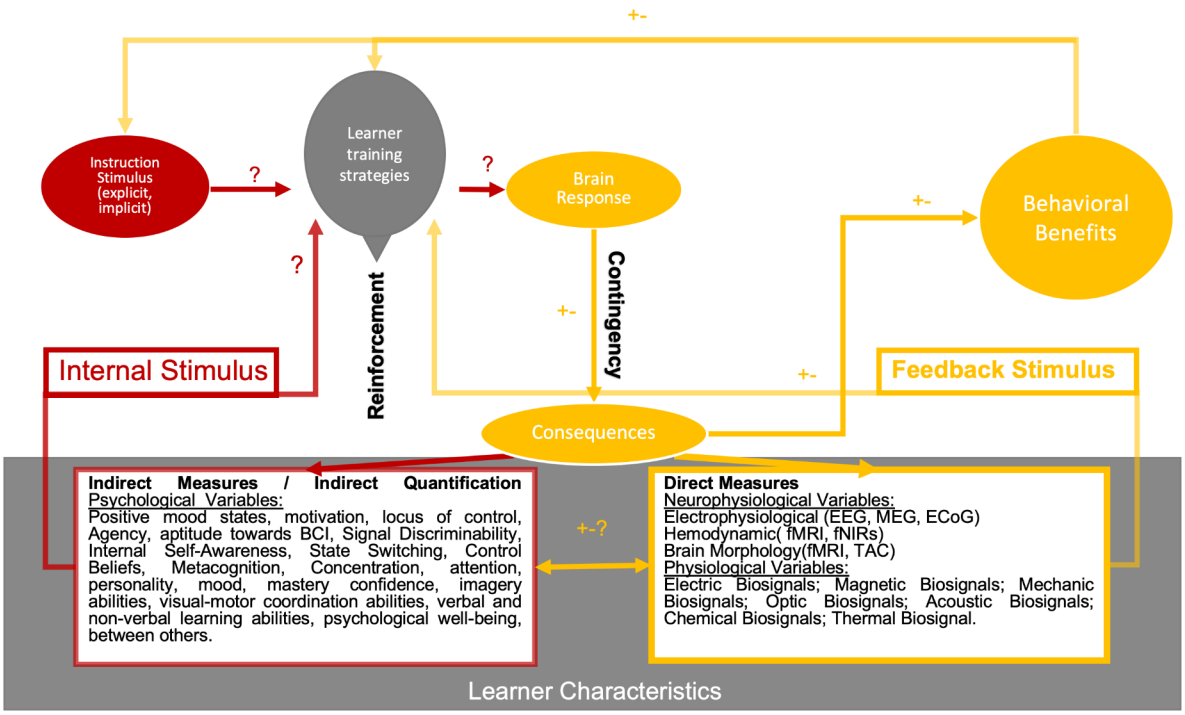


Figure 2 - Shaping and chaining learner Neurofeedback factors. Red colour signals less researched topics, while yellow signals topics that currently have more research.

Figure 2 summarizes the intertwined factors of NF closed-loop learning. The colour scheme red represents the most disregarded factors in the literature: instructions, learner training strategies[11], and internal stimulus reinforcement. The colour scheme yellow represents the most researched factors: brain response, contingency, feedback stimulus (temporal contiguity, shaping, and chaining of feedback), behavioural benefits (memory, performance, among others). Nonetheless, all these factors still have a wide error range. Thus research still lacks in these areas.

From the factors above, we direct our attention to the influence of instructions, explicit or implicit, on voluntary control of internal stimuli. Explicit strategies entail informing the subject of a specific means for SR, while implicit approaches supply no such instruction and allow the subject with extra room to explore different strategies. Recent studies using implicit strategies have challenged conventional wisdom indicating learning within a single session (Shibata et al., 2011). Indeed, implicit strategies may be more helpful since compliance to a suggested cognitive strategy cannot be quantitatively confirmed, and it may be difficult for some people to understand or report (Silvia E. Kober et al., 2013; Sitaram et al., 2017). Leading us to question: is it possible to implicitly prime the Self (the learner) to optimize self-regulation?

Our strategy was to *"outsource"* the control of NF to external stimuli (implicit strategies), capitalizing on superior accuracy and temporal resolution comparing to a human operant internal stimulus. In this way, we could prime the human operant, which in turn can scaffold the optimal internal stimulus. In the simple sense, our priming framework has the objective to be an enabler of voluntary control through implicit strategies. We attempted to prepare the Self with implicit instructions (stimuli) to facilitate internal stimuli.

Our learner-centric approach led us to question: *"why are people not primed with the necessary tools for SR"*? Tools that help standardize the internal stimuli (mental states) instead of only having rest state tasks as baselines and NFT for learning to self-regulate the brain activity. Voluntary control may come naturally to some, but for the majority, that is not a fact. This inefficacy problem is the most validated in NF literature. It cannot be disregarded, and a critical question remains: are there really non-responders, or are they not responding to current protocols designed around the technical factors and forget about the central learner factors?

1.3.3 The "optimal" state

Following the previous question, we also pondered the existence of an *"optimal"* state (within the homeostatic range of states) to learn voluntary control of brain activity, and if there is, can we implicitly instruct the brain to go towards that state?

Indeed, in the literature, we found the hypotheses of an *"optimal"* state to increase performance in voluntary NF self-regulation. In this state, the learner should be more: engaged, focused, undistracted, and mindful of the experiment without judgement of present tasks. Contrarily, the learner should avoid: self-related thinking (self-monitoring), ruminating, distractive and task-unrelated thoughts (E. J. Davelaar et al., 2018; Silvia E. Kober et al., 2017; Manuel Ninaus, Kober, et al., 2013; Witte et al., 2013; Wood et al., 2014). Therefore, understanding how to influence individual SR learning ability through training methods could be the key to unlock predictors and optimize NFT and vice-versa. In Figure 3, we summarize the *"optimal"* state.

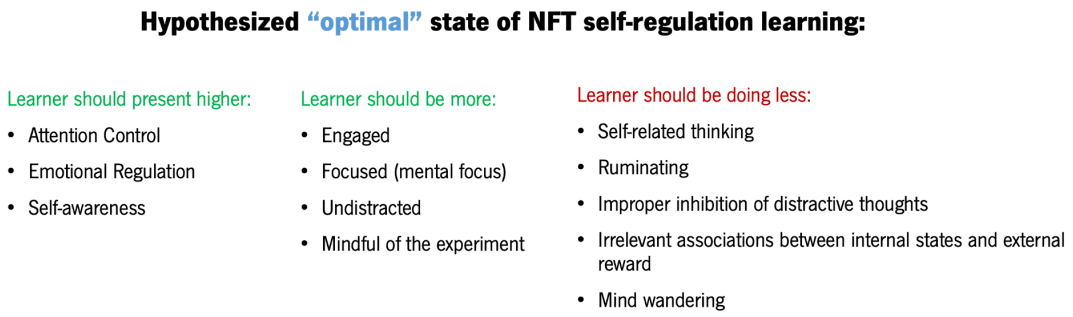


Figure 3 - Optimal state summary. This diagram summarizes the hypothesized "optimal" state of NFT that the learner should reach.

1.3.4 Dual-process Learning Theory

Following this line of thought, Wood and colleagues (Wood et al., 2014) come upon the dual-process theory in an attempt to better specify the concept of self-control/self-regulation[3] in BCI and NF research. Given the wide variety of cognitive and emotional processes associated with the self-control of brain activity and BCI learning, it is beneficial to define a comprehensible but straightforward framework to evaluate each of these processes' common and unique contributions. As the name indicates, the dual-process categorizes the whole mental activity into two main types of processing: more automatic and capacity-free processes (i.e., type I processes) versus more controlled and capacity-limited processes (i.e., type II processes)[17].

Automatic and controlled processes determine self-control of brain activity in very different ways. Nonetheless, not every cognitive process is necessary and sufficient to perform a specific BCI and NF task, but instead, a small subset may play a key role. Therefore, based on the differentiation between automatic versus controlled processing as well as necessary versus unnecessary processes, (Wood et al., 2014) defined a framework of self-control of brain activity with three networks (Figure 4):

- Local control network: automatic (which are influenced by the feedback signal) and controlled (e.g., verbalizations and self-instructions) processes both necessary and sufficient to perform BCI and NF tasks. The more the feedback reflects the activity in this network, the more efficient is the learning process.
- Organistic control network: automatic processes irrelevant or hindering in the context of the NF (such as rumination, mind wandering, past and future thoughts). Therefore, it may be essential to monitor any signs of negative influences originating in organismic control networks.
- Central control network: controlled processes not strictly necessary for BCI and NF learning. Examples of these processes can be improper strategies, improper self-instruction *("I am not doing this right!"*), over-instructions *("I need to control the feedback, focus on the reward, focus!"*) and excessive attention to the Self (*"Am I doing this right? Does the feedback change when I change strategies?"*), that withdraw resources from the local control network. In this network, the controlled processing is mainly under conscious control and can be modulated directly by instructions.

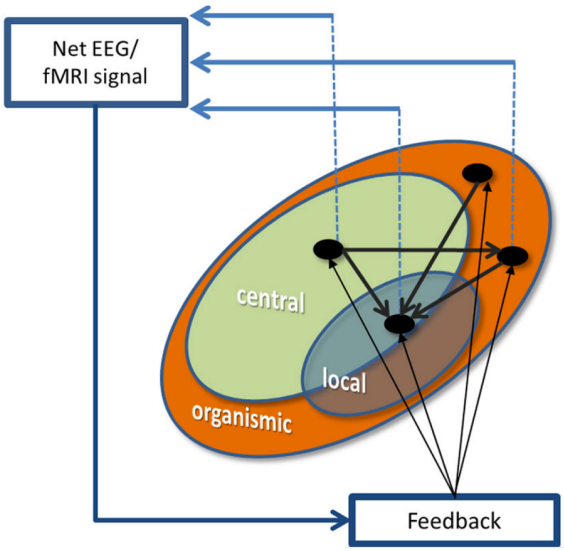


Figure 4 - Schema of different types of self-control of brain activity, adapted from the source (Wood et al., 2014). Specific cognitive processes such as motivation, mood, attention, and executive functions are represented by black dots. Black arrows connecting the dots represent the interactions between the different cognitive functions. Two dots are depicted over the domain of the organismic control network to illustrate that these processes are largely independent of one another. The contribution of the three types of self-control to physiological signals is represented by the dashed lines linking the specific cognitive processes to the physiological signals being recorded for BCI and NF learning.

In summary, (Wood et al., 2014) defined a framework contrasting the necessary and unnecessary processes for an *"optimal"* NF learning. To reach this *"optimal"* state, any BCI and NF learning aims to magnify the signal produced by local control networks and suppress as much as possible the activity on the other two networks (Wood et al., 2014). To do that, they also presented the following solutions. On the one side, participants should learn to decouple irrelevant from those relevant automatic processes. One way to achieve this is to monitor the automatic processes regulating, for instance, adverse emotional reactions and to have a more selective schedule of reward and punishment. On the other side, participants should learn to use the central control networks to inhibit irrelevant cognitive activity operating under conscious control, such as excessive attention to the Self (Leary et al., 2006). Direct verbal instructions (external) or self-instruction (internal) can achieve this (please see examples above in the definition of the central control network).

These solutions point toward monitoring automatic processes and instructing central control network processes, supporting our vision for a framework that primes the subject with stimuli (implicit or explicit instructions, for automatic or controlled processes) and monitors if the subject is reaching the NF target. Leading us to the testable question: can this kind of framework support the learning to self-control the target? In the next section, we present suggestions to answer this question.

1.3.5 Dynamical systems theory & Control theory

In a similar attempt to unlock the secrets of direct SR of brain oscillations, Ros et al. followed by Davelaar et al. (E. Davelaar, 2017; Tomas Ros et al., 2014) accommodated their conceptualization within the framework of dynamical systems theory and revisited NF learning from the engineering (control theory) and the neurobiological perspective (Hebbian and homeostatic rules).

The brain as a dynamical system of states

Introducing time into the analyses takes into account that brain oscillations are non-stationary, i.e., their oscillatory parameters are not constant across time. Interestingly, such time-varying behaviour can be accommodated within the framework of dynamical systems theory. In essence, a system's operation can be represented in state-space, which is best visualized as a multidimensional energy landscape (Tomas Ros et al., 2014). This landscape can be simplified to 2-dimensions and envisaged as a ball with random energy (i.e., noise) traversing hills and valleys or 3D like maps (Gu et al., 2018) as described in Figure 5.

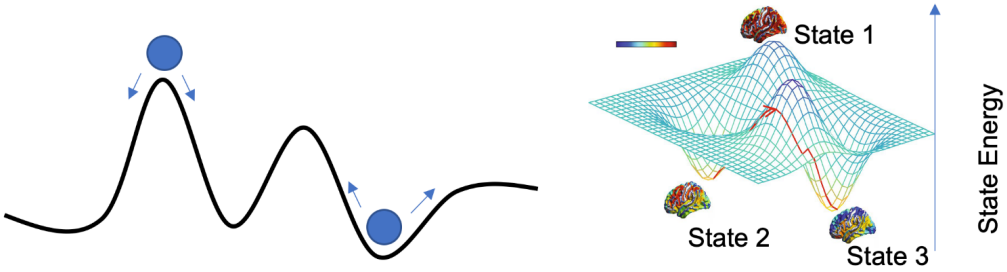


Figure 5 - A visual portrayal of state-space landscapes. On the left, a hill and valley represent a repellor (top) and an attractor (bottom). It was based on (Tomas Ros et al., 2014). While on the right, one can see a similar "walk" in a 3D representation, source (Gu et al., 2018).

However, is there explicit evidence of attractor-like signatures in the brain? Amazingly, it seems that oscillations with distinct frequency *"peaks"* exhibit attractor properties, such as delta and alpha rhythms (Freyer et al., 2011; MacIver & Bland, 2014). Firstly, alternating (de)synchronization patterns can be understood to display non-random statistical properties, exemplified by different temporal distributions (i.e., dwell-times) of low versus high synchronization states. Such state transitions, known as bifurcations, may be driven by both internal (Freyer et al., 2011) as well as external (Avella Gonzalez et al., 2012) network activity (neuron activity driven by cholinergic input and trains of action potentials that activate excitatory synapses). Secondly, phasic or tonic[18] alternations between EEG frequencies may also be seen as reflecting dynamic transitions between attractors (Tomas Ros et al., 2014).

Dynamical systems theory points to a related topic, criticality. From the laws of thermodynamics, critical systems are said to operate at the edge of chaos. That is to say, at an optimal *"sweet spot"* between order and disorder, which paradoxically affords flexibility and stability (Hellyer et al., 2016; Pastukhov et al., 2013). Practically speaking, the brain exhibits both stability when generating consistent behaviour and variability when learning new patterns. Nevertheless, this is insufficient to prove the brain operates near criticality. However, an ever-growing body of work has emerged on neuronal avalanches and temporal auto-correlations, suggesting that the brain may indeed operate near criticality, which would endow it with maximal dynamic range, information transmission, and capacity (Tomas Ros et al., 2014).

Therefore, beyond the general clinical view that NFT normalizes the brain, the neurocognitive perspective adds that NFT increases the neural efficiency or brings the brain closer to self-organized criticality, favouring maximal information transfer (E. Davelaar, 2017; Tomas Ros et al., 2014) — pointing again in the direction of an *"optimal"* state.

Hence, Ros et al. (Tomas Ros et al., 2014) speculate that abnormal synchronization patterns emerge from plastic changes in brain-state attractor landscape(s), which mutually shape and are shaped by

system criticality. Manifesting as subcritical or supercritical regimes that characterize disease (Poil et al., 2012), and by restoring these pathological oscillatory signatures toward normative values found in the healthy population (e.g., power, phase-locking, peak frequency, 1/frequency) would restore the near-critical regime required for optimal information processing (Shew & Plenz, 2013; Thatcher et al., 2009). The same can be said for healthy individuals and their capacity to self-regulate and restore their normal states (e.g., from stressful state to relaxed state).

Additionally, Shi Gu et al. (Gu et al., 2018) go further using dynamical systems to hypothesize that brain state transitions with high energy differences would be difficult for humans to perform on demand. Evidence suggests that the pattern of connections between brain regions directly informs not only the ease with which the brain may control state transitions (Betzel et al., 2016; Gu et al., 2015, 2017), but also the ease with which one can externally elicit a state transition using non-invasive neurostimulation (Muldoon et al., 2016). The existence of such an energy landscape motivates the fascinating question of *"how does the brain transition between states? Which walks a healthy* (*or diseased) brain might take through this landscape?"*. Such walks or dynamical trajectories may be determined by energetic inputs to specific brain regions (Gu et al., 2015), either by external stimuli or neuromodulation (Muldoon et al., 2016). In this context, network control theory may offer explicit predictions about the optimal dynamic trajectories that the brain may take through a set of states to move from an initial state to a target state with little energetic resources. In addition to inputs to single regions, changes in a cognitive task – for example, elicited by task-switching paradigms – may also drive a specific trajectory of brain states. Indeed, it is plausible that the asymmetric switch costs observed between cognitively effortful and less effortful tasks (Proskovec et al., 2019; Wu et al., 2015) may be explained by characteristics of the energy landscape defined by structural connections between task-activated brain regions (Gu et al., 2018; Zhu et al., 2019).

In tandem with these ideas, our framework intended to reset *"for a few moments"* some of the self-related thinking (trying states) by focusing the attention on present sensations (sensing states) and, possibly, lower the switching cost of state transitions throughout NFT and drive a specific trajectory of brain states, which should get the subject closer to NF target state.

Control theory, multi-stage framework & network control

Ros et al. (Tomas Ros et al., 2014) used insights from control theory[19], with closed-loop feedback models as a cornerstone (Grychtol et al., 2010; Marken, 2009), to propose a *"better"* conceptualization of NF learning.

Their multi-stage control theory framework is subsumed in Figure 6, going from *"bottom-up"* automatic processes of neural synchronization, followed by *"top-down"* controlled regulation of internal brain states. The circuit consists of a Controller (green), which regulates the control parameter until the output of the System (blue), measured by the Sensor (red), matches the internal reference value or set-point (±). In NF terms, the neurobehavioural conditioning can be condensed in the following stages: 1st stage, fluctuating feedback signals, stochastic & unconditioned neural variability; 2nd stage, fortuitous events may lead to neural variability to infrequently generate activity that meets the threshold for reward; 3rd stage, sensory-representation of above-threshold followed by a reward feedback signal (e.g., dopamine, serotonin), leading to the memorization of the distinct neural/behavioural state, the so-called internal set-point; 4th Stage, subsequent feedback loops try to reproduce set-point, leading to feedforward strategies (i.e., adjustment of the controller based on mental disturbances).

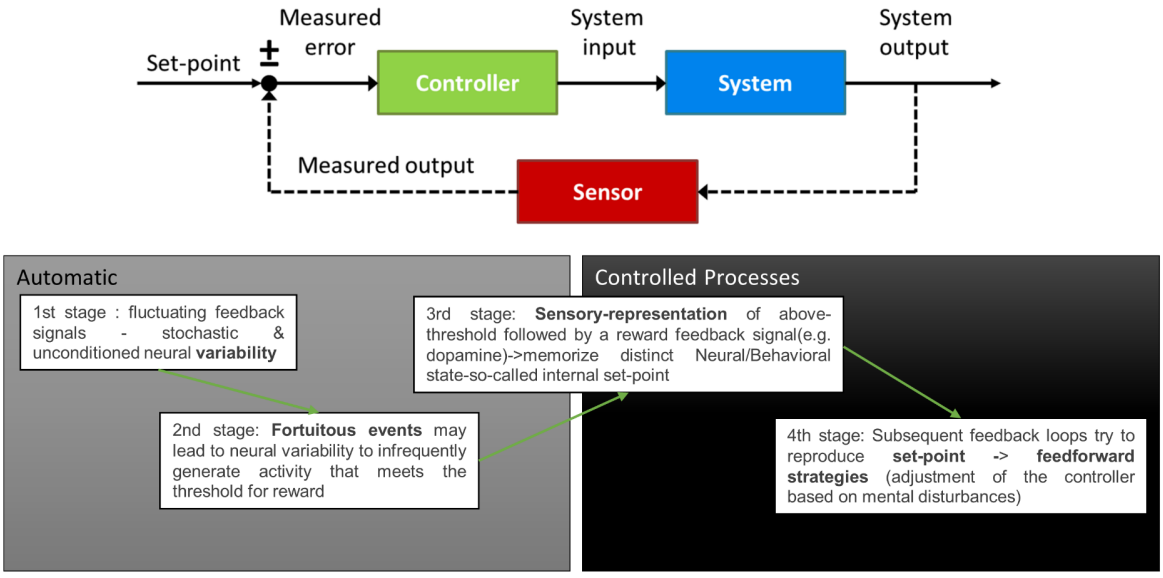


Figure 6 - Diagram of NF control framework. It was adapted from the source (Tomas Ros et al., 2014). NFT closed-loop stages from automatic to controlled processes

In a review paper, Birbaumer et al. (Birbaumer et al., 2013) largely agree with the first two stages described above of trial-and-error and reinforcement learning but disagree in the controlled processes. Highlighting the importance of motivational signals to stabilize the desired response plan through primary

and secondary reinforcers, but the subjective experience is not seen as a potential secondary reinforcer, i.e., they only viewed NF learning as an implicit learning mechanism. However, this view does not account for the complete picture. Instead of assuming only implicit or explicit learning processes, the multi-stage theory allows for both components. Davelaar (E. Davelaar, 2017) further suggests the results of activation in the anterior insula and its role in interoception[20], and it could suggest a subjective mental representation based on proxies of bodily sensations. This representation could appear during stage 2 and be consolidated in stage 3, influencing learning as a secondary reinforcer.

Davelaar (E. Davelaar, 2017) goes deeper and connects the multi-stage theory with network control. In stage 1, the striatal-exploration stage, the frontal or executive system generates representations that create an activation pattern in the striatum. These frontal representations are goals that activate associated response plans. The striatal representation or response plan will modulate the activation of the thalamus and thereby the EEG signal recorded in the cortex (three smaller blue squares). Stage 1 involves changing the synaptic connections between the frontal and striatal representations, using reward as the primary reinforcer. In stage 2, the thalamic-consolidation stage, a stable frontal representation is present, and the synaptic modifications occur between the striatum and the thalamic nuclei. Modifications in stage 2 may lead to further stage 1 learning. In the final stage 3, the interoceptive-homeostasis[20] stage, which is not obligatory, a distinctive internal representation of the consequences of the target brain state becomes associated with the reward and, in turn, a secondary reinforcer.

Ros (Tomas Ros et al., 2014) and Legenstein et al. (Legenstein et al., 2008, 2010) agree to the view that a reward-modulated Hebbian learning rule governs synaptic plasticity. They further suggest that the NFT system essentially augments the sensory repertoire, allowing the brain to ‘‘sense” the neuroelectrical patterns and thus make them amenable to control in a homeostatic manner. In addition, they argue that feedback signals need to be presented above the threshold for awareness to be effective. Although they do not provide explicit mechanisms by which NFT operates, as suggested by Davelaar (E. Davelaar, 2017). Instead, they use dynamical systems theory to argue that NFT brings a disordered brain into a regime where there is maximal information transfer, which explains the benefits on cognitive and creative abilities of NFT - for reviews in these benefits see (John H. Gruzelier, 2014c, 2014d).

Thesis fundamental hypothesis

Given the evidence that the brain respects the previous control theoretical principles, it is reasonable to hypothesize that the direct sensing accomplished by a BCI enables control of specific brain oscillations

that might otherwise fall outside the scope of conscious awareness. Therefore, the first advantage of NFT may be to enlarge the cerebral sensorium and thereby enable implicit control of covert brain activity that may have no direct behavioural correlates (e.g., focus on sensory information, auditory hallucinations) (Tomas Ros et al., 2014). This line of thought points towards implicit instructions/stimuli (e.g., SR techniques: meditation, praying, interoception, between others) that could also complement and support the effects of NFT.

Ros et al. (Tomas Ros et al., 2014) asked, *"What can be gained by forming a human-computer hybrid for control of brain activity?"* Based on control theory, they hypothesize that such a hybrid BCI may enable human controllers to *"outsource"* their sensory-feedback processing and augment it with that of the computer, capitalizing on both its superior sensing accuracy and temporal resolution. A testable hypothesis that stems from this interpretation is that NF-assisted control could prove more effective than an unassisted human operator.

Therefore, following this line of ideas, developing a virtual machine controller that supports self-regulation can be the path moving forward. Pointing again towards the hypothesis that external stimuli can prime & scaffold SR of NF.

1.3.6 Instructions design for NFT

Research in the instructional design field, educational psychology, and human factors have identified the key elements for efficient training across several different skills, e.g., language, mathematical, memory, or motor skills, making them generic and relatively skill independent. Even though NFT approaches are instructional designs (they aim at teaching the BCI skill), most of them, unfortunately, do not follow guidelines provided by these research fields (Lotte et al., 2013). In the following lists, guidelines for the design of feedback, pre-training instructions and tasks are summarized.

Good feedback should be (Enriquez-Geppert et al., 2017; Hattie & Timperley, 2007; Lotte et al., 2013; Moreno & Mayer, 2007; Shute, 2008; Sitaram et al., 2017):

- Non-evaluative, should not only indicate the task performance.
- Supportive: show how to improve the task; reduce uncertainty; provide a feeling of competence (Deci & Ryan, 2010; Ryan & Deci, 2000), increasing intrinsic and extrinsic motivation.
- Timely: the feedback presentation should ideally reach a zero delay to synchronize perfectly between actual brain activity and the feedback presented.

- Specific: self-explanatory, clear, purposeful & meaningful.

Instead, the feedback usually is evaluative, corrective, and non-specific (crude, simple, unclear about task purpose) (Lotte et al., 2013).

Good pre-training instructions should have the following characteristics (Lotte et al., 2013):

- Clearly defined Training procedure & goals/objectives.
- Demonstration of successful NF with feedback correctly performed.
- Explain Feedback: is more effective when goals are clearly defined and specific (Hattie & Timperley, 2007; Moreno & Mayer, 2007); learn to ignore potentially erroneous intuitions about the meaning of the feedback.

Instead, crucial historical bias has disregarded the instructions design (Sulzer et al., 2013).

Good training tasks should (Lotte et al., 2013):

- Provide engagement, involvement, excitement, interest, efficiency, and mastery of confidence, incompetence, fear, among others.
- Address the following parameters: challenge; novelty; appealing environments (Ecologic validity (Sollfrank, 2015; Sollfrank et al., 2016), gamification (Lumsden et al., 2016)); variability.
- Focus on Personalization:
    - Should provide intrinsic motivation:
        - Feeling of competence (tasks progressive and adaptive – complexity & scaffolding).
        - Feeling of autonomy (free or self-paced sessions).
        - Relatedness (emotional appealing & management).
    - Identification of variations that are more suited to the kind of user characteristics.

Instead, tasks are mostly system-paced (not self-paced), boring and repetitive (Lotte et al., 2013).

Therefore, tasks need to be involving, engaging, progressive, and promote an adaptive learning environment. Feedback should engage the feeling of competence. Mood and motivation are essential precursors, and the strongest motivation, intrinsic motivation, is anchored in basic urges (Kleih et al., 2010; Femke Nijboer et al., 2010). In this way, with importance to our study, stimulation can scaffold the desired mental task. It is an easy-to-manage starting point for training that can complement the NFT. Such a gradual transfer from well-known or straightforward tasks to new tasks initially minimizes the users' cognitive demand during training (Lotte et al., 2013). Hence it minimizes the risk of frustrating and

demotivating them. For these reasons, we found another pointer suggesting the need to prime the subject in scaffolding the desired mental task and the desired mental state in instructions design.

1.3.7 NFT specificity

Three of the cardinal theoretical assumptions inherent in the practice of neurofeedback concern issues of specificity. (1) Frequency band specificity: the assumption of a separation of the training outcome from the chosen band from adjacent flanking and other spectral bands. (2) Topographical specificity: selecting electrode placement according to the behavioural or neurophysiological processes to be modified. (3) Outcome specificity: the choice of bands for training based on their putative psychophysiological salience for outcome in terms of presumed cognitive/affective performance correlates (John H. Gruzelier, 2014b).

Evidence suggests frequency band non-specificity in the current protocols, i.e., evidence supports a dynamical shift of the target band and the adjacent flanking bands after training. Therefore, the subject does not target the amplitude of only one specific frequency band. After training, the subject has more amplitude gains in the target bands than flanking bands (John H. Gruzelier, 2014a, 2014b; van Lutterveld et al., 2017). Indeed, evidence is most in favour of band non-specificity within and across sessions. However, there is some evidence of specificity across session baselines (John H. Gruzelier, 2014a, 2014b; van Lutterveld et al., 2017). The evidence is complex regarding bandwidth specificity. In addition to the training band, the NF process itself and its non-specificity calls on a range of processes (such as learning, attention, motivation, effort, reinforcement monitoring, among others) that may invoke several bands. Non-specificity was the more prevalent outcome, though interestingly less so with successive baseline carryover, which is the more enduring goal for feedback learning (John H. Gruzelier, 2014b).

Regarding topographical specificity, there is little support from the experimental studies. However, the frontal locus shows the most changes following training, though this is not an exclusive locus. Even posterior training predominantly leads to stronger frontal than posterior effects. Notably, while the executive processes involved in learning through feedback involve the frontal lobe and manifest during training, the long-term effects outlive the actual learning of SR and represent the mastery of learned SR (John H. Gruzelier, 2014b).

Regarding the outcome specificity, behavioural outcome gains can be significant for the training band and/or correlate with it, indicating specificity of the behavioural outcome, even where frequency non-specificity rules (John H. Gruzelier, 2014b).

1.3.8 A representation of the mental system: epistemology of perception, from automatic sensations to controlled concepts

Without getting into detail, as this is outside of the scope of this Bioengineering dissertation, a simple mental system of thought is represented in Figure 7 diagram. Following the epistemology laid out by Kant (Kant, 1899), we can define how our mind combined with our Self represents reality, from sensations to concepts. Starting from representing reality that is purely a perception of the mind that can be separated in perception through the senses (self-as-object, as defined by William James and Damasio (Damasio, 2010; W. James, 1890)) and the knowledge (self-as-subject, as defined by William James and Damasio). These two perceptions are interconnected and affect each other. Kant further distinguishes between two different fundamental types of representation: intuitions and concepts. Intuitions are "immediate representations" that represent things directly, automatically. Concepts are "mediate representations" representing general characteristics of things. Kant divides intuitions into empirical and pure and discusses how sensations (automatic processes) transfer to concepts (controlled processes). From this processes transfer, from automatic to controlled, we bridge this epistemology with the engineering scope already detailed within the multi-stage control theory of NF learning. In this way, we broadly represent a complete mental system of thought processes, from automatic to controlled.

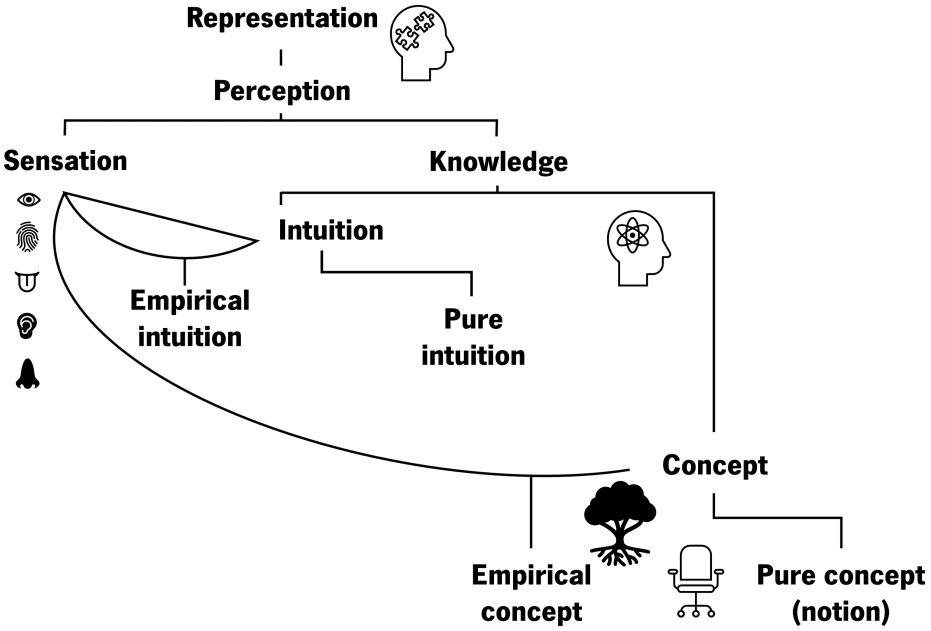


Figure 7 - Diagram of Kant system of thought. Adapted from (Kant, 1899). From sensations (automatic processes) to concepts (controlled processes)

1.3.9 Framework model: putting all together

Based on the merits of the previous frameworks, we arrive at the building blocks for our framework model: (1) Control theory, (2) Multi-stage NF learning theory, (3) dynamical-systems theory (E. Davelaar, 2017; Gu et al., 2018; Tomas Ros et al., 2014), (4) dual-process theory (Wood et al., 2014), (5) epistemology (Kant, 1899) and instruction design (Lotte et al., 2013). From these, we get a good foothold of what our NF learning framework can entail. In the following diagram (Figure 8), we try to put it all together, so the reader gets the full picture.

The Learner can be considered a dynamic system with an uncertain number of free parameters, a grey box model, an overly complex system. Fundamentally, we do not seek a black-box approach that offers optimal prediction. Instead, we seek a first-principles model that can provide an intuition for system function and can be used to generate hypotheses that can be tested in future empirical studies (Gu et al., 2018; Tomas Ros et al., 2014).

The system's internal *"optimal"* set point is when the target is reached after several runs. Our research aims to support the learner to get into this optimal state by answering the question: What can be gained by forming a human-computer hybrid to control brain activity?

Our framework intends to reset *"for a few moments"* some self-related thinking (trying states) by focusing the attention on present sensations (sensing states) and trying to lower the switching cost of state transitions throughout NFT. It initially minimizes the cognitive demand on the users during training. Hence it minimizes the risk to frustrate and demotivate them and drive a specific trajectory of brain states closer to the NF target state.

Suppose the NF system essentially augments the sensory repertoire, allowing the brain to ''sense" the neuroelectrical patterns and thus make them amenable to control in a homeostatic manner. In that case, we will try to support the NF to enlarge the cerebral sensorium through implicitly *"outsourcing"* sensory-feedback processing to extrinsic neurostimulation. Using the computer as a virtual machine controller of the brain system, capitalizing on its superior sensing accuracy and temporal resolution. Towards the hypotheses that external stimuli can prime & scaffold SR of brain states through NF (E. Davelaar, 2017; Gu et al., 2018; Tomas Ros et al., 2014).

From a multi-stage point of view, we will try to lower the transition cost to reach the internal set point. Trying to start from an optimal variability state, where the user has more fortuitous events above the threshold (E. Davelaar, 2017; Tomas Ros et al., 2014).

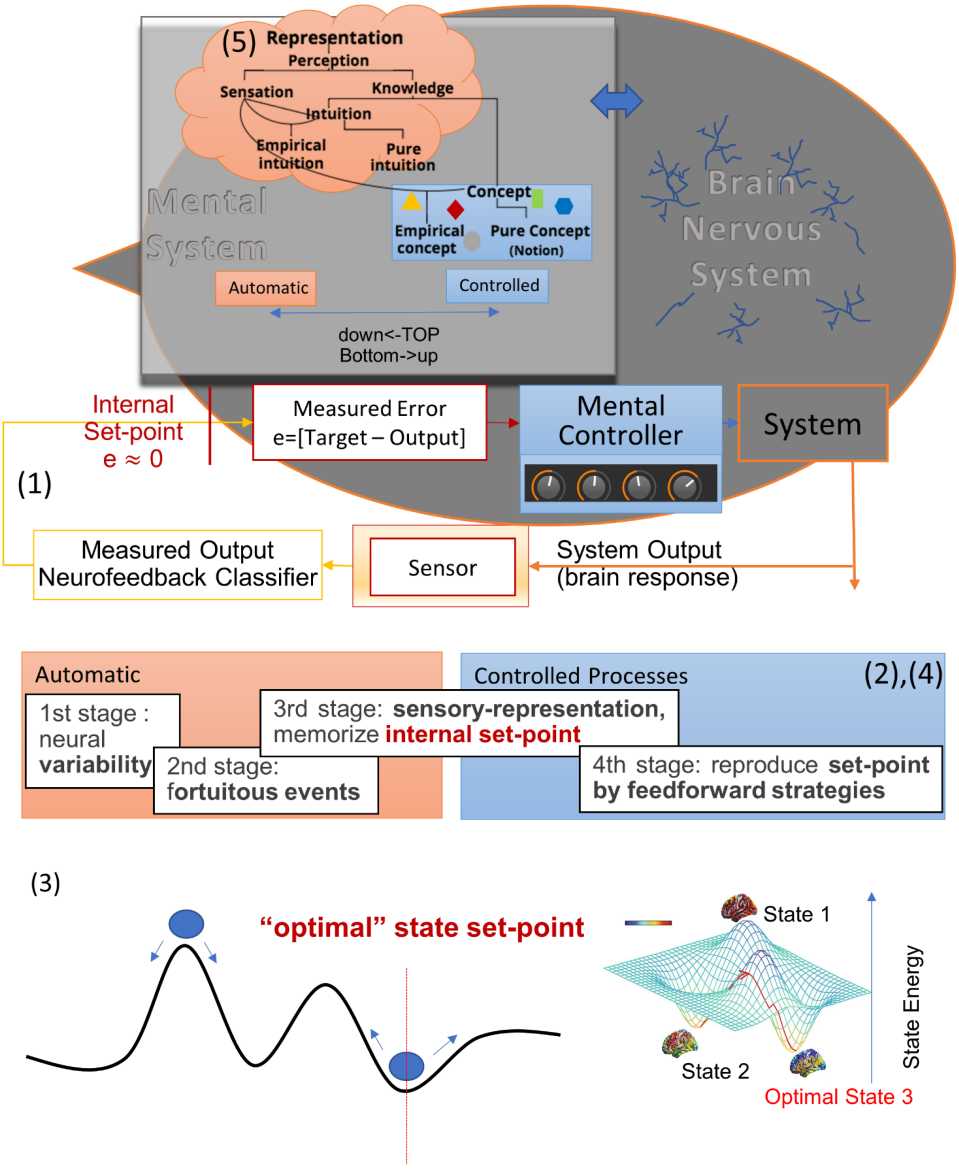


Figure 8 - Neurofeedback Learning Model. (1) Control theory (2) Multi-stage Neurofeedback learning theory, (3) dynamical-systems theory, (4) dual-process theory, (5) epistemology.

Literature uses dynamical systems theory to argue that NF brings a disordered brain into a regime with maximal information transfer (near criticality). Which in turn, explains the benefits on cognitive and creative abilities of NFT (E. Davelaar, 2017; John H. Gruzelier, 2014b, 2014d; Gu et al., 2018; Tomas Ros et al., 2014). We hypothesize that the framework can support these transitions (automation and personalization) and facilitate the transition between automatic and controlled mental processes of attention, enabling the user to reach a state in which SR of brain activity is facilitated. In this way, the proposed framework is intended to facilitate the brain control state transitions with the help of external eliciting state transitions using non-invasive neurostimulation. The hypothesis that stems from this interpretation is that NF-assisted brain control could prove more effective than an unassisted human operator.

CHAPTER 2

The Framework

This chapter is based on the following scientific publication:

NeuroPrime: a Pythonic framework to research the priming of brain states. (accepted)

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2. CHAPTER 2 - THE FRAMEWORK

Our aim is to enable human controllers to *"outsource"* their own sensory-feedback processing and augment it with that of the computer, capitalizing on both its superior sensing accuracy and/or temporal resolution. For that, we developed a bypass of the internal stimulus that can prime and scaffold self-regulation of EEG NF. Using the previous NFT factors diagram (Figure 2) and projecting the bypass over it, we show our goal in Figure 9.

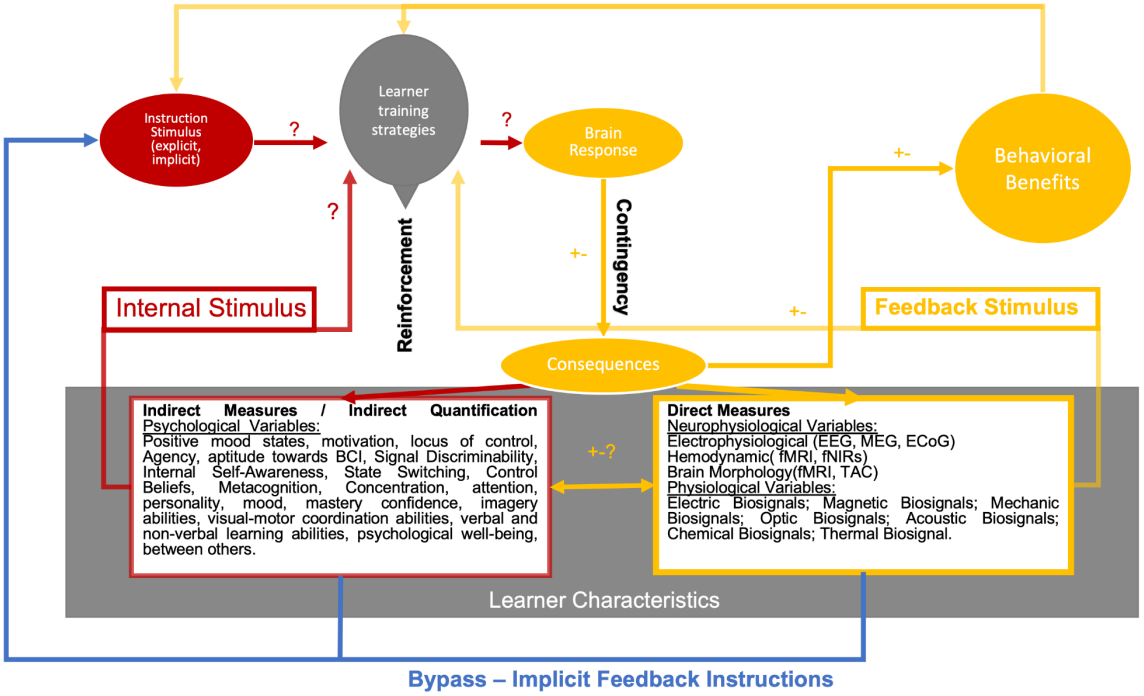


Figure 9 – Bypass, implicit feedback instructions. Using direct measures and self-reports has data to inform a computer controller and, based on its precision, select the best instruction stimuli for the next feedback loop.

Therefore, we aimed to create a framework[9] to research the transitions between states and study the brain as a dynamic system. From this point of view, we want to find the personalized *"walks"* between states and, specifically, to find the walk to the *"optimal"* state to learn SR (Figure 10).

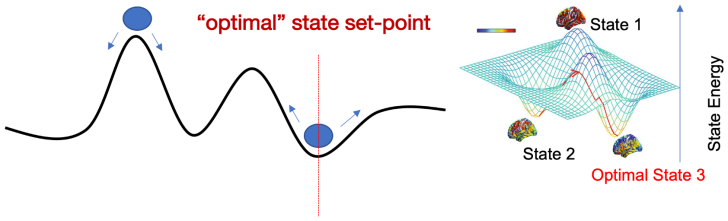


Figure 10 - Internal *"optimal"* state stet point, representation in 2D and 3D. On the left, a hill and valley represent a repellor (top) and an attractor (bottom) with a possible "optimal" target set-point. While on the right, one can see a similar "walk" in a 3D representation.

2.1 Framework design

NF as a closed-loop (where the brain activity is continuously fed back to the neural system) can be applied as an experimental method to investigate the causal character of specific neural events (such as brain oscillations) within cognition and behaviour. This procedure is defined as brain-state dependent stimulation (BSDS) (Enriquez-Geppert et al., 2017; Jensen et al., 2011; Royter & Gharabaghi, 2016).

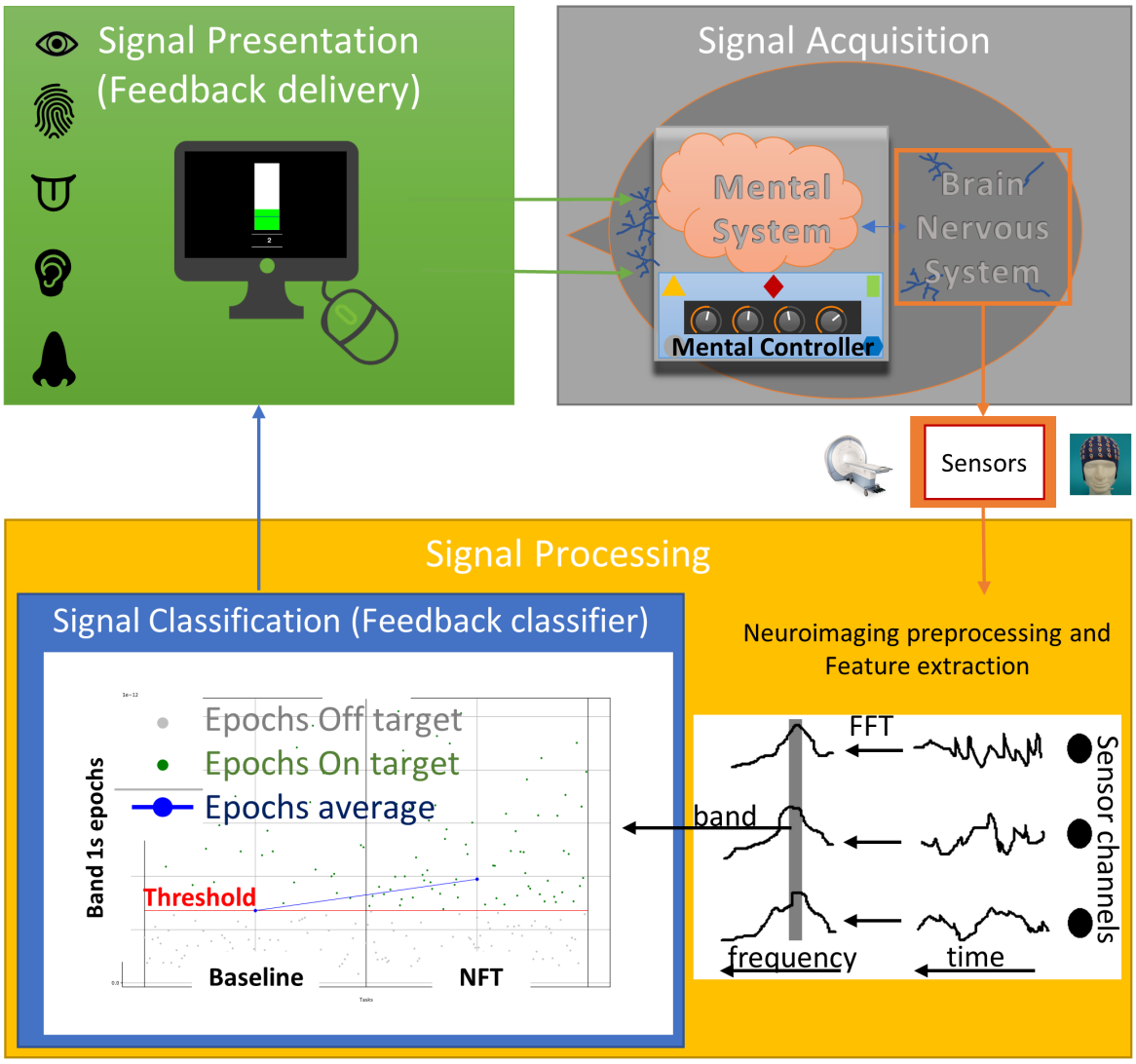


Figure 11 – NFT design diagram. The NFT is divided into the signal presentation, the feedback delivery interface; signal acquisition, the data; signal processing and classification, the feedback feature extraction, and classifier.

NFT closed-loop design can be divided into three parts, as depicted in Figure 11: signal presentation (SP), signal acquisition (SA), signal processing and classification (SPC). Summarizing, SP deals with the graphical user interface (GUI) used to present the NF (stimuli and feedback modality, feedback presentation and timing). SA deals with the acquisition of the signal from the learner, the data structure

and storage. Lastly, the SPC uses the data acquired for online data pre-processing, feature extraction and feedback generation.

Our priming framework training design follows the BSDS experimental method to investigate the functional role of certain target oscillations or brain states. It is envisioned as a closed-loop stimulator, meaning that the stimulus is updated by the brain states of the participants, as can be found in Figure 12.

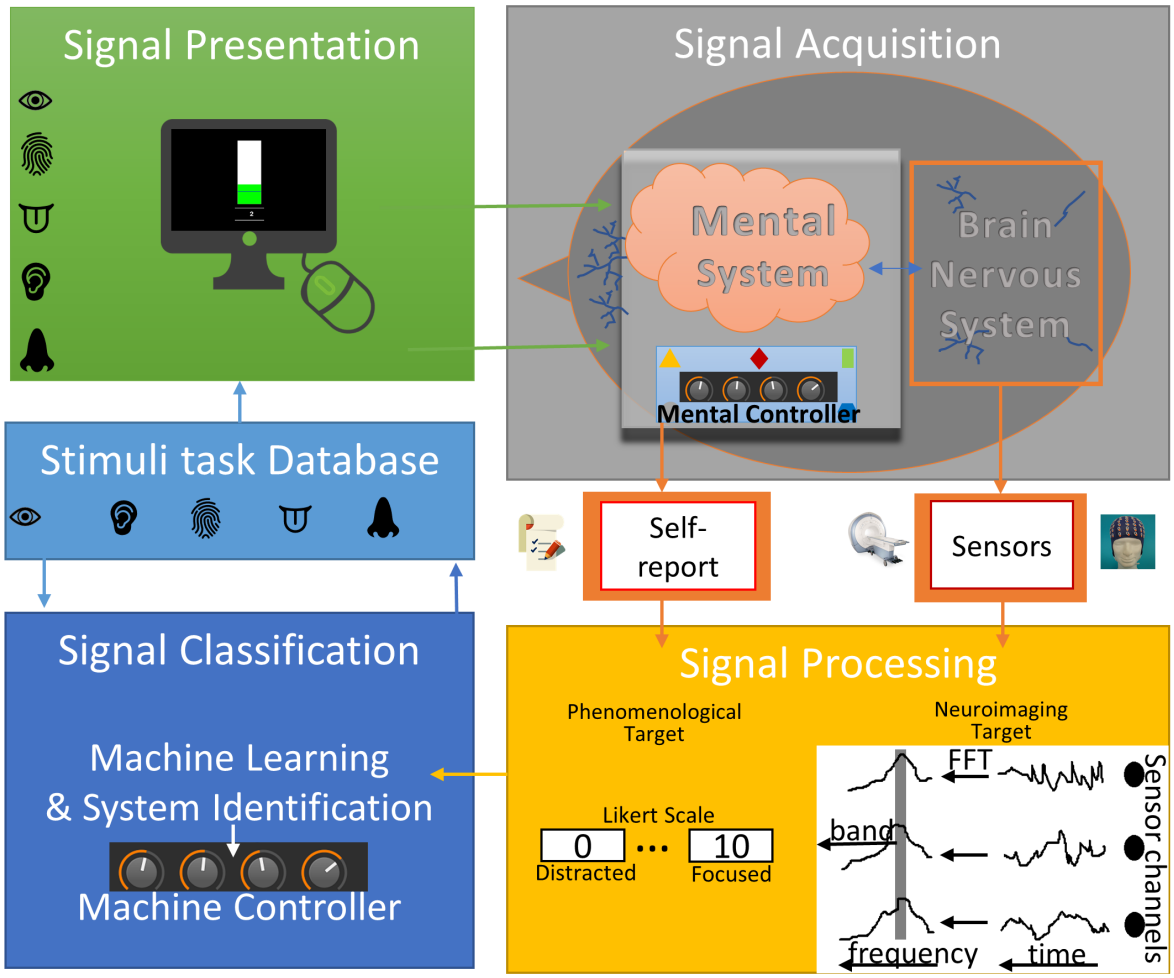


Figure 12 - Framework design diagram. The framework has an architecture similar to NFT's: signal presentation, the feedback and stimulus presentation; signal acquisition, the data; signal processing, phenomenological and neuroimaging feature extraction; signal classification, the machine learning controller decoding and classifying mental states; stimuli task database, the database with the stimulus categories to be presented to the user.

2.1.1 Signal Presentation

The signal presentation should support explicit NFT with stimuli targeting implicit neural responses. Temporally, the stimuli can be presented before, after, or during NFT. In this study, the experiments applied the stimuli before the NFT (pre-NFT) as a priming stimulation. Additionally, the presentation design was guided by instructions design (please go back to section **1.3.6**)

2.1.2 Signal Acquisition

NF plus the neurophenomenological[10] target offers a new way to relate the phenomenological structure of subjective experience with a real-time objective characterization of large-scale neural operations continuously over the course of the experiment.

Besides EEG, self-reports (qualitative) and other biodevices (quantitative) can also be added for more precise signal acquisition and classification (please check chapter **5** for a combined implementation of self-reports and biodevices). The possibilities are endless, but for instance, body biomarkers to infer the emotional engagement of the subject by using indirect signals can provide the big data needed to push this framework classification to *"higher heights"* (Ghiasi et al., 2020; Shu et al., 2018). In fact, indirect signals of emotional processing could be gathered by picking variations of the activity of the anatomical structures linked to the emotional processing activity in humans, such as the activity of sweat glands on the hands, the variation of the heart rate (Vecchiato et al., 2010) and real-time facial expressions detection (Bartlett et al., 2005), through video recording and machine learning. In particular, by monitoring autonomic activity using galvanic skin response (GSR) devices and the Heart rate Variability (HRV), it is possible to assess the *''internal''* emotional state of the subject, measuring the level of the autonomic system. In fact, GSR is actually viewed as a sensitive and convenient measure of indexing changes in sympathetic arousal associated with emotion, cognition, and attention (Boucsein et al., 2012; Critchley, 2002; Posada-Quintero & Chon, 2020). In addition, the link between the HRV and the sympathetic/parasympathetic vagal balance has also been suggested (Beauchaine, 2001; Graziano & Derefinko, 2013; Malik et al., 1996; Montano et al., 2009; Zahn et al., 2016).

2.1.3 Signal Processing

Neuroimaging targets

As already introduced, current EEG literature relates the SR *"optimal"* state (see **1.3.3**) with up-regulation of alpha rhythm or/and SMR (both linked to attentional processes), but also with correlation with surrounding bands (J. Gruzelier et al., 2010; J. H. Gruzelier et al., 2014; John H. Gruzelier, 2014c, 2014d; Hanslmayr et al., 2005; Klimesch et al., 2007; Silvia E. Kober et al., 2017; Silvia Erika Kober et al., 2015; van Lutterveld et al., 2017; Zoefel et al., 2011). An example of this is shown by van Lutterveld et al. (van Lutterveld et al., 2017), who found that the correlated effects between effortless awareness

and amplitude reduction in gamma-frequency range within the posterior cortex (posterior cingulate) were also observed within the alpha, delta, theta, and beta frequency range. This band non-specificity is described in **1.3.7**. In fact, current evidence is lacking in the specificity between alpha and SMR NFT, as reviewed by Gruzelier the need to (John H. Gruzelier, 2014b): *"contrasting alpha-2 up-training with up-training the SMR amplitude; clarifying alpha's role by comparing alpha-1 and alpha-2, or even a threefold alpha classification".*

In the following section **2.2**, this similarity in outcomes of the two bands is further detailed and how they relate with MM and the *"optimal"* state.

Phenomenological targets

Exploring the phenomenological experience is an essential complementary mechanism to understand the NF data. The challenge is how to transform the qualitative data into objective quantitative data. Davelaar et al. (E. Davelaar, 2017; E. J. Davelaar et al., 2018) have experimented with guided reports through interviews, while others like Garrison et al. (Garrison, Santoyo, et al., 2013) used self-reports (e.g., *"on a scale from zero to ten how did you feel during the task?"* 0 = distracted; 10 = focused).

Phenomenological analyses have established that different NF protocols are related to different subjective experiences (Edge & Lancaster, 2004) and that differences in learning success may in part be due to differences in subjective experiences (E. Davelaar, 2017; E. J. Davelaar et al., 2018).

2.1.4 Signal Classification & Stimulus database

We approached the problem through a framework that should learn how to guide the user to an attentive mental state using a sequence of stimuli (simple or/and complex). It is based on NF learning theories (operant conditioning, dual-process theory, control theory, dynamic system, and multi-stage theory, as we already described), intra-individual differences, system identification, and machine learning. Additionally, our theoretical framework should follow an ADO approach (Sanchez et al., 2014) as already introduced in **1.2.6**. In the paper, Sanchez et al. showed the benefits of adaptative real-time (online) approaches and the contrasts to classical (offline) approaches. The classical approach is characterized by a sequential ordering of the main experimental steps: experimental design specification occurs prior to data acquisition, followed by data analysis and hypothesis testing. In contrast, the adaptive approach operates in real-time and proceeds with design optimization, data acquisition, and analysis at each experimental stage or trial. The online approach enables hypothesis testing to be optimized at the individual level by adapting the

experimental design based on past observations. This is the general principle of ADO, which can be extended to advanced computational models of electrophysiological responses thanks to brain-computer interface (BCI) technology, with the aim of optimizing experimental conclusions.

Instead of a white-box system based on first principles (e.g., Newtonian principles) - such models are overly complex, and possibly even impossible at the moment, due to the complex nature of the many systems and mental processes - a much more common approach is to start from measurements of the behaviour of the system and the external influences (inputs to the system), and then try to determine a mathematical relation between them without going into the details of what is happening inside the system. This approach is called system identification. As a future perspective, an example of a system identification mathematical relation is the dynamic neural fields (DNFs), which have been introduced as a mathematical model for pattern classification in neural populations (S. I. Amari, 2014; S. ichi Amari, 1977; Wilson & Cowan, 1973). The architecture of DNFs reflects the hypothesis that strong recurrent interactions in local populations of neurons form a basic mechanism of cortical information processing. These interactions support the existence of self-stabilized representations that allow the implementation of cognitive functions and explore learning mechanisms on neural networks, already explored by our group (Erlhagen et al., 2006; Erlhagen & Bicho, 2014).

The vision is to combine system identification and machine learning - e.g., using reinforcement learning, deep learning for time series forecasting with long short-term memory networks, multilayer perceptron's, convolutional neural networks, between others - to try to emulate the learner mental controller (i.e., the subject mental controller that tries to learn to voluntary self-regulate brain activity through mental strategies). This way, assisting and outsourcing the identification of mental strategies to the computer (virtual machine controller, for more detailed information, please go back to **1.3.5** and **1.3.9**). This virtual machine controller will select the subsequent best external stimuli (external instruction strategies) for optimal NF-based SR (Lewis et al., 2012; Ljung et al., 2011; Tomas Ros et al., 2014). These interactions are represented in the diagram depicted in Figure 13.

In summary, the parameters extracted from different signal time-series analyses can be combined using pattern classification and neural network techniques. These techniques allow the investigation of nonlinear patterns in data that might distinguish subjects into meaningful classes or categories of stimulation that affect them at the individual level (Beckmann et al., 2020; Institute of Medicine (US), 2004; Wriessnegger et al., 2020). This way, outsourcing our mental controller to a virtual machine controller that can lead the person to a specific mental target.

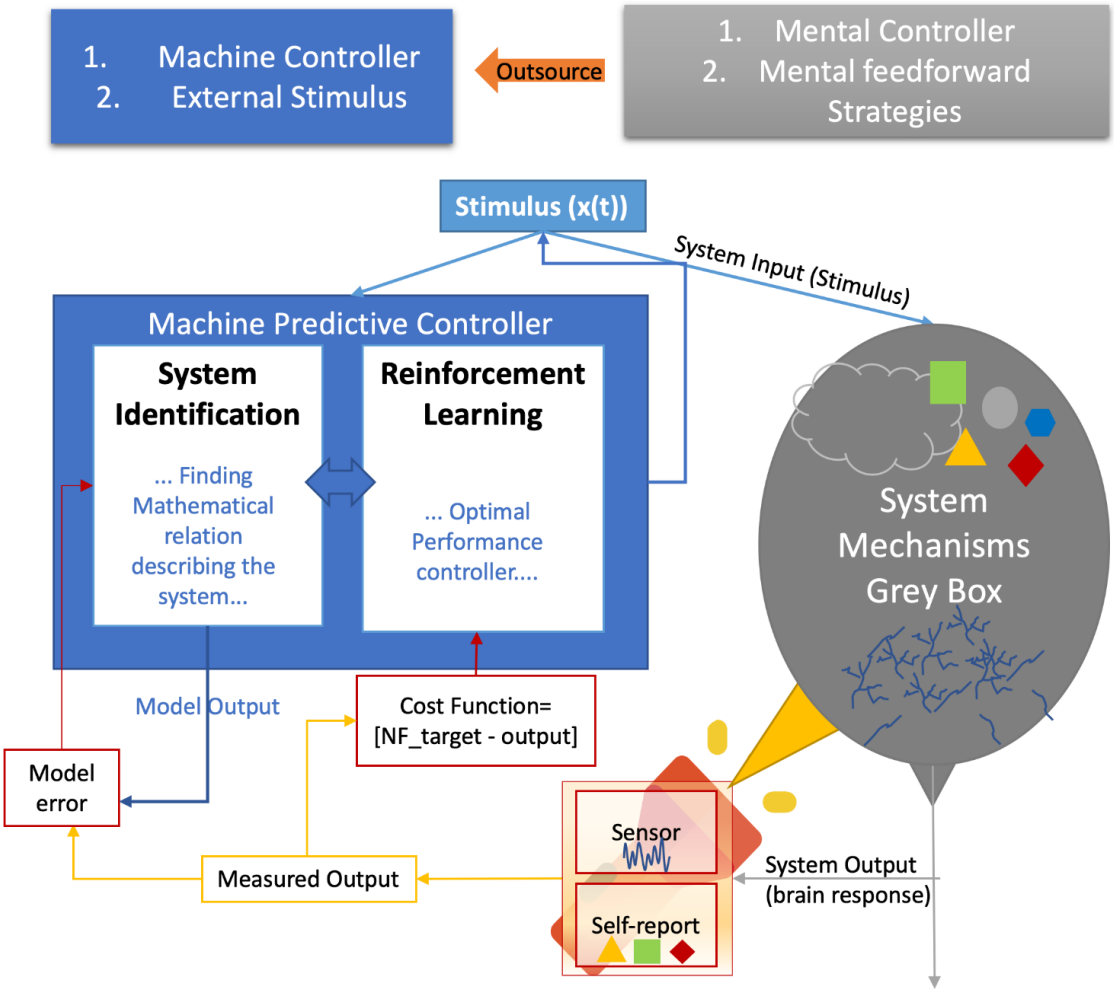


Figure 13 - Framework theoretical design. Systems theory identification and reinforcement learning emulate the learner mental controller, assisting and outsourcing the identification of mental strategies to the next best external stimulus for optimal Neurofeedback self-regulation.

Due to the workload of implementing this theoretical framework and the lack of a multidisciplinary team (see Figure 13), a *"divide and conquer"* task strategy was followed. The implementation was divided into three parts. (1) Develop open-source software for fast and straightforward integration of advanced closed-loop applications. (2) Answer the question: Does priming with external stimulation increase the SR of NF? This can be further divided into four main questions. Regarding the targets, *"Which mental/brain states can be optimal for learning SR of brain activity?"*. Concerning the stimuli, "How can we non-invasively stimulate the previous optimal state?". Measurements-wise, *"How can we measure the target performance (learning and behavioural outcomes) of each individual?"*. Regarding the framework experimental temporal Design, *"What is the best temporal design to implement the framework?"*. (3) Automate the framework and optimize priming personalization: adapt convolutional neural networks to learn the sequence of stimulus that leads the subject towards the desired *"optimal"* state (e.g., using reinforcement learning, deep learning for time series forecasting with long short-term memory networks, multilayer perceptron's, convolutional neural networks, between others).

The aims of this thesis were tasks (1) and (2), uncover aspects of the *"optimal"* mental state to self-regulate brain activity with NF (targets, stimuli, measurements, and temporal design) and demonstrate that external stimulation increases SR of NF, before advancing to task (3). From an abstract standpoint, the scientific contribution of this thesis is to reflect on what a *"Self-regulation assistant human-computer machine"* can be and what its operational fundamentals are. Developing some groundwork and propose an answer to the following question: within the behaviourist epistemology and through the theoretical-practical device developed, what is the ideal design to obtain and maximize SR and what are the fundamentals/methodologies for reaching this?

2.2 Framework simplification using MM stimuli

The software framework architecture is prepared for the personalized machine learning priming with an ADO approach. However, before advancing and following the *"divide and conquer*" strategy, the priming effect on the learning ability to voluntary self-regulate brain activity, and by consequence NF, needs to be demonstrated. The simplest way is to find a priming technique that leads the person closer to the literature hypothesized *"optimal"* state.

As discussed before, one technique with similar priming targets as NFT is MM of focused attention forms. Mindfulness effects involve general and large-scale brain networks (Tang, 2017; Tang et al., 2015), as does the NFT (Silvia E. Kober et al., 2017), because they involve multiple aspects of mental functions (attention, self-awareness, emotional regulation, between others) that use complex interactive networks in the brain - default mode network, executive network, fronto-limbic network, between others (Tang et al., 2015). As an example, stroke patients with limited brain activity in certain networks get better accuracy in controlling BCIs in those regions by training MM (Ramli et al., 2019).

Effective MM in EEG reports reveals similar correlates of up-regulation of alpha and SMR, as pointed out in the previous section. The most replicated electro-neurophysiological correlates of MM include phasic increases[18] in the amplitude of EEG alpha oscillations during MM practice and increased resting EEG alpha amplitude. MM and EEG alpha NF have both been shown in the past two decades to improve attentional performance and increase the entire 8 to 12-Hz EEG alpha amplitude (Aftanas & Golosheikin, 2003; Cahn & Polich, 2006; Chiesa & Serretti, 2010; Chow et al., 2017; J. Gruzelier et al., 2010; Lagopoulos et al., 2009; Lomas et al., 2015; Navarro Gil et al., 2018; Tang, 2017; Tang et al., 2015). The self-reports from SMR protocols show a subjective experience relatively close to the MM experience:

"The SMR generally emerges when one is motionless yet remains attentive" (Silvia E. Kober et al., 2017). Whereas the standard instruction to increase SMR is being mentally focused and physically relaxed, verbal reports about what NF responders actually do to increase SMR range from *"doing nothing in particular"* to concentrating on the feedback display (Silvia E. Kober et al., 2013, 2017; Witte et al., 2013). Additionally, the *"optimal"* state definitions of learner versus non-learner (Chow et al., 2017; E. J. Davelaar et al., 2018; Mladenović et al., 2017; Ramli et al., 2019; Wood et al., 2014) also point to a connection to focused attention forms of MM, that involve training an individual to better sustain their attention toward an intended object (e.g., the sensation of respiration) and away from external (e.g., sounds) or internal (e.g., thoughts, mind wandering) sources of distraction. Therefore, through SR training, meditation has the objective of a healthier mind-body connection within homeostatic states (Eberth & Sedlmeier, 2012; Kabat-Zinn, 2003; Sierpina, 2005; Tang et al., 2015; Williams & Kabat-Zinn, 2011).

Mindfulness training causes neuroplastic changes in the structure and function of brain regions involved in regulating attention, emotion, and self-awareness. Similarly, in NFT, a hypothesized *"optimal"* mental/brain state should be reached for optimal SR of brain activity. For that, irrelevant mental processes should be decreased, and relevant mental processes should be intensified (Tang, 2017; Tang et al., 2015; Wood et al., 2014): evaluative self-referential processes[13] should be decreased, present-moment awareness[6] with non-judgemental attention (acceptance) should be promoted, and a shift in evaluative self-referential processing (affective, subjective) towards a more self-detached and objective analysis of interoceptive[20] and exteroceptive sensory events (greater awareness, meta-awareness) should be more evident.

As a final reminder, we strived to develop the framework foundations that will pave the way to reach the following objectives:

- Stimulate states pre-NFT and study within and between subject differences.
- Develop groundwork to create a framework that learns what stimuli supports the user to achieve certain state targets (Brainwave calibration). This framework is envisioned to have the following capabilities: find personalized mindful states; standardize brain cognitive and emotional states before training SR (in NF or other types of training); reduce self-related thinking; target implicit, automatic, bottom-up mechanisms; a scaffold for mental strategies (Virtual Machine Controller)
- Research training strategies, specifically the mental state's sensitivity to stimulation categories.
- Develop personalized protocols based on instructional design, control theory, dynamical system theory, multi-stage theory, and dual-process theory.

- Attain new insights into the mechanisms of learning to voluntary self-regulate brain activity.

2.3 Measures assessing framework successful control

Theoretically, an NFT framework implies that any observable measure of brain activity can be extracted and tested for volitional control. Nonetheless, what constitutes successful control, and how to quantify it? In the engineering sense, successful control can be viewed as enhancing the signal-to-noise ratio of a parameter relative to a control condition, a reference condition (e.g., resting state, sham, or sensory stimulation without control), which could be administered sequentially or interspersed randomly in the experiment (Tomas Ros et al., 2014). Dempster and Vernon (Dempster & Vernon, 2009) suggested three major measures that can be used to assess feature changes (the changes of extracted features from measures like EEG) of brain activity during NF:

1. Changes in absolute values of frequency band amplitude/power (e.g., (Angelakis et al., 2007)).
2. Percentage of time in brain activity target (tBAT), basically the percent time spent in the desired brain state. Thus, this is the time spent above or beneath a specific threshold when self-regulating one's brain activity.
3. Integrated change, based on *"integrated alpha"* defined by Dempster and Vernon, the multiplication of the absolute amplitude (1.) with tBAT (2.).

However, more oscillatory parameters are reported to be volitionally controlled, including phase-locking (Brunner et al., 2006) and nonlinear fractal dimension (Q. Wang et al., 2011).

Based on these measures, one can assess feature changes in four different ways (Enriquez-Geppert et al., 2017) : (1) within-sessions, for instance, by comparing the beginning of each session with the end of a training session (sessions can be arbitrarily divided into blocks or segments for statistical analyses); (2) possible changes in these measures within a session observed as a difference relative to a baseline measurement, where participants neither try to control their brain activity nor receive any feedback; as (3) changes observed from session-to-session, and also as (4) changes across sessions relative to a baseline measure.

Afterwards, hypothesis testing may be applied to test whether, during NFT, there is a significant difference in the mean together with a reduction (or no change) in the variability of the controlled signal (between the different conditions). With respect to existing methods in the literature, this approach is technically

equivalent to an analysis of variance (ANOVA) or a Student's *t*-test, which similarly account for a variable's mean and variance. If multiple confounding variables are involved, it might then be appropriate to use multivariate analysis of covariance (MANCOVA) (Tomas Ros et al., 2014).

Additionally, measurement-wise, as discussed in section **2.1.2**, besides EEG, self-reports and biodevices can be used to assess qualitative and quantitative emotional processing enabling a mixed-method approach – e.g., the experiments implemented in chapters **4** and **5** involved collecting, analyzing, and integrating quantitative and qualitative research in a single study.

2.4 Framework experimental design: time considerations

The temporal design is also one of the key players of the framework. As such, the theoretical framework was translated into an experimental session design and implemented. During this Ph.D. project, we implemented two experiments (chapters **4** and **5**) using the simplified framework described in section **2.2**. Therefore, the framework - theory, hardware, and software - evolved along with two experimental designs. In this section, we discuss the basis for their experimental design.

NF, the brain activity that is fed back to the system in a closed loop, can at least have three main uses (Enriquez-Geppert et al., 2017): 1) as a therapeutic tool to normalize patients' deviating brain activity to influence symptoms; 2) as so-called peak-performance training to enhance cognitive performance in healthy participants; 3) as an experimental method to investigate the causal role of specific neural events (such as brain oscillations) for cognition and behaviour which is known as a BSDS.

Our experimental framework design is an adaptation of a closed-loop BSDS design and a simple NFT protocol to test the question: does mindfulness, focused attention on stimuli, play a role in NF SR? The methodology of a BSDS is to substitute the NFT learner (explicit NF), who is actively engaged and adapting strategies to alter the brain activity in the intended direction, by a stimulator device (implicit NF), who is adapted online to present an experimental stimulus (Enriquez-Geppert et al., 2017). Hence, our framework for studying brain states and stimuli that complement the NFT for a better SR performance uses the two methodologies together for a loop of implicit and explicit training. The reason being that priming implicitly the target brain state can help explicitly control it. Nonetheless, because we are taking

the first steps with this framework, we randomized two MM stimuli instead of adapting the stimulus online to see if it makes sense to go forward with a closed-loop machine learning BSDS framework.

For BSDS, as an experimental tool to investigate the functional role of oscillations (like alpha or SMR), active control groups play a relatively minor role. Here, a single session within-subject or within-group design - a repeated measures design, i.e., independent observations of every outcome condition for the same person or unit of measure at different time points or "within" the same person or phenomena, e.g. (John H. Gruzelier, 2014b) - is sufficient to investigate specific features of oscillations and their association with behavioural performance - e.g., comparison of behavioural effects when a stimulus is presented at high amplitudes versus low amplitude or within phase versus out-of-phase (Enriquez-Geppert et al., 2017). Nevertheless, we decided to add a control no-priming group (CG) for single-session within- and between-groups analysis.

A single-session design is enough to investigate specific features of oscillations and their association with behavioural performance between and within groups (Enriquez-Geppert et al., 2017) – in our case study, comparison of behavioural effects when MM stimulus is presented versus a resting task. Most MM and NFT intervention studies involve multiple sessions taking place over the course of several weeks, while an emerging literature has investigated the subjective (phenomenological) and neural effects of brief, single-session interventions (Chow et al., 2017; E. Davelaar et al., 2016; Hanslmayr et al., 2005; Peeters et al., 2014; T. Ros et al., 2014; Shibata et al., 2011; Wells et al., 2012). Gruzelier states that while one cannot anticipate durability of outcome enhancement following a single session, and concluding a null outcome about learning potential would be premature, single-session experiments have practical advantages in addressing some research questions and by recruiting larger groups of subjects which allows an increase in statistical power compared with the labour intensive smaller scale studies (John H. Gruzelier, 2014b; T. Ros et al., 2014). Also, when the cognitive paradigm is neurophenomenologically[10] linked to brain activity (e.g., use of MM tasks that are linked to the target state), and the NF is not used only as a training per se (e.g., investigate the functional role of oscillations in self-regulation), a single-session regulation is possible (Garrison, Scheinost, et al., 2013; van Lutterveld et al., 2017). Davelaar et al. (E. J. Davelaar et al., 2018) further add that future work could address the replicability of the association between learning success and subjective experience, especially when using multiple training blocks in a single session, thus, pointing in the same direction of our topic of study. With regard to MM, some studies have described successful modulation of emotional regulation capacities during a single session (Arch & Craske, 2006; Chow et al., 2017). The single session was divided into short intervention blocks instead of one continuous block. This decision was made based on the following contextual

hypotheses. Naïve subjects probably need short tasks for more focused attention. The interval between blocks should enable the participant to rest and select the start of a new block (self-paced session). Short blocks enable to test of the immediate effects of priming in the subsequent NFT in each block. The use of short blocks is essential to evaluate the mindset/subjective experience (with state self-reports) during the different tasks on the session. Lastly, task randomization for various conditions (e.g., eyes closed or eyes open) is straightforward within short blocks.

To understand these decisions, one must read the details in chapters **4** and **5**. Also, this type of short blocks design probably has some limitations in the level of priming (attention control, emotional regulation, and self-awareness states) achieved per block, yet it seems suitable for naïve populations. As such, participants chosen were naïve or did not perform, at least in the last year, meditation and NFT. They were also healthy male and female subjects, with no history of psychiatric or neurological disorders, also no psychotropic medications or addictive drugs, and with normal or corrected-to-normal vision.

Of note, when using a paradigm with eyes open (EO) and eyes closed (EC), one has to include not only visual but also auditory cues that signal the end of the task. So, each task has an auditory bell at the end, and if NFT is with EC, then the visual feedback needs to be translated to audio. In addition, when choosing the eyes protocol, one must be aware of the literature surrounding the objective of the intervention and choose accordingly. In this project, another distinguishing feature is to use both EO and EC conditions for possible comparisons between different tasks within- and between-groups. Previous single-session studies (Eva Maria Hammer et al., 2012; Hanslmayr et al., 2005; Peeters et al., 2014; Tomas Ros et al., 2013; Wells et al., 2012) have tended to use EO conditions for comparisons with the majority of NFT literature in multi-session designs (Angelakis et al., 2007; J. Gruzelier et al., 2010; Nan et al., 2015; Van Boxtel et al., 2012; Zoefel et al., 2011). As an example, the alpha amplitude is generally seen as a function of reduced sensory input from the thalamic nuclei to the cortex, and keeping the EO will naturally suppress alpha amplitude (around 80%) relative to an EC condition (D. Vernon et al., 2009). Thus, EO provides a lower baseline from which to attempt to increase the alpha amplitude, presumably more amenable to intervention effects via NFT (Barry et al., 2007; Chow et al., 2017; Nan et al., 2018; D. Vernon et al., 2009). Nevertheless, NFT with EC should also be conducted to ensure comparability with MM, which is most often practised with EC (Chow et al., 2017; Lomas et al., 2015). Also, as proposed by Chow et al. (Chow et al., 2017): *"Future studies would do well to compare MM with NFT in both eyes-open and eyes-closed conditions."*. However, the notion that EO and EC NFT may rely on distinct processes and elicit distinct behavioural or cognitive changes asserts that EO data should not be directly comparable to EC data (D. Vernon et al., 2009). Additionally, both EO and EC resting state baselines can be used as

predictors of NFT performance (Nan et al., 2015, 2018; Reichert et al., 2015; Wan et al., 2014). In chapters **4** and **5,** we show different considerations when implementing both conditions for possible comparisons.

Before the training session starts, the participant is verbally instructed with a GUI representation about how each task works (pre-Training instructions). They are essential to baseline all the subject knowledge but also to prepare them for the experiment. Then, during the training session, the initial baseline threshold should be chosen, and one can make the threshold adaptive to the subject and change it accordingly (e.g., based on extreme conditions if the subject during the NFT is above the threshold 90% of the task the threshold should be increased for the next NFT). The last block serves as the outcome block for comparison with the first block. The differences between the CG and the experimental group (EG) reside in the use of priming tasks. While the CG is only stimulated with resting tasks (no-priming), the EG is primed with randomized mindfulness focused attention forms, breathing bodily sensations meditation, named *"breathing mindfulness"* (BM), and the imagery of calm place sensations meditation, named *"imagery mindfulness"* (IM). These external priming stimuli are pure instructional audio manipulations to lead the person from a subjective trying state to a more sensing state. These transitions can be referred to as belonging to the trying-sensing continuum discussed by Davelaar and colleagues (E. J. Davelaar et al., 2018).

2.5 Framework ethical approval

This thesis project, including the framework experiments, was submitted for ethical approval and were evaluated by an Internal Review Board (IRB), the local research ethics committee of the University of Minho - *"Subcomissão de Ética para as Ciências da Vida e da Saúde"* (SECVS). The project was approved for human trials, and all the protocols in this thesis were in accordance with the Declaration of Helsinki. Additionally, other side experiments were implemented under its umbrella, namely a validation of a wireless device, James One, used to acquire Galvanic Skin Response (GSR) and Heart Rate Variability (HRV) data: validation in psychophysiological studies (Moreira et al., 2019) and validation of the photoplethysmogram (PPG) sensor (Correia et al., 2020). The James One device was also used in the second experiment of this thesis (section **5.3.6-GSR & HRV**). For the approval Document (ID: SECVS 011/2018), please refer to **Appendix I – Ethics** for the signed approval.

CHAPTER 3

NeuroPrime: Python Open-Source Framework

This chapter is based on the following scientific publication:

NeuroPrime: a Pythonic framework to research the priming of brain states. (accepted)

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3. Chapter 3 – NeuroPrime: Python open-source framework

The framework for the online experimental paradigm was built from the ground up on Python open-source language, synthetizing and using the best parts we extensively tested of specific BCI and EEG modules for signal acquisition, signal processing/classification, and signal presentation (diagram in Figure 14). Signal Acquisition: pycorder, pylsl, and mushu (Lopez, 2016; Venthur & Blankertz, 2012). Signal processing/classification: wyrm and MNE (Gramfort et al., 2013; Venthur & Blankertz, 2014). Signal presentation: pyff and psychopy (Peirce, 2007; Venthur et al., 2010). Other important packages, pandas for managing data, matplotlib for graphs, numpy for arrays, scipy for specific algorithms, pygatt for Bluetooth connectivity with GSR and HRV PPG sensors, and also pyqtgraph for real-time graphical interfaces (Gold et al., 2015; Group, 2007; McKinney, 2010).

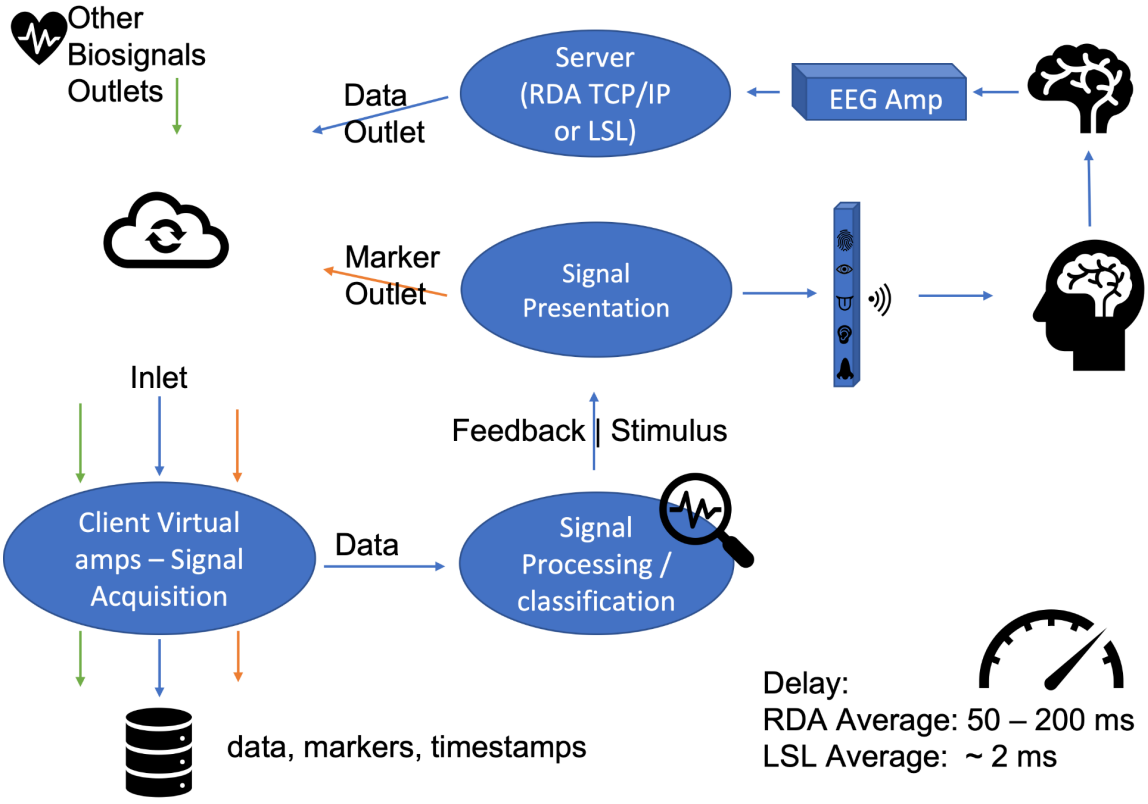


Figure 14 – NeuroPrime. Online closed-loop BCI Python framework. It is comprised of 3 main parts: signal acquisition, signal processing, and signal presentation.

This framework was built following the necessity for further expandability, utility, and usability from the neuroscience community. In fact, Python has excellent modules in machine learning that could help

optimize and automate the paradigm of priming subjects in future experiments. Also, the code is ready to use with any EEG amplifier that can connect with the lab streaming layer (LSL) (Lopez, 2016).

The name chosen for the package was NeuroPrime, a befitting name combining neuromodulation and priming. Go online for more information on NeuroPrime and access to the last version (N. M. C. da Costa, 2020). The software will be available as soon as the NeuroPrime paper is published. Consequently, in the coming months, if one has an EEG, then one can try out the framework, use it for research, and contribute to its development.

In the following sections, we go deeper into the Pythonic structure of each of the three parts that constitute the software: signal acquisition, signal presentation, and signal processing (& classification). They work together to bring the framework online. Additionally, we also refer to offline processing.

3.1 Signal Acquisition

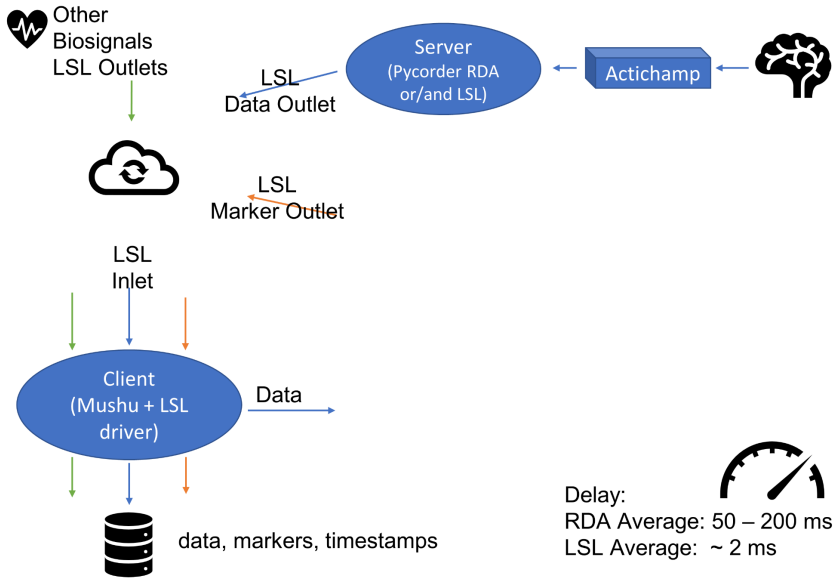


Figure 15 - Signal acquisition diagram and main packages used. In this figure, we break up the previous figure into the components of signal acquisition - input data and markers from servers and output data to client storage and processing.

When using Human-computer Interfaces (HCI) in experiments, one always has to use special hardware (e.g., EEG, GSR sensors, PPG sensors, or other amplifiers) to acquire the signals. This hardware usually comes with its private software, and different vendors have different formats for saving and online streaming. Additionally, these types of experiments require synchronization markers. Markers are label signals that mark certain time points in the data. These markers are also distinct between vendors. In

summary, signal acquisition is comprised of data servers (outlets from amplifiers) and data clients (inlets to storage and further processing).

Therefore, in order for the signal acquisition to be open-source, it has to meet certain requirements: software that runs on all major operating systems (OS); supports a wide range of EEG hardware; produces and outputs data in a standardized format independent from the amplifier used; receives markers via network interface; that is free and open-source software.

For that, we found in the Python library great software like pylsl and mushu. Also, specifically in our case, the amplifier from Brain Products used in this thesis (actichamp) has a Python driver for signal acquisition named pycorder. Nonetheless, one can use our toolbox with any amplifier supported by LSL.

Pylsl

LSL is the magic behind the streaming of data, allowing for a wireless open-source design. LSL is an overlay network for real-time exchange of time series between applications, most often used in research environments. LSL has clients for many other languages and platforms that are compatible with each other. Pylsl is the Python interface to LSL. This way, one can submit (outlet) and request (inlet) data from the network using Python. In addition, many of the most known amplifiers are supported already, and if it is not supported, one can create the driver (Lopez, 2016).

Pycorder

Pycorder is outdated but is a solid package with a built-in remote data access (RDA) server. It enables the configuration of the EEG: electrode impedance check, signal data visualization, reference selection, selection of working modes (default and shielding mode[23]), and saving. It is an essential package to work with the amplifier. However, in closed-loop real-time applications, it can be substituted by the LSL server app (Brain Products GmbH, 2015, 2017) with shorter delays of about 2 ms, while the pycorder RDA server is about 50-200 ms. The RDA delay is still within the accepted range for EEG NFT (Enriquez-Geppert et al., 2017; John H. Gruzelier, 2014b), and the RDA server can also be used in conjunction with the LSL app to create a data outlet stream that will then be pulled from the network by pylsl inlet request (Figure 15).

Mushu

Mushu is a package that creates an amplifier class with the necessary methods to configure, start, stop, save and quit the signal acquisition on the client side (Venthur & Blankertz, 2012). Mushu is still maintained, but certain limitations were patched during development, mainly concerning the saving (relative timestamps instead of only absolute timestamps) and bad interaction with the pylsl driver. This patch, named *"mushu_patch"*, is located in the *"signal_acquisition"* folder.

It is a great and simple package with retrieval and online streaming of EEG data. However, in the future, instead of the patch developed for mushu, an even simpler amplifier class should be created to work directly with pylsl without the need for mushu. The versatility of mushu is to be able to function as a Python library or a stand-alone server (with some amplifier divers already built-in for streaming data and markers online). Using the software as a Python library was convenient because our signal processing is in Python, and we could use it to create a single application (Figure 15).

Data structure

We use two types of saving structures: one that follows the MNE Python package standard Neuromag FIF file format (Gramfort et al., 2013) and the mushu numpy format (Venthur & Blankertz, 2012). The fif format is a more complex file that can save more information and can be directly used by MNE. Markers and data are all saved in the same file, while the mushu saves in 3 files data (.dat), markers (.markers), and meta (.meta). For the data, each received packet from the amplifier mushu translates the data into a matrix where each column is mapped to a channel (i.e., channel 1 to column 1, etc.), and the rows maintain the ordering of the measured values per channel in time. Having the EEG data stored in NumPy arrays is convenient and efficient on those arrays, that is mandatory for the later signal processing steps.

The interchange between formats is also easy to do. The same can be said for the import of data to matlab. Nonetheless, in the future, a potential better idea is to port entirely to MNE format. In this way, mushu and wyrm will be a deprecated complexity.

NeuroPrime signal acquisition

As referred before, we developed a *"mushu_patch"* for a better saving procedure and integration with pylsl. The developed algorithms and specific functions are located in the appropriate folder named *"signal_acquisition"*.

3.2 Signal processing & classification

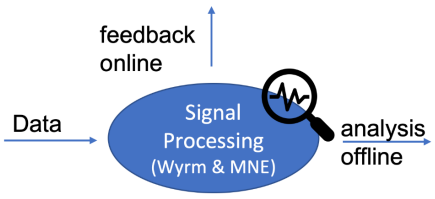


Figure 16 - Signal processing diagram and main packages used. Input data and output specific features for online feedback presentation or offline data analysis.

The signal processing of any online BCI system (Figure 16) is responsible for transforming brain outputs into actionable signals by detecting and extracting specific patterns from the brain signals. In order to detect those patterns, the raw brain signals have to be preprocessed, and specific features (representing the patterns) have to be extracted and classified (M. X. Cohen, 2019).

The libraries we decided to use for this part were wyrm and MNE.

Wyrm

We selected the wyrm package due to its ease of use, speed, and integration with the signal acquisition package mushu and the signal presentation package pyff. Wyrm tries to cover both toolbox aspects: wyrm can be used as a toolbox for offline analysis and visualization of neurophysiological data, and in real-time settings, like an online BCI experiment (Venthur & Blankertz, 2014). The list of algorithms includes: channel selection IIR filters, sub-sampling, spectrograms, spectra, baseline removal for signal processing, Common Spatial Patterns, Source Power Co-modulation, class wise average, jumping means, signed r2-values for feature extraction, Linear Discriminant Analysis with and without shrinkage for machine learning, among others. It is worth mentioning that the data structure is readily compatible with scikit-learn (Pedregosa, F. and Varoquaux et al., 2011). Therefore, a wide range of machine learning algorithms is at one's disposal (cross validation, support vector machines, k-nearest neighbours, independent- and principal component analysis, and many more).

Additionally, with importance to online BCI closed-loop experiments, wyrm provides a block buffer and a ring buffer. The block buffer is used for a more robust online subsampling buffer. This buffer is a first-in-first-out (FIFO) buffer that returns data in multiples of the desired block length (unlimited in size). For example, the subsampling from 1000 Hz to 100 Hz internally works by returning every 10th sample from the data to be subsampled. When subsampling chunk-wise, we must make sure that the data to be

subsampled has a length of multiples of 10 samples in order to avoid losing samples between the chunks of data. If the amplifier does not support the configuration of the block size, one can use Wyrm's implementation of a block buffer. (Venthur & Blankertz, 2014). As such, as an example, in our online framework, the RDA data server has a minimum chunk size of 50 ms (for 1KHz returns 50 samples), and to make sure we use chunks of multiples of 50 ms (100 ms, 200 ms, ..., n*50), we set the block buffer time to 50 ms. In the ring buffer, we can append small chunks of data in each iteration of the online loop and get the last milliseconds of the acquired data to perform the classification. For example, a 1000 ms ring buffer where, on average, 100 ms chunks of data are appended in each iteration of the online loop will always have the last 1000 ms of acquired data to perform the classification. This implementation has a guaranteed upper bound for read and write operations as well as a constant memory usage, which is the size of the maximum length of the buffer in memory (default 1024 samples). For Example, for the extreme case of storing the last 60 seconds of 64 bit data, sampled with 1kHz and 128 channels (≈60 MB), reading an entire buffer will take ≈25 ms as well as writing when storing more than 60 seconds at once. Writing will usually be much faster, as one usually stores only a few milliseconds of data per run. In that case, writing will be a fraction of a millisecond (Venthur & Blankertz, 2014).

MNE

Nonetheless, wyrm has only the necessary functions for online/offline preprocessing, processing and classification, and is not constantly updated. Therefore, we found MNE-Python for advanced processing and with active update and maintenance by the community (Gramfort et al., 2013). The MNE-Python package provides a complete pipeline for MEG and EEG data analysis: covers preprocessing, forward modelling, inverse methods, and visualization; advanced analysis for time-frequency, statistics, and connectivity; enables fast and memory-efficient processing of large data sets. While MNE-Python is designed to integrate with packages within the Python community, it also seamlessly interfaces with the other components of the MNE suite, like, for example, the MNE-matlab, because it uses the same Neuromag FIF file format, with consistent analysis steps and compatible intermediate files. Therefore, going forward, we expect to fully transition to MNE-Python for signal processing and classification.

NeuroPrime signal processing

For signal processing, we developed an online/offline pipeline for closed-loop NF and offline data analysis of NF data, named *"nftalgorithm"*, a children class of *"eegpipeline"* that imports functions mainly from

"eegfunctions". The *"eegpipeline"* standardizes and defines the necessary methods for the pipeline: initiate vars, input data, preprocessing, processing, postprocessing, and output data. These developed algorithms and specific functions are located in the appropriate folder named *"signal_processing"*.

3.3 Signal Presentation

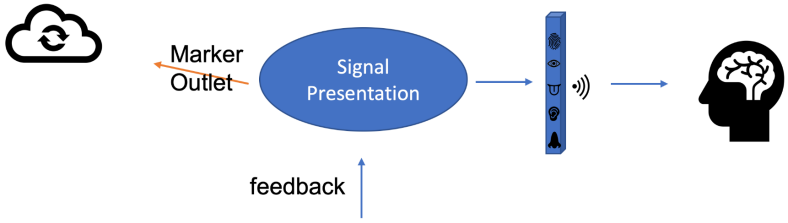


Figure 17 - Signal presentation diagram and main packages used. Input feedback data and output to interface and synchronization markers.

Feedback and stimuli presentation is another fundamental piece of any BCI system, which relates to the interaction and interface with the end user. While in the stimuli presentation, the interaction is passive (i.e., the subject does not control anything in the presentation with his thoughts), in the feedback presentation, the interaction is active, where the participant intentionally tries to modulate the signal that is being presented (Figure 17).

The presentation applications need to receive data from the signal processing and send markers to the signal acquisition. Furthermore, they should give researchers conducting experiments some means for interaction with the running application. Another important aspect is the usability of the package by the community of researchers. Therefore, a framework should make the development of feedback and stimuli applications as easy as possible by providing the proper infrastructure.

The packages meeting these requirements are pyff and psychopy.

Pyff

Pyff is a very solid and straightforward package for researchers familiar with Python. Pyff provides a platform for developing and running feedback and stimuli applications (Venthur et al., 2010). Pyff also provides some standard BCI paradigms (stroop test, oddball, among others). The limitations with pyff are the fact that it is outdated, it is not maintained, and it is yet to be ported to Python 3.

Psychopy

Due to pyff limitations, we also implemented psychopy functions. Psychopy provides a richer and research-friendly environment (both for experienced or non-experienced programmers) for developing feedback and stimuli applications. It is also actively updated and maintained (Peirce, 2007). Therefore, psychopy should become the main package for signal presentation and construction of session paradigms in the future.

NeuroPrime signal presentation

For the signal presentation, we developed a feedback and stimulus application class named *"feedbackclass"* that supplies all the necessary methods for creating a pyff task. Then, from this class, we implemented a loop class named *"loopfeedbackclass"* that enables a continuous and sequential construction of multiple tasks within a session (two different applications are described in chapters **4** and **5**). These algorithms and specific functions are located in the appropriate folder named *"signal_presentation"*. Additionally, the stimuli used for the signal presentation are inside the root folder *"stimulus"*.

3.4 Offline data analysis

The offline data analysis pipelines were performed in the Python MNE package (Gramfort et al., 2013) for advanced signal processing/classification and automation of the pipeline. We first did a visual inspection of noisy channels and bad epochs. Then, we used that know-how to extract features, plot data from within and between subjects, create group profiles, among others. Using a factorial design analysis of group subjects using Pandas package and JSON files, we were able to parse to excel and create a database quickly. These data analysis functions are located in the folder *"utils/data_analysis"*.

3.5 Integration of all packages

Simplicity and reusability are the foundation of the NeuroPrime package, as it is intended to be an open-source project to be used by the neuroscience community. It is also intended to be a BCI hub that evolves by synthesizing the best packages the Python community has to offer in terms of signal processing, signal presentation, and signal acquisition. Therefore, it should supply an easy and simple structure to update

and connect new packages within the same design. This way, considerable effort was directed to its structure design and simplification of the methods. This work can be fully appreciated in the scripts online (N. M. C. da Costa, 2020), whereas, in this section, we provide an overview.

For that, we decided to follow Python hierarchical class construction (the root directory for the source code is *"src"*). An initial class, named *"initbciclass"*, initiates all the methods and modules from signal acquisition, signal processing, and signal presentation. This class is the hub for connecting and working with all the packages, is where all the fundamental functions reside. From this class, we can develop child classes for each task needed on a BCI session.

In Figure 18, we provide an example of the simplicity of constructing a *"testclass"* for a resting task located in the folder *"brain_interfaces"*. To entirely run the *"testclass"*, one first needs to simulate the signal acquisition data and signal presentation markers. For simulating the signal acquisition, one has two methods the script *"file_stream_player"* or the *"outlet_actichamp"* inside folder *"utils/simulate"*. The *"file_stream_player"* is the preferred method, which makes use of the data sample in the folder *"sampledata"*, while the *"outlet_actichamp"* generates a sinusoidal signal. The "outlet_pyffmarker" inside folder "utils/simulate" should be used for the signal presentation, which generates markers similar to the pyff signal presentation. Secondly, one needs to run the *"testclass".* Each variable inside the script serves a specific purpose described in the figure (for the complete documentation, please go to the package online).

code python GUI output

```
In [ ]: from initbciclass import initbciclass

In [ ]: class testclass(initbciclass):
            def init(self):
                """
                INIT Global Constants
                """
                #1.INIT Parent Class
                initbciclass.init(self)
                #2.Alter or add other functions

            def on_play(self, markernumerate=0):
                """
                PLAY
                """
                ##UPDATE/RESET
                self.update_file_path() #update filename with runtrial_nr

                #Instructions
                self.INIT_TEXT="\n\n\n\n\nTASK 1: Estado de Repouso, 2 min!"

                #Stimulus
                self.STIMULUS_TEXT ="\n\n\n\n\n\n\n\n\n\n+"
                self.PROTOCOL_TYPE =  "REST"
                self.PROTOCOL_DESIGN = "normal" #normal, ABA
                self.STIM_TIME = 60*1
                self.subtask='rest'+"_"+str(markernumerate)
                self.START_MARKER = "START_"+self.subtask
                self.END_MARKER = "END_"+self.subtask

                #START loop of data
                self.start_time = time.time() #start time
                self.on_loop()
                self.end_time = time.time()  #end time
                self.elapsed_time =self.end_time - self.start_time

In [ ]: #1.Start Class
        test = testclass()
        #2.SAVE information
        test.SAVE = True
        test.FOLDER_DATA = "C:/Users/admin.DDIAS4/Desktop/ncosta/testdata"
        test.GROUP = 'TEST'
        test.SUBJECT_NR = 1
        test.SESSION_NR = 1
        #INIT Methods - Saving, Acquisition and Presentation
        test.on_init()
        #start experiment
        test.RUNTRIAL_NR = 1 #1st trial
        test.on_play(markernumerate=test.RUNTRIAL_NR)
        test.RUNTRIAL_NR = test.RUNTRIAL_NR+1 #2nd trial
        test.on_play(markernumerate=test.RUNTRIAL_NR)

        #quit
        test.on_quit()
```

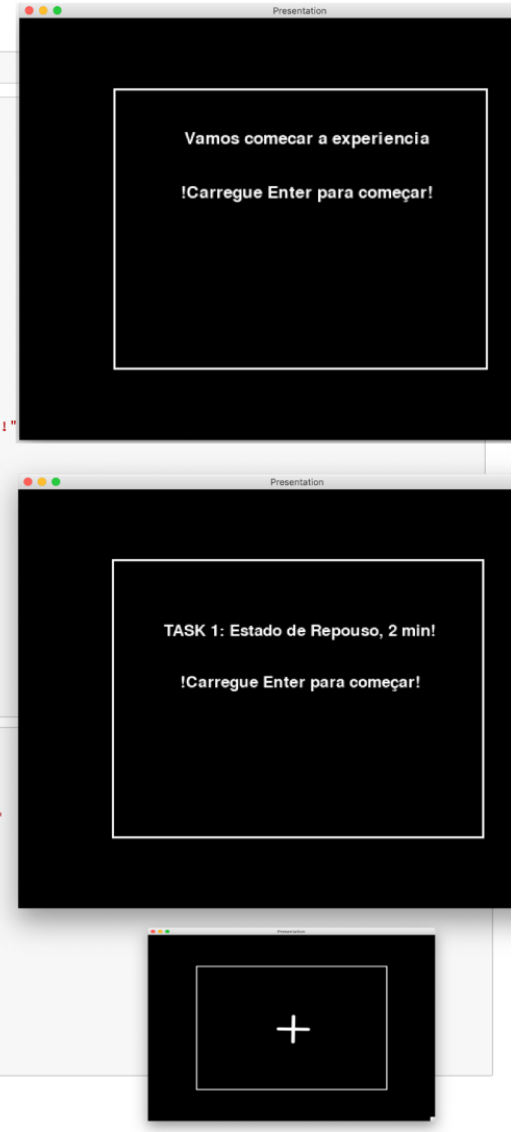


Figure 18 - Example of a resting task using the "initbciclass". The notation used in coding is Python language on the left, while on the right is the GUI output of the script.

Additionally, as one can see, this hierarchical class inheritance serves to simplify, debug, and as a means of quality assurance for each task class, where each task is tested individually but then can be ensembled in a BCI session. An example of a complete BCI, developed for E2 (one of the experiments described in this thesis, see chapter 0), can be found in the folder *"brain_interfaces"*. There, one can find child classes for: the rest baseline task, named *"restclass"*; the priming task, *"primeclass"*; the NFT task, *"nftclass"*; the self-report class, *"reportclass"*; and the BCI class that initiates all the other tasks and creates the necessary experimental session. Thus, each class works as standalone, great for debugging, but can also be ensembled to create a closed-loop real-time NFT session.

For easy deployment of experiments, a *"start_gui"* batch initiates the necessary Python environment and a basic GUI (Figure 19) to start all the amplifiers, signal acquisition, signal presentation, and signal processing (batch scripts located in the *"batchs"* folder). Additionally, the root folder named *"modules"* is the directory for modules that need to be inside of the package for simplicity, like pyff.

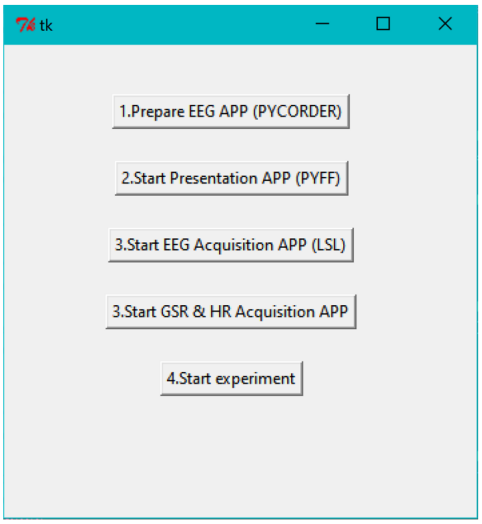


Figure 19 - Start GUI. This simple graphic user interface helps the technician setup the experiment. 1) Preparing the amplifier. 2) Initiate the presentation app. 3) Initiate the acquisition app. 4) Initiate other amplifiers like the GSR and HRV PPG. 5) Start the BCI session.

One of the requirements was a software that runs on all major operating systems. As such, NeuroPrime was developed and tested on Mac OS and Windows OS, and, depending on the hardware requirements, it will run in all major OS that can run the Python packages needed. Currently, the package has some limitations or, more appropriately, a to-do list: parse the package completely from Python 2.7 to Python 3; documentation needs to be reviewed and simplified; variables nomenclature needs to be reviewed for standardization (e.g., standardization of uppercase and lowercase); deprecated code should be removed; implementation of machine learning algorithms; among others. In retrospect, this package is stable in the current version but should be continuously simplified, tested, and updated to meet the criteria of new experiments.

This section offered a quick overview of the package developed, and detailed information will be added to (N. M. C. da Costa, 2020).

CHAPTER 4

First Framework Application: Pilot Study

This chapter is based on the following scientific publication:

Priming with mindfulness affects our capacity to self-regulate brain activity? (N. M. C. Da Costa et al., 2020)

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4. CHAPTER 4 - FIRST FRAMEWORK APPLICATION: PILOT STUDY

To pilot test a priming framework and find how it can stimulate the learning to voluntary self-regulate brain activity using MM focused attention stimuli, we implemented an intervention on 33 participants. This experiment is referred to in this thesis as Experiment 1 (E1) and will be detailed in this chapter.

4.1 Participants

EEG signals were acquired from a sample of 33 healthy young adult participants (20-31 years old), voluntarily Recruited (with no incentive unless the chance to experiment NFT) from the University of Minho, via advertisement email, telephone, or directly with the participants.

The inclusion criteria were the following: population of healthy subjects with no history of psychiatric or neurological disorders, no use of psychotropic medications or illicit drugs, with normal or corrected to normal vision, agreement to participate in the study, and voluntary signature of the informed consent, and no prior experience regarding NFT and MM.

After recruitment and pre-screening, sixteen control group participants (CG; N =16) were randomly matched to seventeen participants of the experimental intervention group (EG; N =17). Of the 33 participants, 22 were women, and 11 were men.

During the study, there were no participants withdrawn, and no adverse events were recorded. The protocol was in accordance with the Declaration of Helsinki and approved by the local Research Ethics Committee (University of Minho, SECVS, **Appendix I – Ethics**).

After addressing the following exclusion criteria of EEG visual inspection of artefacts and assuming epoch rejection parameters of peak-to-peak (100 μV) and flatness of the signal (0.5 μV), no participant was excluded. We discuss this further in the following sections.

4.2 Hardware and software setup

Hardware

The hardware described here is shown at the end of this section in Figure 21. EEG signals were acquired with a 32 channels amplifier ActiCHamp® (Brain Products GmbH) and two batteries (1). The cap (EASYCAP GmbH), (2), has a unified optimized layout based on an international 10-20 localization system for better cable arrangement (Timm, 2016). The ground is located at Fpz position and is a reference-free montage, as shown in Figure 20. Any referencing is done post-hoc (after acquisition) in the software.

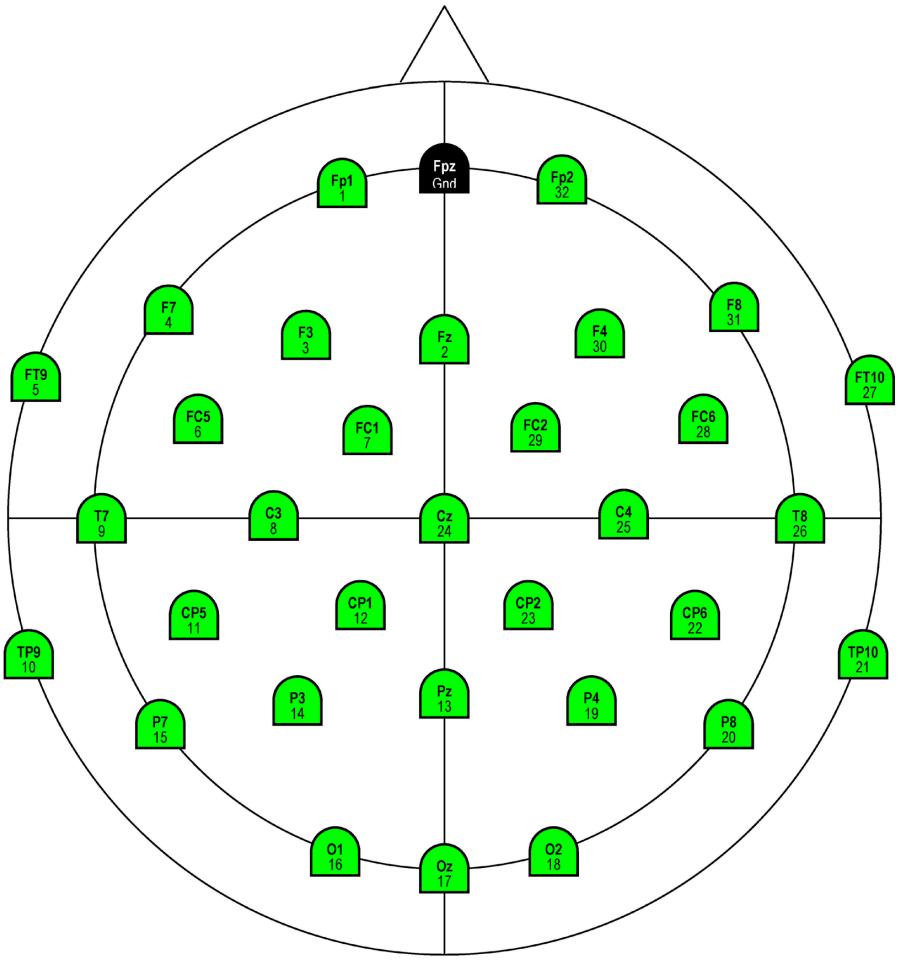


Figure 20 - 32 Channels Easycap Montage Layout. It was adapted from the unified optimized layout based on an international 10-20 localization system (source Brain Products GmbH).

Before electrode (3) placement, the skin was prepared with a mild skin cleaner (4), ethanol 70% V/V, to help improve impedance and conductance of electrodes. Electrodes were affixed with a high conductive viscosity electrolyte gel for active electrodes SuperVisc® (EASYCAP GmbH) (5). Impedances were checked before starting the experiment to be below 30 kOhm and critical channels below 10 kOhm.

The computer screen (6) was placed 60 cm from the edge of the table. The mouse (7) was only used by the investigator, while the keyboard (8) was placed at the edge close to the participant to allow interaction with the task interface. For the audio, wired headphones from Asus® (9) was used. A cup of water was always present for the subject to drink if needed.



Figure 21 – Experimental Hardware Setup. On the right, the experiment environment and the cap. On the left and middle is the remaining hardware.

Software

The online experimental paradigm was built from the ground up on Python open-source language, synthetizing and using the best parts of specific BCI and EEG modules. For more detail, go back to chapter **3**.

The offline data analysis pipelines were in: Brain Vision Analyzer (Brain Products GmbH), for visual inspection of channels, epochs, and planning processing pipeline; NeuroPrime and Python modules like MNE, for advanced signal processing/classification and automation of the pipeline.

4.3 Experimental design

Overviewing the experimental design, each subject received a single-session intervention. For descriptive trait measures, we used a sociodemographic and a mindfulness questionnaire, the Five Facet Mindfulness Questionnaire (FFMQ) (Baer et al., 2008; Gregório & Gouveia, 2011). The training session was divided into 3 blocks. While the CG, in all the three blocks, only received EO REST followed by the

EO SMR NFT protocol, the EG, in blocks 2 and 3, received EO rest state task (REST) followed by the EC Pre-training Priming Protocol (PRIME) and finally the EO SMR NFT. The EC condition during PRIME stimulus was intended to test the hypothesis that a more profound priming occurs in the absence of visual information, while the EO condition was implemented due to its general use on NFT interventions. Finally, a post-framework questionnaire was filled, asking about perception (task success, task difficulty, mental effort, awareness level), mental strategies, and two critical observations were directly asked by the investigator and registered for reference, based on (Garrison, Santoyo, et al., 2013).

The diagram in Figure 22 shows in greater detail E1's design, and in the following sections, we break down and further detail each part of the experiment design.

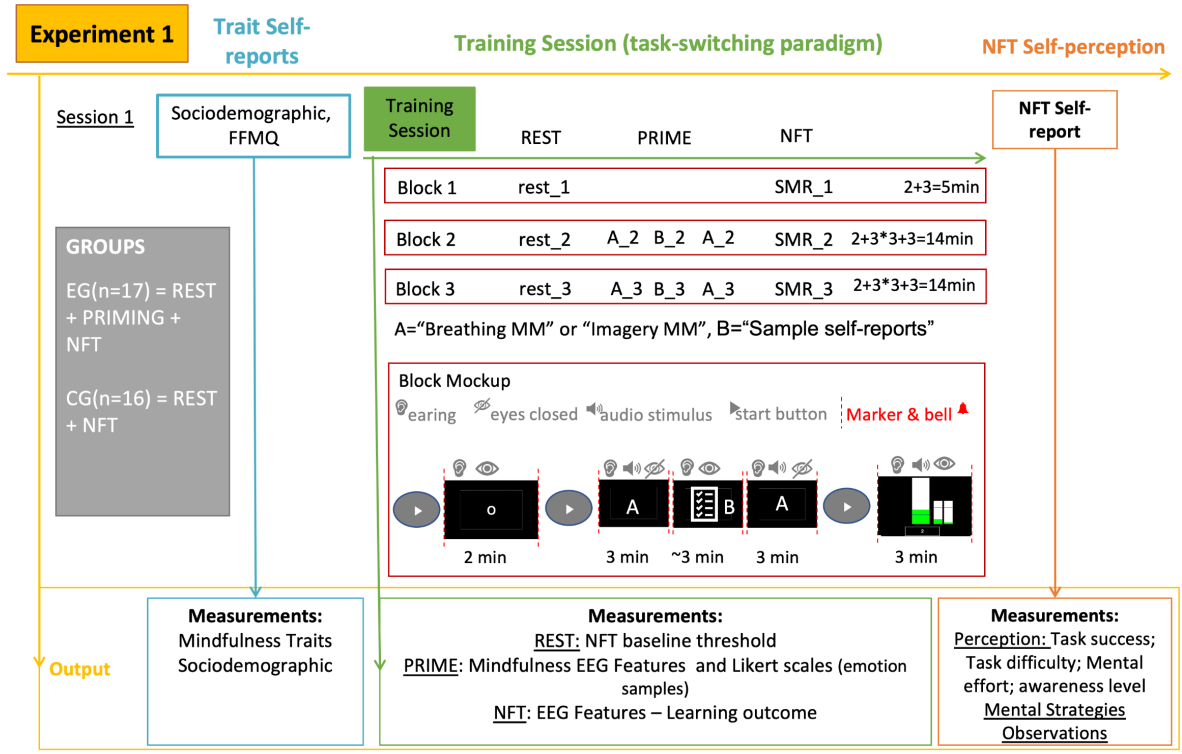


Figure 22 - E1 design. Time flows from left to right, top to bottom. In a single session, first, the subject fills the sociodemographic and the FFMQ. Then, the training starts. There are three blocks in total, and each begins with the REST task with EO, then PRIME, and finally NFT. PRIME is not applied in the Control group. PRIME follows an (A)(B)(A) design, where stimulus (A) is randomized between breathing or imagery mindfulness-guided practice, while (B) are Likert scale questions in random order. NFT bars represent the neurofeedback presented to the subject, and the horizontal line within the bars represents the thresholds.

4.3.1 Questionnaires & Self-report measures

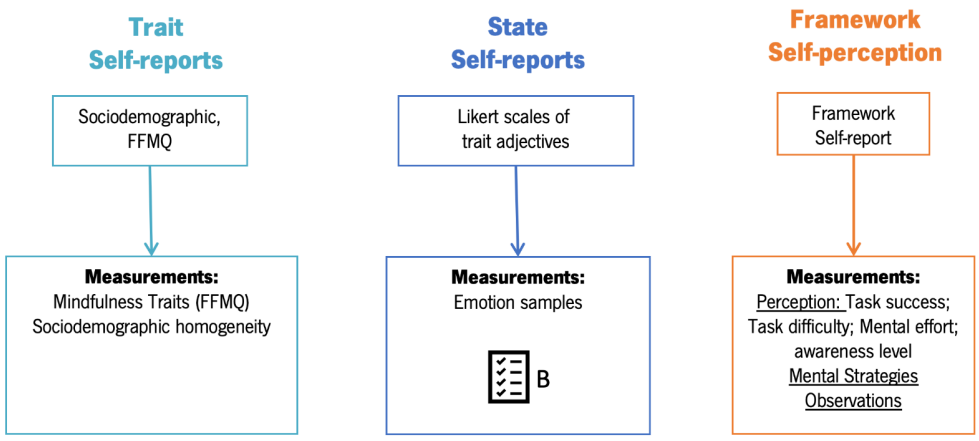


Figure 23 - Self-reports of E1. This diagram represents the three types of self-reports used: traits, states and framework self-perception.

In this section, we break down the self-reports used (Figure 23) in the E1.

Traits

For descriptive baseline purposes, participants completed first a sociodemographic questionnaire, then a standard scale of mindfulness traits, the FFMQ (Baer et al., 2008; Gregório & Gouveia, 2011).

Sample States

In order to assess the immediate outcome (emotional states) of the MM interventions, we used a similar approach as Garrison et al. (Garrison, Santoyo, et al., 2013). In our case, we choose five adjectives to discriminate the emotional states from *"The Minho Word Pool: Norms for imageability, concreteness, and subjective frequency for 3,800 Portuguese words"* (Soares et al., 2017). The words chosen were *"Motivado/empenhado" = "engaged", "Relaxado" = "relaxed", "Concentrado" = "concentrate", "Cansado" = "weary", "Frustrado" = "frustrated", "Pensativo" = "pensive"*. Then they were converted to a Likert scale from 1 to 5, similar to the PANAS scale: 1) very slightly or not at all; 2) a little; 3) moderately; 4) quite a bit; 5) extremely. Additionally, four questions were added to assess their perception about the preceding task: *"Awareness level about the emotional states previously stated?", "Task success?", "Task mental effort?" and "Task difficulty?"*. Classification also ranged from 1 to 5.

Neurofeedback data plus this sample states can offer a way to relate the neurophenomenological[10] structure of subjective experience with a real-time characterization of large-scale neural operations

continuously over the course of the experiment (E. J. Davelaar et al., 2018). This way is possible to intercept the first and third person data together.

Framework self-perception

In order to assess the perceived outcome of the framework, we developed a simple questionnaire to measure the participant's self-perception (subjective experience). It is based on the questionnaires developed by Garrison et al. (Garrison, Santoyo, et al., 2013). Also, this questionnaire should be viewed as a stepping stone for a neurophenomenological[10] approach in the future, because through its implementation, we were able . to address the following subjective experience (check E1 self-report):

- Experiment perception: task success, task difficulty, mental effort, and awareness level.
- Mental Strategies.
- Observations.

Additionally, three critical observations about the framework (because this was a pilot study) were directly asked by the investigator and registered for reference: *"Were the 3 bars distracting?", "Were the audio-guided instructions distracting?", "In the rest task, did you succeed in relaxing, or did you think about something else?".* The response was only *"yes"* and *"no"*, and *"maybe"* was considered *"yes"*.
For more detail and access to the forms, please go to **Appendix II – Self-reports**.

Specific characteristics

While the traits and NFT self-perception were in paper format, the sample states measured by the Likert scales were part of the PRIME protocol, integrated as a control condition task, as one can see in Figure 22 (B). The adjectives were randomly displayed one after the other on the screen, and the participant needed to select the keyboard number correspondent to the classification. After the adjectives, the four questions (*"Awareness level about the emotional states previously stated?", "Task success?", "Task mental effort?" and "Task difficulty?"*) were also displayed one after the other, as demonstrated in Figure 24.



Figure 24 – Representation of control condition self-report. The traits self-report was presented as a successive randomized sequence of Likert scale questions.

4.3.2 Rest state task (REST)

Rest state task (REST) is a standard task in NFT protocols. It is standardly used to evaluate subject baseline and compute the initial NFT threshold, basically with the objective of finding the individual resting state condition (Enriquez-Geppert et al., 2017).

In E1, REST has a pre-task screen with instructions and the task screen. In the pre-task screen, REST tasks instructions were to *"keep the eyes open focused on the point."* and the standard *"Try to relax!"* instruction. Then in the task screen, with EO, the participant needed to focus on the point in the centre of the screen and relax. The following Figure 25 is the GUI used in the task screen.

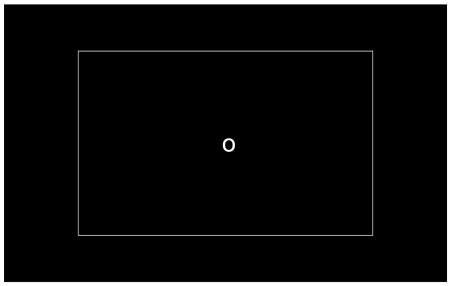


Figure 25 - GUI representation of the rest task screen. A black screen represented the rest task screen with a point in the middle.

The REST pre-task screen is necessary for various reasons: user's own pace (the user selects when to start); relaxation and resting of previous task/block; signal artefacts control. In the REST pre-task screen, the subject is introduced to the task and is instructed to focus and relax before using the key *"Enter"* to start the task. The text instructions with translation are in **Appendix III – Instructions** section **E1 REST task instructions**.

4.3.3 Pre-training Priming Protocol (PRIME)

Training design

The basis for PRIME is the BSDS training design to investigate the functional role of certain target oscillations (brain states).

In BSDS, the use of an active control group is not necessary to study the functional role of brain states guiding stimulation. However, the current priming framework is not a closed-loop stimulator (meaning that the brain state does not update the stimuli), but instead a fixed randomization of two MM stimuli (BM and IM), therefore control conditions and an active control group are necessary to compare with the target conditions.

The conditions had a within-subject ABA design to simplify the analysis of stimuli dependent oscillations. (A), target condition with eyes closed: PRIME stimulus, comprised of mindfulness-guided audio, aiming to promote awareness and reduce self-related thinking. Also, in condition (A), each subject received two PRIME stimuli double-blindly randomized between blocks 2 and 3. (B), the inverse condition with EO: evaluation emotion questionnaire to promote self-related thinking, using Likert scales with state adjectives, during which participants viewed adjectives and were tasked to *"think about and decide"* if the words described them, based on Garrison et al. (Garrison, Santoyo, et al., 2013). With the ABA design, we tried to: score the participant's subjective experience, deepen the priming before the NFT and investigate the role of the priming stimulus. We choose to keep the eyes closed during PRIME stimulus due to the hypothesis that a more profound priming occurs. Additionally, a control group was added for priming versus no-priming, between-subjects comparison.

Mindfulness Meditation Intervention (MM)

In this framework, mindfulness meditation (MM) tasks are pure instructional audio manipulations guiding the person toward reaching the desired subjective experience and target brain state before the subject starts the NFT task. To this purpose, participants were primed with audio-guided MM instructions, adapted from previously published procedures (P. A. Frewen et al., 2014), reviewed/transcript to Portuguese by a specialized mindfulness psychologist, and recorded by a hospital nurse on macOS using Garageband® software.

These meditation instructions are consistent with recent psychological conceptualizations of MM that emphasize the development of attentional abilities combined with a specific, non-judgemental attitude toward the different mental experiences that may arise during MM (Chow et al., 2017; Lutz et al., 2008; Tang, 2017; Tang et al., 2015).

Following the ABA design, the EG participants performed a total of 6 minutes (min) of eyes-closed MM: (A) 3 min of guided audio, then (B) self-report concerning the MM states, and finally repeated (A) the same 3 min MM guided audio. Using Likert scales self-report, we score the emotional state after doing the first MM. Then, the participant was primed again before receiving the NFT (see the sequence in the block mockup in Figure 22).

Two consecutive bells marked the end of the ABA intervention, then followed by the NFT.

Bodily focused attention on breathing (BM)

In the breathing mindfulness task (BM), participants were primed with audio-guided MM instructions, with the focused attentional target being on bodily breathing sensations. Breathing focus was chosen due to its simplistic nature and because it is the most standardly used bodily target for naïve populations and the more recurrent in literature(P. A. Frewen et al., 2014; Tang et al., 2015). In **Appendix III – Instructions**, section **E1 BM instructions**, one can find the manuscript for the text instructions in Portuguese, used in each of the screens, and the audio instructions with the time marker.

Imagery focused attention on a calm place (IM)

Similarly, the participants were primed with the same ABA procedure, but the focus of attention was a mental image of a calm place. Such was devised to simulate the use of mental strategies[11] during the neurofeedback where the user should embrace the mental strategy with a non-judgemental attitude and disengage from too much self-related thinking. A large number of studies indicate that imagery tasks in modalities as visual and auditory usually evoke brain activity patterns that overlap to a considerable extent with the patterns observed during actual perception (Damasio, 2010). Therefore, this IM stimulus contrasts with breathing bodily sensations and probably stimulates processes closer to the ones used during internal neuromodulation strategies[11]. In **Appendix III – Instructions**, section **E1 IM instructions**, one can find the manuscript for the text instructions in Portuguese, used in each of the screens, and the audio instructions with the time marker.

4.3.4 SMR Neurofeedback training protocol (NFT)

Training Design

SMR NFT protocol was based on Chow et al. and Kober et al. (Chow et al., 2017; Silvia E. Kober et al., 2017), which consists of a Pre-post training design to investigate single-session SR performance of SMR upregulation (12-15Hz), and simultaneous downregulation of theta (4-7Hz) and beta (21-35Hz).

The SMR protocol aimed to investigate the trainability of SMR after priming versus no priming the subject and assess subject phenomenological experience during the training. Therefore, a protocol was set up, including an active control group (only NFT). Participants of the control group were pseudo-randomly matched to the experimental group. They received NFT without the pre-training.

As we showed in the NFT diagram in Figure 11 section **2.1**, NFT closed-loop design can be divided into three parts: signal presentation (SP), signal acquisition (SA), signal processing and classification (SPC. Summarizing, SP deals with the GUI used to present the NF (feedback modality like audio or video, feedback presentation, and timing). SA deals with acquiring the signal from the learner, the data structure, and storage (already detailed in section **3.1**). SPC is the core of the training protocol (the *"brain"* of the closed-loop if you wish). It uses the input data acquired for online feature extraction, threshold and feedback calculation of feature changes, online artefact rejection, online feedback generation and outputs the feedback to the presentation. As such, we dedicate the subsequent sections to define the methods used for SPC and how they interact from one side with SA and from the other with SP.

Online feature extraction

Feature extraction is driven by the hypothesis[21] that up-regulation of SMR has some relation to the optimal state.

The bands to extract the NF were fixed frequency for more easy inter-individual comparisons. This study did not use the participant's individual alpha frequency (IAF) – defined as the frequency exhibiting the highest EEG amplitude within the alpha band (M. X. Cohen, 2019; Klimesch, 1999). Furthermore, since we were trying to find the effects of priming versus no-priming within the SMR band, we chose not to add this complexity to the study.

Subjects received SMR neurofeedback from their scalp Cz site (midline somatosensory cortex in accordance with the international 10-20 system), where the SMR is generally maximal (Silvia E. Kober et

al., 2017). Therefore, Cz was used as the channel to calculate the reward (SMR band) and inhibit bands (theta and beta bands).

Threshold & feedback calculation of feature changes

Cz EEG spectral densities estimated from 1.024 s segment of 1024 samples, updated every 1s with new data, using a discrete Fourier transform with Hamming windows (WELCH method with n_fft=1024, n_per_seg=1024, n_overlap=0)[22]. The sampling rate of 1kHz. For further detail, please refer to section **4.4**.

SMR (12-15Hz) was the reward band (i.e., the band that the participants aimed to increase) and theta(4-8Hz) and beta(15-35Hz) the inhibit bands (i.e., the bands that the participants aimed to decrease). The objective for the inhibit bands was to be an implicit cue to reduce involuntary artefacts, like eye blinks and muscle movements (M. X. Cohen, 2019). This protocol was based on Kober et al. (Silvia E. Kober et al., 2017; Silvia Erika Kober et al., 2015).

The reward and inhibit bands feedback are calculated as the mean power of the Cz channel during the task.

The thresholds for each new block are recalculated from each block rest state. Reward band threshold was the mean power of the Cz channel during the resting state, while for the inhibit bands, it was the mean power plus one standard deviation (SD) of the Cz channel. Following the statistical, empirical rule that for a normal distribution, almost all observed data will fall within three standard deviations of the mean or average, thus, 68% of the data falls within one standard deviation, and 50% of the data falls within the mean. Meaning, in statistical terms, the subject in the reward band has a positive cue if the data falls above 50 % (negative<50%) and in the inhibit bands receives a positive cue below 68% (negative>68%). These rules are based on Kober et al. (Silvia E. Kober et al., 2017; Silvia Erika Kober et al., 2015).

This adaptative threshold is of importance on single session designs with naïve populations. The initial threshold is bound to change significantly compared to the initial threshold (check section **E1 within-subject session profiles** in **Appendix IV – Additional results**).

Amplitude changes of SMR, theta, and beta were then compared to this dynamic threshold.

Online artefact rejection & confounders

Signal activity during an experiment can be biased or correlated with non-neuronal artefacts that can be technical (experimental setup), physiological, and demographic, acting to increase within-group variability (confounders). Technical: electrical noise, poor electrode preparation, experimental conditions (session design) (Enriquez-Geppert et al., 2017). Physiological: such as muscular activity (high frequency artefacts (>20 Hz) and eye-movements like blinks and saccades (3-5Hz), also named electrooculographic (EOG) artefacts (M. X. Cohen, 2019). Demographic, like gender and age, because power spectra change during maturation, lifestyle choices, hobbies, between others (Clarke et al., 2001).

In this E1, signal acquisition, as described in section **3.1**, used the LSL Actichamp app as the server. The default parameters are to use Actichamp shielding mode[23] reference-free montage. Due to the fact, this was the pilot study, and we had an experimental environment with unknown noise, we decided to maintain the default parameters. The shielding mode on Actichamp can correct some of the noise that is not common to all the channels, but the disadvantage is that this correction is not reversible.

To reject possible physiological artefacts, we processed five channels and used an average reference to automate epoch rejection in the sensor space. As the main aim was to remove epochs with artefacts in the Cz channel (channel used to calculate the SMR neurofeedback), this channel, as well as Fp1, Fp2, Fz, and Pz, were selected for this automation. Fp1 and Fp2 were chosen for their relationship with EOG and muscle artefacts, and Fz, Cz, and Pz reflect most of the noise topography but are less affected by movement artefacts (cable and electrode movement), than for example, temporal electrodes. Additionally, the usage of only these five channels allowed faster online processing times (M. X. Cohen, 2019; Enriquez-Geppert et al., 2017; John H. Gruzelier, 2014b; Sitaram et al., 2017).

Online Feedback-generation & presentation

Simple stimuli were selected for feedback presentation. Three vertically moving bars depicted power changes in three bands (SMR, theta, and beta), as one can see in Figure 26. The larger SMR bar in the centre and the small bars, from left to right, are theta and beta (the inhibit bands), while the horizontal blue line is the threshold. Positive feedback, corresponding to successful regulation, was presented when the reward frequency (SMR) was above the threshold (Power/threshold >1) and the inhibit frequencies (theta and beta) below the threshold (Power/threshold <1). Also, successful maintenance of this state over 1024 ms was considered a reward epoch, and positive feedback was retrieved in the form of one

point and added to the previous points. Negative feedback (unsuccessful regulation) when SMR below threshold or theta or beta above the threshold.

The positive feedback was represented by visual (colour change and point accumulation) and sound cues (point sound), similar to Kober et al. (Silvia E. Kober et al., 2017; Silvia Erika Kober et al., 2015). Visually, green corresponded to successful regulation (an activity that was enhanced relative to the start-baseline) of each frequency, while red to unsuccessful regulation. As such, positive feedback was represented by the colour green simultaneously in all bars, and if this state was maintained over 1024 ms, the sound of a new point added to the box below the bars was audible (Figure 26).

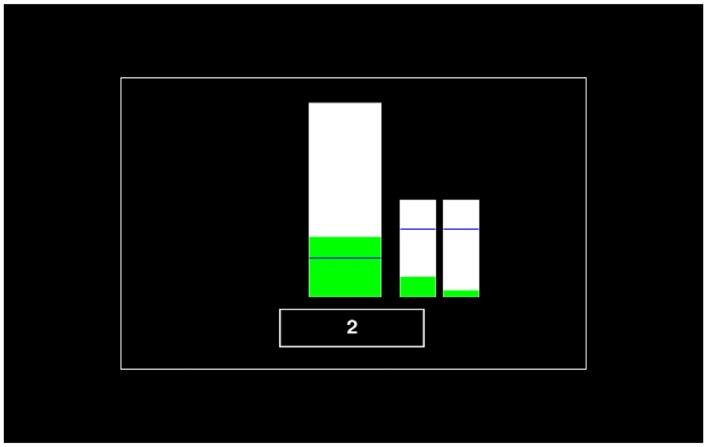


Figure 26 – E1 neurofeedback presentation GUI. This image shows successful regulation when the inhibitory band's amplitude is below their respective threshold and the reward amplitude is above the threshold.

4.3.5 Additional framework training characteristics

Provision of neuromodulation strategies

The investigator was in the room with the participant in the whole experiment.

Because participants were naïve to MM and NFT, they received verbally, as an example, a collection of possible strategies on how to self-regulate their brain activity (e.g., *"Explore mental strategies: like focus on something on the screen; positive thoughts, negative thoughts, neutral, and others"*). They were instructed to test these as well as strategies by themselves in order to select the best working mental operation to change their brain activity in the intended direction.

The main objective was to make as many points as possible. For that, they were instructed that the primary objective was at least to pass the central bar above the threshold as many times as possible while the other two bars should be below the threshold (Figure 26). However, to achieve the maximum

number of points, the secondary objective, which was more difficult, was to maintain the central bar above the threshold for longer periods of time while maintaining the inhibition bars below the threshold.

Number of sessions

The protocol was performed in a single session with both within-subject and between-group design. Within-subject design, for straightforward comparison of behavioural effects when different stimuli are presented. Between-group design, for comparisons between priming and no-priming.

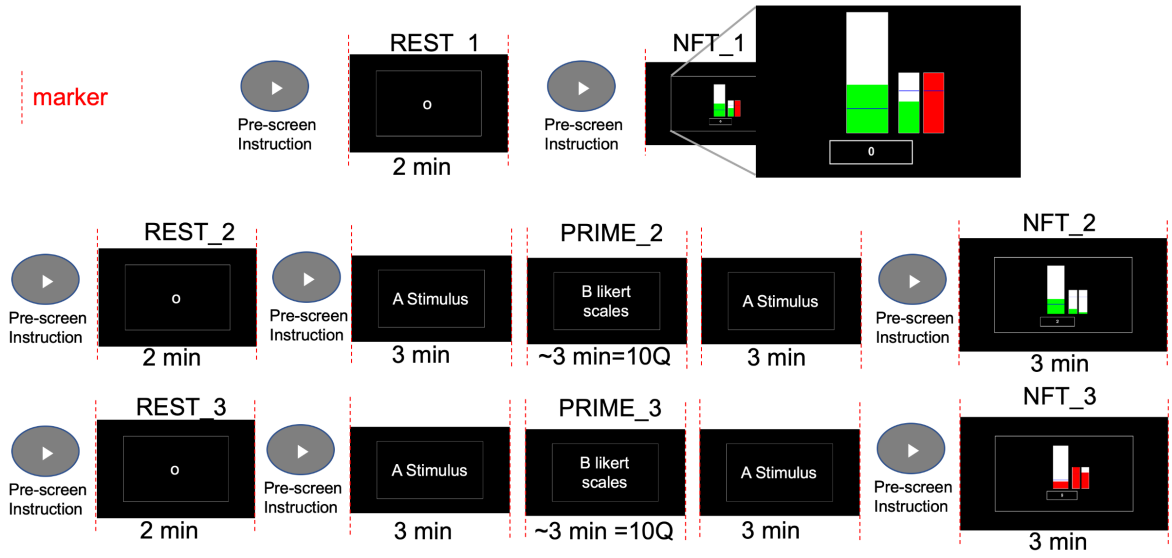


Figure 27 - GUI representation of the entire session of EG. Three short blocks are represented with the respective tasks.

Figure 27 shows a GUI representation of an entire session from the EG. The difference for the control group is the PRIME tasks. Therefore, both group sessions are constructed as follows:

- 3 blocks:
    - Block 1:
        - CG: REST (2 min) + NFT (3 min);
        - EG: REST (2 min) + NFT (3 min);
    - Block 2:
        - CG: REST (2 min) + NFT (3 min);
        - EG: REST (2 min) + PRIME (IM | BM, 3 min) + NFT (3 min);
    - Block 3:
        - CG: REST (2 min) + NFT (3 min);
        - EG: REST (2 min) + PRIME (IM | BM, 3 min) + NFT (3 min);

The list presented above shows the randomization (BM|IM) of blocks 1 and 2. The PRIME stimuli were randomized between two combinations: 1) BM, IM; 2)IM, BM.

Study blinding

EG and CG were pseudo-randomized, meaning that the subjects were blind to their group. BM and IM were randomized and double-blinded between blocks 2 and 3, meaning that both the subject and the researcher were blind to the stimuli.

4.4 Data analysis

The following data analysis is illustrative of the features that can be extracted from this type of experiment in within-subjects analysis and between-groups analysis. This should be viewed as a pilot analysis, an iterative step in developing the pipelines that will later be used in the final E2 (next chapter).

EEG online and offline processing algorithms are very similar but with different objectives. While online analysis is made to correctly represent the real-time SMR brain activity from the Cz electrode, offline processing goes more into detail and aims to retrieve data for statistical analysis to inspect what is changing in the brain. This way, the pipeline for both types of analyses can be divided into the following sequential processes: input data, pre-processing, processing, and output data.

4.4.1 EEG input data

In the online loop, the data is updated and processed at every 1024 ms in each iteration. On the other hand, offline has no loop. Instead, the data to be processed is the entire length of each task, then during the pre-processing stage, the data is segmented into epochs of 1024 ms, and each epoch is processed individually (discussed in the next section).

4.4.2 EEG pre-processing

After importing the data, we proceeded to the data reduction step. The offline data was thoroughly inspected using visual tools from Brain Vision Analyzer (Brain Products, Germany). First, the data before the task and after the task was removed. Then, channels were visually inspected, abnormal channels

with constant artefacts were rejected, has to not interfere in the subsequent processing steps. In both offline and online, continuous EEG measurements were filtered with a low cutoff value of 1 Hz and a high cutoff value of 40 Hz using a finite impulse response (FIR) filter. The original sampling rate of 1 kHz was maintained to not lose resolution on the fast Fourier transform (FFT). Afterwards, offline, the rejected channels were interpolated. Then in offline and online, EEG data was re-referenced using a common average head reference algorithm, meaning that an average of EEG activity at every electrode site was used as a reference, thereby removing noise common to all sites. After re-reference, we selected five channels for further processing: Fp1, Fp2, Fz, Cz, and Pz. As previously discussed, they were chosen for simple, faster, and easy processing of the target feature changes (section **4.3.4-Online artefact rejection & confounders**). Offline continuous EEG data were then segmented into 1024 ms (≈1s) epochs and processed individually. In both online and offline pipelines, we excluded epochs with abnormally large amplitudes with a maximum peak-to-peak of over ±100 μV and also based on the flatness of the signal with a minimum peak acceptance of ±0.5 μV (exclusion criteria).

Additionally, offline epochs contaminated by spurious gross-movement and other non-stereotyped artefacts were also identified by visual inspection and additionally rejected. After this, during offline, participants were excluded for further analyses of EEG if they had less than 40 % of the 1 s epochs after artefact rejection and pre-processing (after empirical testing, we set the threshold to 40% has the exclusion criteria).

Finally, to simplify the inspection of subjects after pre-processing, they were graded in 3 groups (good, medium, and bad) depending on the end results of pre-processing. Good subjects after artefact rejection and pre-processing had consistently good signal-to-noise ratio along the tasks (= no artefacts in all task epochs after rejection). Medium subjects after artefact rejection and pre-processing had a medium signal-to-noise ratio along the tasks (= some artefacts in epochs per task after rejection). Bad subjects after artefact rejection and pre-processing had a bad signal-to-noise ratio along with the tasks, or some tasks had less than 40% of the epochs (= some tasks presented a high quantity of artefacts per epoch or tasks were missing). Thus, from the initial 33, 16 were good, 15 were medium, and 2 were bad. However, none of the participants was removed due to the low number of subjects. Only the bad tasks (= met the exclusion criteria) were removed. Also, it is essential to note that the artefact rejection was laborious, spurious gross-movement, and other non-stereotyped artefacts were identified in temporal and occipital channels, possibly due to defective signal acquisition. Such can be the consequence of preparation of channels, reference free-montage, shielding mode, LSL server/client. These limitations are further discussed in section **4.6**.

4.4.3 EEG processing

The next step was a data transformation using spectral analysis on continuous offline EEG and during each online epoch. EEG power spectrum was calculated by using Welch's power spectral density (PSD) estimate using the *"pwelch()"* function from MNE.

Continuous EEG was transformed using an FFT and averaged in the frequency domain using 1024 points of FFT length, 1024 points hamming window segment, and 0 points of overlapping (n_fft=1024, n_per_seg=1024, n_overlap=0)[22].

For the purposes of this framework experiment, we only analyze the features changes of the Cz channel (the channel used for online feature extraction of SMR, for more detail, go back to section **4.3.4-Online feature extraction**). Also, this channel had the lowest signal-to-noise ratio in all the subjects.

The selected channels PSDs were then grouped into different bands, with a standard alpha peak (AP) of 10 Hz instead of a personalized IAF: delta (2 to 4 Hz, AP - 8 to AP - 6), theta (4 to 8 Hz, AP - 6 to AP - 2), lower alpha (8 to 10 Hz, AP - 2, AP), upper alpha (10 to 12 Hz, AP to AP + 2), overall alpha (8 to 12 Hz, AP - 2 to AP + 2), SMR (12-15 Hz, AP + 2 to AP + 5), beta (15 to 35 Hz, AP + 5 to 35) and gamma (35 to 100 Hz).

4.4.4 EEG output data

Finally, we extracted measures assessing feature changes of brain activity during NFT. Online to obtain the epoch feedback and offline to analyze the brain activity during the intervention. Online NFT feedback and threshold feature changes were already addressed before in section **4.3.4-Threshold & feedback calculation of feature changes**. Therefore we will focus in this section on offline feature changes.

As already addressed in section **2.3**, the three measures proposed by Dempster and Vernon (Dempster & Vernon, 2009; Enriquez-Geppert et al., 2017) for assessing changes in brain activity during NF are:

1. Changes in absolute values of frequency band amplitude [μV] or power [$\mu V^2/Hz$].
2. Percentage of time in brain activity target (tBAT), basically the percentage of time spent in the desired brain state. Thus, this is the time spent above or beneath a specific threshold when self-regulating one's brain activity.
3. Integrated change, multiplication of the absolute amplitude (1.) with tBAT (2.).

From these, we choose to represent two measures within-subject: the relative (epochs) and absolute (epoch average) SMR amplitude of the Cz channel and the tBAT for each NFT task. As one can see in Figure 28, this simplifies the temporal behavioural representation of the session. While between-group, we present the normalized data using the tBAT feature, as it shows more meaningful results than absolute changes in amplitude in this study (see Figure 29).

Based on these measures, we assessed feature changes within-sessions by using each block rest state as the reference and each block NFT as the target, this way, we can observe the changes from block to block. Also, this method was chosen due to the relevant changes of the REST mean PSD between blocks (check **Appendix IV – Additional results**). This makes sense due to the hypothesis that in a single session, design novices (at NFT) have great variations of EEG between blocks (for more detail on the literature of single session design, go back to section **2.4**).

Additionally, this methodology enables the evaluation of the task specificity, assessing whether the target feature or frequency of interest has been predominantly modulated in the REST versus NFT tasks.

4.4.5 Self-reports

The self-reports from paper format (see **Appendix II – Self-reports**) were transcribed to Microsoft Excel® for further evaluation.

4.4.6 Statistical analysis

As pilot E1 was an explorative experiment, the objective of the statistical analysis was to understand if the changes in tBAT measure were significant or not. As such, we analyzed it using a one-sample paired *t*-test by pairing the reference task (NFT_1) with each group's tasks.

4.5 Results

The following results illustrate the features that can be extracted from this type of experiment in within-subjects or within group analysis - a repeated measures design, i.e., independent observations of every outcome condition for the same person or unit of measure at different time points or "within" the same person or phenomena, e.g. (John H. Gruzelier, 2014b) - and between-groups. They served as a proof of concept for the final E2.

4.5.1 Within-subjects

Figure 28 is illustrated as an example of a subject from each group, where it is possible to follow the within session dynamics of the SMR.

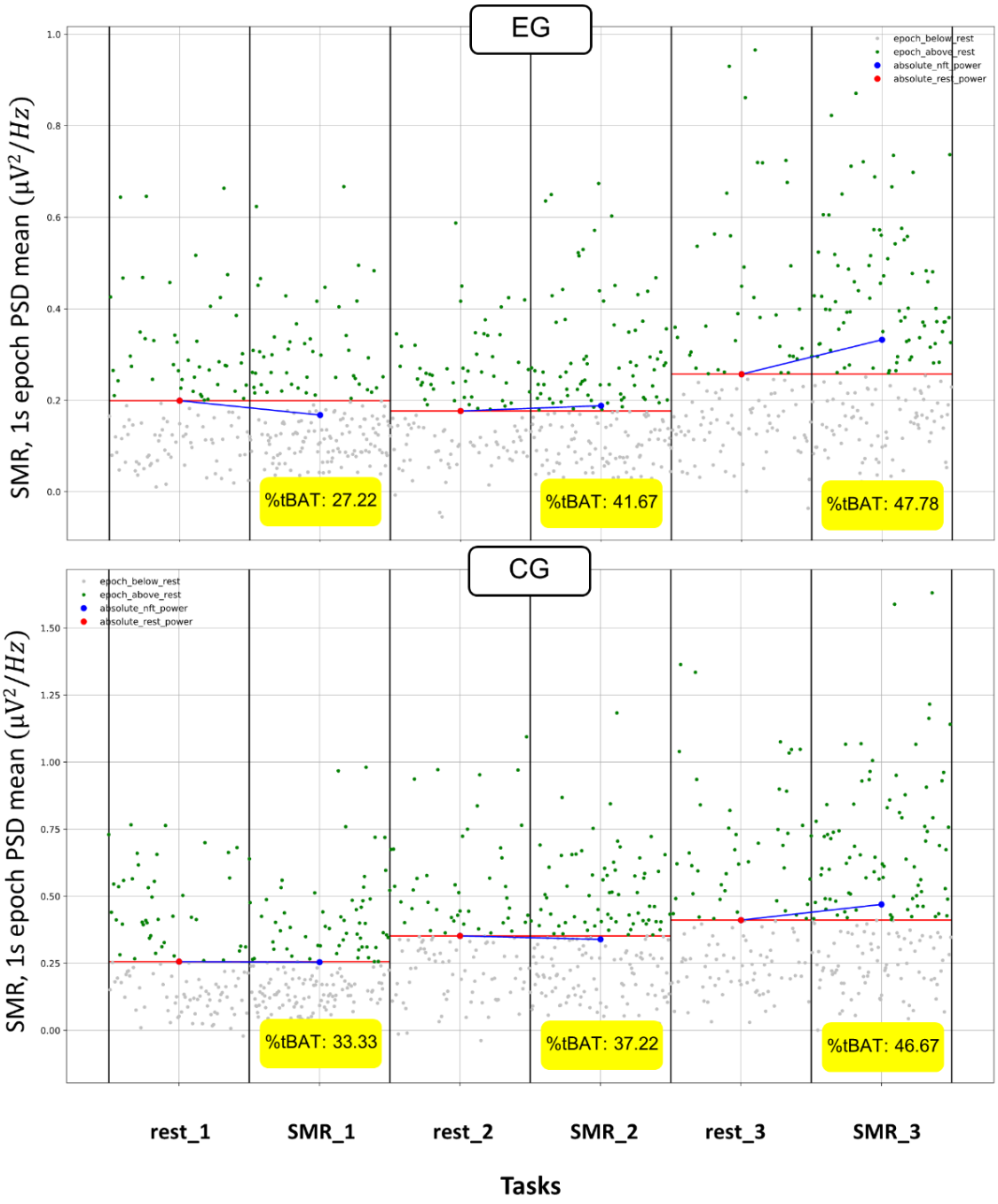


Figure 28 - SMR PSD of Cz channel. Subject behavioural representation during the experiment session. (EG) Representative example of Experimental Group Subject. (CG) Representative example of Control Group Subject. X-axis, Tasks in temporal order, according to the above experimental design. Y-axis, SMR PSD extracted during the Tasks. Red refers to the absolute mean PSD of the rest state. Also, it corresponds to the threshold used in the NFT. Blue is the absolute mean PSD during the NFT task. Green and Grey dots correspond to 1s epochs of SMR. Green epochs are above rest state absolute power. tBAT refers to the percentage of time the subject stayed above the brain activity target during the NFT task.

Remembering the previous section **4.4**, a sliding window of 1024 samples, updated every 1024 samples (1.024 s ≈ 1 s), is used to extract the mean power spectral density of the SMR band. This strategy is used to segment the online data into ≈ 1 s epochs. While offline, a similar strategy is used to segment the data into 1 s epochs. We extracted the SMR mean power for each epoch in REST and NFT in each of the three blocks, represented in Figure 28 as the dots in the graph. The red line in the figure represents the absolute mean PSD of the rest state. Also, it corresponds to the threshold used in the NFT. Blue is the absolute mean PSD during the NFT task. Green and grey dots correspond to 1 s epochs of SMR. Green epochs are above rest state absolute power to indicate that the subject surpassed the threshold. After obtaining the relative NFT mean and the rest absolute mean, we calculate the tBAT (one of the features to inform learning performance during training). The tBAT is described as the percentage of time spent with positive feedback (Dempster & Vernon, 2009), which, in our case, equals the ratio between the number of epochs above the rest task threshold and the total number of epochs. An important observation is that the shift in rest states is erratic. In **Appendix IV – Additional results**, section **E1 within-subject session profiles**, we show extreme cases of this profile. In the following Table 1, we show the tBAT for each subject. This table is used to construct the between-subjects graph in the next section and is essential to summarize the change of tBAT between each NFT task. The statistical change in tBAT measure is tested using a one-sample paired *t*-test by pairing the reference task (NFT_1) with each group's tasks. NFT_1 is the SMR NFT task of the first block, and NFT_2 and NFT_3 are from the second and third block, respectively. Then the subjects were further split into each of the priming conditions IM (IM_NFT_2, IM_NFT_3) and BM (BM_NFT_2, BM_NFT_3). As one can observe from the table, there is no statistical significance, meaning that the mean difference between paired observations is zero. This also reveals that our NFT had no significant effect on the tBAT for both groups.

Table 1 - tBAT for each subject and group average.

CG	NFT_1	NFT_2	NFT_3	EG	NFT_1	NFT_2	NFT_3	IM_NFT_2	BM_NFT_2	IM_NFT_3	BM_NFT_3
S006	22,22	12,22	24,44	**S003**	28,33	62,78	32,78		62,78	32,78	
S008	17,22	17,78	12,22	**S004**	61,67	53,89	32,22	53,89			32,22
S009	28,33			**S005**	15	12,22	17,22	12,22			17,22
S012	1,11	66,11	41,67	**S007**	16,11	23,33	22,22	23,33			22,22
S014	23,33	36,11	0	**S010**	0	8,89	52,78	8,89			52,78
S016	22,22	15,56	7,22	**S011**	27,22	41,67	47,78		41,67	47,78	
S017	31,11	6,11	28,33	**S013**	30,56	16,67	10,56		16,67	10,56	
S019	0	30	44,44	**S015**	15	36,11	2,78		36,11	2,78	
S020	72,22	39,44	38,33	**S018**	55	64,44	82,78	64,44			82,78
S024	0,56	1,67		**S021**	63,89	30	67,22	30			67,22
S025	23,89	10	13,33	**S022**	43,33	94,44	0	94,44			
S026	33,33	37,22	46,67	**S023**	3,33	28,33	6,67	28,33			6,67
S027	24,44	40	27,78	**S028**	3,89	9,44	35,56		9,44	35,56	
S029	0	23,33	2,22	**S031**	19,44	10	14,44		10	14,44	
S030	19,44	38,89	35,56	**S032**	5	13,89	27,22	13,89			27,22
S035	30,56	30,56	66,67	**S033**	7,22	27,78	6,67		27,78	6,67	
				S034	0	37,22	43,89		37,22	43,89	
AVG	21,87	27	27,78	**AVG**	23,23	33,59	29,574	36,60	30,21	24,31	38,54
SD	17,80	16,94	19,26	**SD**	21,33	24,56	23,95	28,69	19,36	17,10	26,42
***p*-value**	1	0.42	0.39	***p*-value**	1	0.19	0.42	0.24	0.41	0.89	0.18

tBAT is the ratio between epochs above the threshold and the total number of epochs. Average (avg) and standard deviation (SD) in each column are also presented. An empty cell means a none value or a missing value (removed tasks due to noise). The p-value is obtained from a paired t-test between the NFT_1 task and each one of the other tasks. NFT_1 is the SMR NFT task of the first block, and NFT_2 and NFT_3 are from the second and third block, respectively. Then the subjects were further split into each of the priming conditions IM and BM.

Concerning the self-reports of each subject in this pilot experiment, the interest was to have an idea of what is needed to report and to understand the subjective experience of the participants. As referred, three critical observations were directly asked by the investigator and registered for reference: *"Were the 3 bars distracting?"*, all the subjects referred that the three bars were distracting, and some found the solution to focus on some other thing than the bars, or only focus from time to time in the bars; *"Were the audio-guided instructions distracting?",* 14 participants said that the instructions on the guided audio distracted them. The reason was the number of instructions during the 3 min. However, they also refer that the second time they heard the repetition that they were able to focus on the task and less in the instructions; *"In the rest task, did you succeed in relaxing, or were you thinking about something else?",*

an outstanding 20 out of 33 reported not to succeed. However, these questions are only valid in the context of this experiment. General conclusions cannot be achieved through this rough method. A more phenomenological approach should be undertaken.

In **Appendix II – Self-reports,** one can check the custom form for E1. The statistical analysis and further comparisons of these additional variables are not in the scope of this chapter, so that they will be used only for further publications in the future.

4.5.2 Between-groups

Even if the tBAT change was not significant for each group (Table 1), to represent the tendency effects of priming versus no priming in this preliminary study, an absolute group mean of the tBAT in each block was calculated from Table 1. The graphic in Figure 29 illustrates the results.

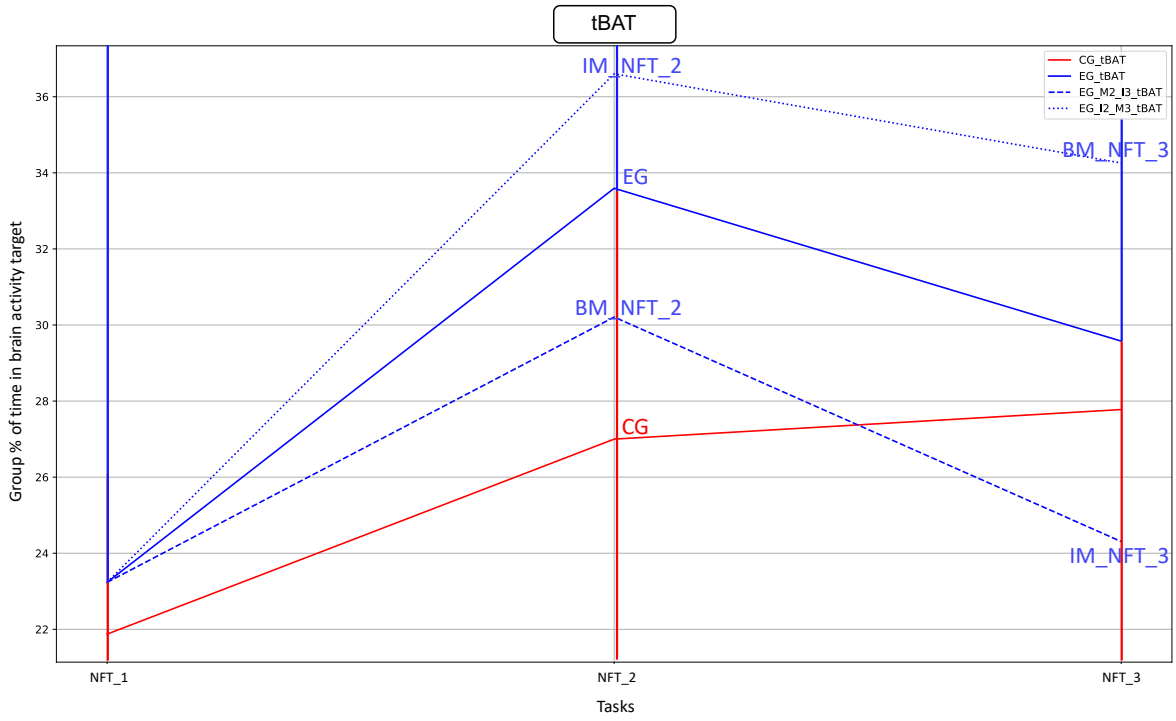


Figure 29 – SMR group tBAT for eyes open. Representation of mean tBAT of subjects from each group (Y-axis) during each NFT trial (X-axis). Red represents the control group. Blue, the experimental group. The bold line represents the absolute mean. Dashed lines represent the NFT block 2 after breathing mindfulness (BM) and NFT block 3 after imagery mindfulness (IM). Points graph line represents the NFT block 2 after IM and NFT block 3 after BM. The error bars are presented as vertical standard deviations (SD).

Red represents the control group. Blue, the experimental group. The bold blue line represents the absolute mean of the EG. Blue dashed lines represent the participants who performed BM_NFT_2 (i.e., NFT block 2 after BM priming) and IM_NFT_3 (i.e., NFT block 3 after IM priming). The blue points graph represents the participants who performed IM_NFT_2 then BM_NFT_3. The error bars are presented as vertical

SDs. A more substantial increase tendency in the PRIME intervention (EG) are visible compared to the no-priming (CG) NF intervention in blocks 2 (NFT_2) and 3 (NFT_3). Additionally, the group who performed IM in block 2 (IM_NFT_2) then BM in block 3 (BM_NFT_3) showed a stronger increase. Nonetheless, as we already described, this preliminary data is not conclusive nor statistically significant (see Table 1).

Some of these results are published in a Frontiers abstract (N. M. Da Costa et al., 2019) and are expanded in the paper (N. M. C. Da Costa et al., 2020).

4.6 Insights from Experiment 1

Participants

In E1, the number of participants was not enough to statistically test the hypotheses of the effects of priming versus no-priming. Also, the sample is lower than other NF intervention studies (Chow et al., 2017; Silvia E. Kober et al., 2017), where generally sampling is around forty (CG, N=20; EG, N=20). However, due to constraints (e.g., time, human resources, lab availability, and recruiting), we only achieved a sample with 33 participants (CG, N=16; EG, N=17). Nonetheless, for pilot testing, it was enough.

Hardware and software setup

We found some setup flaws in the hardware and software that needed to be addressed before a new experiment. In the hardware, we found the following limitations. Wired bulky headphones used for sound stimulation can introduce movement artefacts in some EEG channels data because they touch the electrodes. The lack of straps to tightly pull the cap against the scalp can also lead to movement artefacts. The Self-reports in paper format are not as easy to manipulate as digital, e.g., the use of google forms. Only EEG data was acquired, yet other psychophysiological signal measures can be acquired, like Galvanic Skin Response (GSR) and Heart Rate Variability (HRV), to extract emotional state biomarkers.

In the software, we found limitations in signal acquisition. The LSL Actichamp application had artefact generation problems (Brain Products GmbH, 2015). Due to the lack of a faraday cage in the environment of E1 and the high probability of electrical environment noise, we used the shielding mode[23] of Actichamp, which is indicated to suppress this noise, such as AC power lines, computer displays, wireless equipment.

Nonetheless, this noise correction was irreversible and led to artefacts, so it is advised to use the default mode. The LSL application (APP) is not research-friendly, has minor functionality (see Figure 30), and only enables reference-free montage. Actually, a new LSL browser app (Brain Products GmbH, 2020) was developed to substitute the previous server app (after the conclusion of the experiments conducted during this project). The electrode preparation can be improved when online. During the configuration and placement of the cap, the signal needs a deeper visual inspection to find possible channels with noise and adjust the system accordingly.

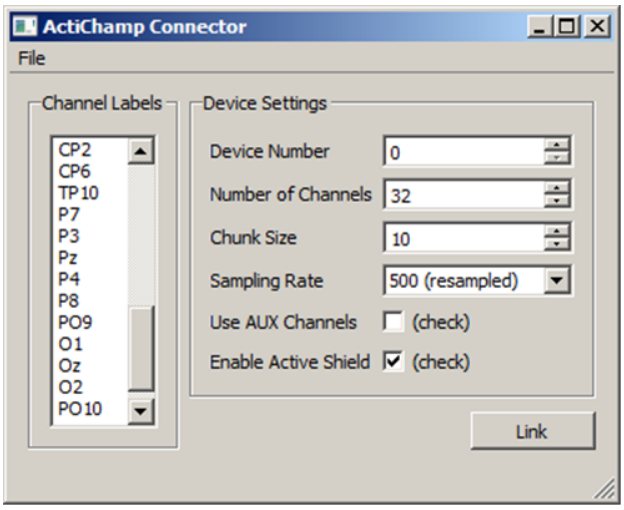


Figure 30 - Actichamp LSL server APP. This server app was available on the LSL GitHub page, please go to (Brain Products GmbH, 2015).

Experimental Design

The experimental environment was not a good EEG Faraday enclosed room with a high probability of electrical environment noise, such as AC power lines, computer displays, wireless equipment. As such, as already pointed out, we used the shielding mode[23] of Actichamp.

PRIME

The priming design was an ABA design that can be repetitive and probably fail to follow the instructions design guidelines, where tasks need to be involving, engaging, progressive, and promote an adaptive learning environment (Lotte et al., 2013). Also, it is essential to note that simplicity and objectivity are required in a single session design to study brain activity effects (Chow et al., 2017; E. Davelaar et al., 2016; Hanslmayr et al., 2005; Peeters et al., 2014; T. Ros et al., 2014; Shibata et al., 2011; Wells et al., 2012), in this case, to study priming versus no-priming.

We decided to keep the eyes closed during PRIME stimulus A because we hypothesised that a more profound priming would occur. However, this makes it difficult to compare the EEG signal between tasks

A and B, as they have two different eye conditions. Also, in the B task, the user needed to use the keyboard to answer the questionnaires, while in the A task, they did not. Therefore, the comparison between A and B was further compromised. In E1, only REST and NFT tasks can be compared.

Regarding the MM audio stimulus, the participant's subjective experience showed that we had too many instructions within the 3 minutes of MM guided stimulus.

REST

REST task was only with EO. This is a significant limitation because the eyes closed protocol can give us important information. Indeed, some predictors of NFT performance use eyes closed (Nan et al., 2018). Additionally, REST, PRIME, and NFT should have the same eyes protocol for comparisons.

NFT

Instructions and provision of strategies were reduced to as little as possible to lower the introduction of possible bias. However, depending on the experimental design, the instructions must be carefully revised to find an equilibrium between necessary and redundant instructions.

We were able to identify increasing trends of tBAT in the PRIME intervention (EG) compared to the no-priming intervention (CG) in blocks 2 and 3 (Figure 29). This pilot analysis seemed to point against the null hypothesis that priming seems to have effects in the NFT SMR protocol developed. Additionally, the group with IM in block 2 and BM in block 3 seems to show a stronger increase of tBAT. It seems that the focus on imagery of a calm place (internal focus on imagery sensations) produces a stronger tBAT than the breathing practice (bodily focus on breathing sensations). This difference can be due to the similarity of cognitive processes used. The internal focus on a calm place and its sensations are probably closer to the *"optimal"* internal focus needed in NFT mental strategies. During IM, we are trying to implicitly target the brain to focus more on *"sensing"* a mental strategy (imagery of a calm place) than focus on *"trying"* to, for example, control the feedback, check the performance of the mental strategy, and other mental strategies used by the subject (E. J. Davelaar et al., 2018). Also, as we hypothesized, the objective is to prime the *"sensing"* state on the subject and expect that during the NFT, the subject is in a more *"sensing"* state than a *"trying"* state. Nonetheless, this preliminary tBAT data is not conclusive nor significant to demonstrate that.

Regarding the feedback presentation using the three bars, it was described by two-thirds (21 subjects) of the population as *"too distractive".* Thus, in this experimental context where we are trying to prime a *"sensing"* state, the SMR protocol with reward and inhibit bars based on Kober et al. (Silvia E. Kober et al., 2017) can have an undesirable effect, as it seems rather distracting for the participants.

Self-reports

In this experiment, we had limited self-reports for subject traits and only mindfulness traits from FFMQ. Also, states self-reports are Likert scales. It would probably be better to find validated state scales and add them to the study. The questionnaire for NFT self-perception should be approached in a more neurophenomenology way. In essence, a disciplined understanding of the subjective experience requires a second-person method which means the rigorous collection of first-person accounts of subjective experience through careful guiding and questioning from a researcher (E. J. Davelaar et al., 2018). Studying neurophenomenology within this framework should be another step to refine it. However, this should be dealt with a multidisciplinary team that we, unfortunately, did not have during this Ph.D. project. In addition, it should account for more variables that could explain and validate the collected data.

Session additional characteristics

The session had too many pre-task pauses per block for the participant to rest before tasks and start when ready. A more continuous experience seems to be required per block, with mainly one pause at the beginning of the block.

Summary

In summary, this analysis seems to point against the null hypothesis: priming seems to have effects in the NFT SMR protocol developed. In E1, it was possible to observe the dynamic shifts from the rest state throughout the session, but also with self-reports, it seems the person is *"trying"* to rest and possibly not *"sensing"* relaxation, pointing in the direction that the participant is closer to a trying state than a rest state. Nonetheless, working with EEG online has its limitations because of the noise in the signal. Any slight movements above the neck, like eye blinks or muscle contraction, can add artefacts to the signal. Attempts were made to prevent and detect such artefacts in real-time and do not include those samples when calculating the feedback. This process is not perfect and can sometimes have false positives, leading to variations in the number of included epochs. Therefore, the error range presented in this analysis is still considerable. However, one should take into account that this is a pilot evaluation. These pilot steps were needed to adjust the experiment requirements, which were met in another experiment described in the next chapter.

CHAPTER 5

Second Framework Application: Evolution of the Experimental Design

This chapter is based on the following scientific publications:

A multivariate randomized controlled experiment about the effects of mindfulness priming on EEG Neurofeedback self-regulation serious games (N. M. C. da Costa et al., 2021)

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5. CHAPTER 5 - SECOND FRAMEWORK APPLICATION: EVOLUTION OF THE EXPERIMENTAL DESIGN

In an effort to meet the requirements learned from E1, we implemented a new intervention with 62 participants, following the current NFT guidelines in instructions design (Lotte et al., 2013), training, reporting, and experimental design (Enriquez-Geppert et al., 2017; Lubianiker et al., 2019; Rogala et al., 2016; Tomas Ros et al., 2020; Sitaram et al., 2017). This experiment throughout the thesis is referred to as Experiment 2 (E2).

5.1 Participants

The participants eligible for this study were Portuguese-speaking healthy subjects, aged 18 to 43 years, with normal or corrected-to-normal vision. At study entry, they needed to be naïve or did not perform NFT, at least in the last year. Exclusion criteria were a history of psychiatric or neurological disorders and the taking of psychotropic medications or addictive drugs. In addition, they were requested to give voluntary written informed consent, approved by the ethics committee.

Initially, 121 participants were eligible for inclusion. In total, 83 were assessed for eligibility, and 62 participants were eventually randomized over two interventions: the experimental priming group (EG, N = 31) and the control no-priming group (CG, N = 31). Of the 62 participants, 37 were women, and 25 were men (percentage in Figure 31).

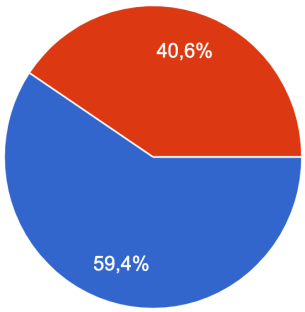


Figure 31 - Gender graphical representation of the 62 participants (f=37, m=25). Blue, woman percentage. Red, men percentage.

Also, the priming stimuli sequence (SS) and the eyes sequence (ES) of open and closed eyes (EO | EC) were randomized and double-blinded - the subject and the investigator did not know. The intervention groups were also randomized and single-blinded to the subject. The randomization criteria were to balance the groups in sample number and gender. ES was randomized between two sequences: ES1) EO, EC, EC, EO; ES2) EC, EO, EO, EC. The PRIME stimuli were also randomized between two sequences (PS): PS1) BM, IM, BM, IM; PS2) IM, BM, IM, BM. While the CG had a stimuli sequence of only REST tasks (RS): REST, REST, REST, REST.

Sixty-two participants completed the study, there was no participant dropout, and no adverse events were recorded. EEG power spectra during the different task conditions were available for 60 participants (N = 30 EG, N = 30 CG). EEG missing data were due to technical reasons (N = 1, subject 16) and outliers at baseline tasks (N = 1, subject 48). Auxiliary measures like the battery of self-reports and GSR measures were available for the 62 participants, while the HRV was missing data due to technical reasons (N = 3). As such, we selected the 60 participants from EEG for further analysis in this chapter. In Figure 32, we present the flow diagram of this single-session randomized controlled experiment.

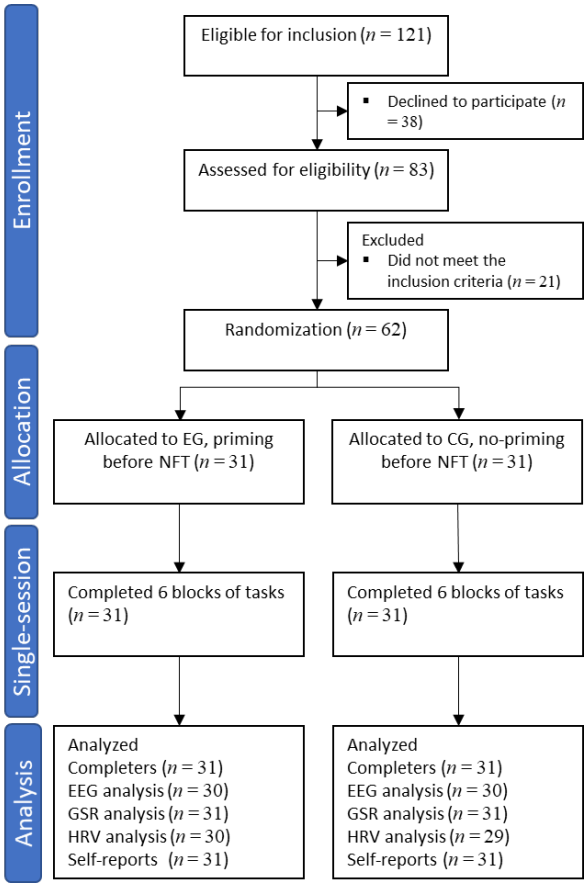


Figure 32 - Consort flow diagram of the randomized controlled intervention. Of the 121 participants eligible for inclusion, 38 declined to participate, and 21 did not meet the inclusion criteria. Sixty-two participants were randomized and allocated to the priming and no-priming group. There were no dropouts, and all the subjects completed the tasks. During analysis, missing data from subjects in EEG and HRV were detected, and one CG subject with outlier EEG data was removed.

Procedure

All the protocols were in accordance with the Declaration of Helsinki, and the reported study was approved by an Internal Review Board (IRB), the local Research Ethics Committee of the University of Minho (SECVS), please refer to previous section **2.5**. Written informed consent was obtained before participation. Participants were recruited from the University of Minho community. Intervention measures included questionnaires (psychological traits and states), neuropsychological tasks, EEG, GSR and HRV.

Randomizations

A two-way parallel-group study with balanced randomization in sample and gender was conducted (EG | CG). Randomization was conducted using Python *"random"* package. First, a list of subjects was created with balanced groups (EG | CG, EO | EC, BM | IM) in sample and gender, and then the list was shuffled using the *"random.shuffle()"* function (check Table 2 for the group's sample). From the schedule time slots for experimental acquisition - slot 1 (9 a.m. to 11 a.m.), slot 2 (11 a.m. to 1 *p*.m.), slot 3 (1 *p*.m. to 3 *p*.m.), and slot 4 (3 *p*.m. to 5 *p*.m.) - the participants would choose the slot to be allocated, and they were allocated following the rule first come/first served.

Power Analysis

From a priori analysis, for two dependent groups, a total sample size of 54 (i.e., 27 per group) was calculated - using G*power version 3.1.9 (Faul et al., 2007) - to be sufficient to detect a medium effect size (f = .25) in a between moments repeated measure (RM) analysis of variance (ANOVA) with an alpha of 0.05 and a power of 95% (i.e., testing same group intervention on different tasks). While for two independent groups within-moments, a total sample size of 60 (i.e., 30 per group) was only sufficient to detect a large effect size in a one-way ANOVA (f = .47) and a *t*-test (f = .86) with an alpha of 0.05 and a power of 95% (i.e., testing different group interventions on the same task). As such, 60 participants were considered adequate to find medium and large effect sizes in the main outcome variables.

5.2 Hardware and software setup

Hardware

The hardware setup was similar to E1 (see section **4.2**), the new additions for E2 can be seen in Figure 33, and they were: (10) straps to pull tight the cap against the scalp; (11) Bluetooth wireless headphones for a lesser impact on the electrodes, aiming to reduce artefacts; (12) a new biosignals device the James One from MindProber, to assess Galvanic Skin Response (GSR) and Heart Rate Variability (HRV); (13) a tablet used to acquire the self-reports answers digitally using Google Forms®.

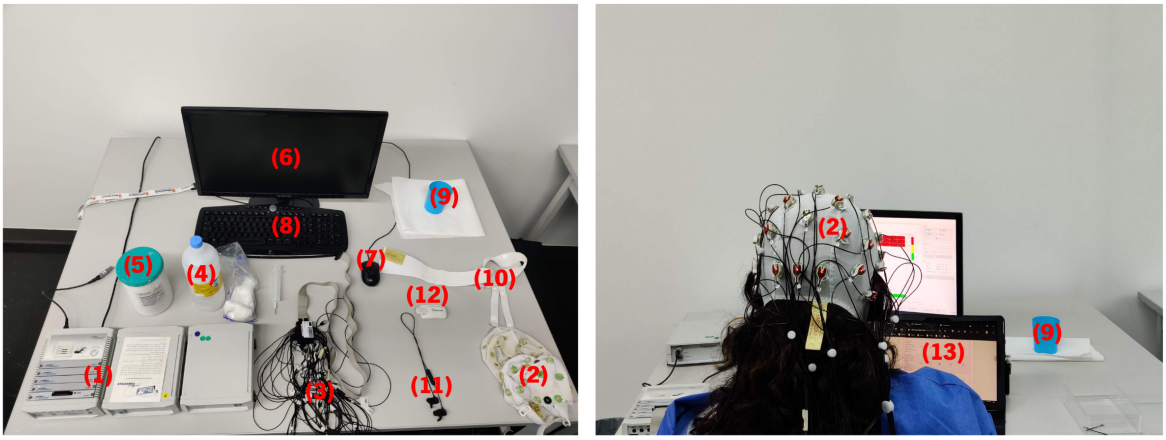


Figure 33 – Experimental hardware setup. On the right, the experiment environment with the subject and tablet (14). On the left is the remaining hardware.

Software

The online experimental paradigm was built using NeuroPrime. For more detail, go back to chapter **3**.

The offline data analysis pipelines were in Brain Vision Analyzer (Brain Products GmbH) for visual inspection of noisy channels, noisy epochs, and planning the processing pipeline. Additionally, NeuroPrime (with Python modules like MNE) was used for advanced signal processing/classification and automation of the pipeline.

5.3 Experimental Design

E2 takes the learning from E1 and builds upon it, resulting in a new experiment. In the following list, we highlight the changes made from E1 to E2 :

- enlarged group sample for statistical purposes (N = 62 Healthy subjects, 18 and 43 years);
- updated the software framework to a simpler interaction with hardware for better visual inspection of noisy channels, and consequently without the need of a shielding mode[23];
- addition of other biodevices (GSR and HRV) to investigate possible biomarkers of emotional states (e.g., arousal, alertness, task engagement);
- used a process-based approach (Lubianiker et al., 2019) for the experimental design to better organize the experimental pipeline and follow the current guidelines on experimental design (Enriquez-Geppert et al., 2017; Tomas Ros et al., 2010);
- include other self-report traits, such as Emotion Regulation Questionnaire (ERQ) and Depression Anxiety and Stress Scale (DASS), and self-report states, Profile of Mood States (POMS) and Toronto Mindfulness Scale (TMS) for finer detailing the subjective experience;
- revised the training session blocks and tasks to simplify the testing, the single session design was divided into 6 short blocks to accommodate the eyes open and eyes closed protocol;
- eyes open and eyes closed protocol were randomized between blocks to ensure comparability with MM and NFT literature (for more detail, please go back to section **2.4**);
- changed the control condition, while in E1 we had ABA design to account for trying versus sensing condition, in this E2, we used REST task as the trying condition;
- changed the feedback target to alpha rhythm in the Pz channel, for keeping with the majority of literature in NFT and MM (for literature detail, please go back to **2.2**);
- measurement-wise, as tBAT did not yield significant results in E1, we choose to present E2 significant results in this thesis using the absolute alpha amplitude of the Pz channel, and in future publications, analyse and present tBAT.

This new experimental design enables the study of linear feature changes, within-group (i.e., between tasks same group) and between-groups (i.e., same task or combination of tasks in different groups), on the REST, PRIME, and NFT tasks. These linear feature changes enable to test the main objective: whether the PRIME MM tasks before the NFT can facilitate or scaffold the transition to the target brain activity, alpha (see Figure 34).

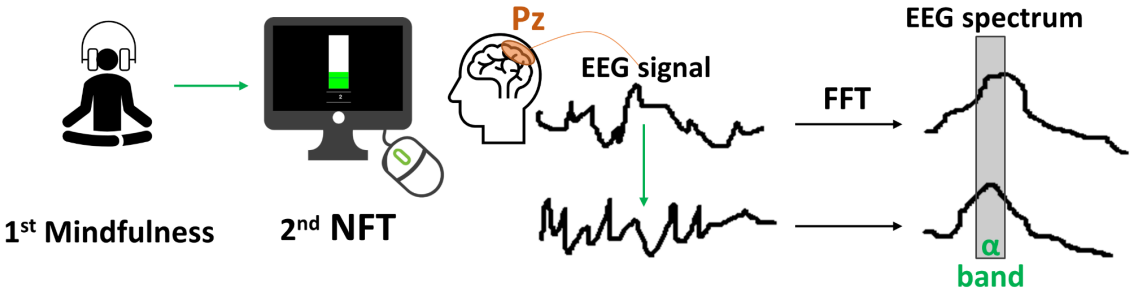


Figure 34 - Objective diagram. The external mindfulness stimuli prime the subject to facilitate/scaffold the transition to the target brain activity alpha (α) in the Pz channel during NFT. The EEG spectrum physiological change is also represented.

Summarizing the experiment design (see Figure 35), initially we acquired 62 participants grouped in 2 interventions, but only 60 were further analyzed (as discussed in section **5.1**): no-priming CG ($N = 30$), priming EG ($N = 30$). Before the intervention, each participant was instructed about the tasks and did the battery of trait self-reports. During the interventions, each participant of CG did a single session of no-priming, while the EG did a single session of priming. The session was divided into s6 blocks (B), with 14 tasks (T). The first and the last block are equal for the two groups, named Block in (Bin) and Block out (Bout). Bin is used to extract the initial baseline threshold from REST EC and EO tasks (T1 and T2 respectably), the first EO NFT, and the first emotional states (using the TMS and POMS). At the end of Bin, the participant is also asked if he understood the pre-training instructions (for the verbal instructions, please check **Appendix III – Instructions** section **Pre-training verbal Instructions**). Bout has the same tasks as Bin and serves as the outcome block for comparison. The 4 blocks between Bin and Bout, B1 to B4, are different for EG and CG: all participants were randomized between ES1 and ES2 (2 blocks for each condition EO | EC); CG participants went through a repetition of 4 blocks of REST task (no-priming) followed by the NFT task; EG were further randomized between PS1 and PS2 (with 2 blocks for each condition BM | IM) with each block having the PRIME task followed by NFT task. After the intervention, participants were tasked to describe the perceived outcome of the experiment and the mental strategy they have used to gain control over the moving bars. The reports were recorded electronically. E2 design enables the study of linear feature changes, within-subjects, and between-groups, of the REST, PRIME, and NFT tasks.

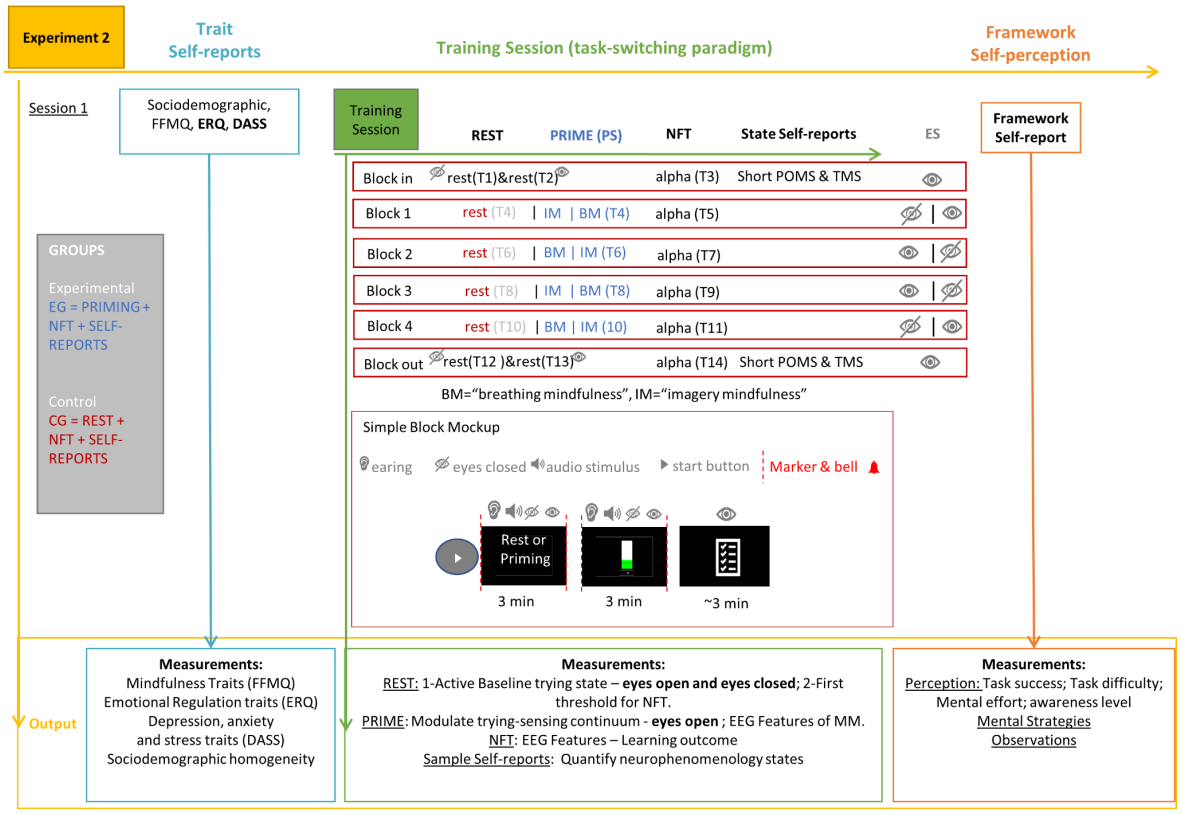


Figure 35 – E2 design. Time flows from left to right, top to bottom. In a single session, first, the subject fills the traits self-reports, then the training starts. There are 6 blocks in total. Block in and Block out each begins with rest state with eyes closed then eyes open, followed by alpha NFT and ends with the state self-reports. From block 1 to 4, in the EG, first is the PRIME task, then NFT. In the control group, PRIME is substituted by REST. PRIME stimuli are randomized between IM and BM. Also, from blocks 1 to 4, eyes closed and eyes open are randomized between blocks. In the diagram, the "or" signal is represented by "|". It is used to separate the task for each group or the randomizations of ES (EO | EC) between blocks and the randomizations of PS (BM | IM).

As in E1, the differences between the control and experimental groups reside in the priming tasks. While the control group is only primed with rest tasks, the experimental group is primed with randomized mindfulness focused attention forms, breathing bodily sensation (BM), and imagery of calm place sensations (IM). These priming stimuli were chosen with the objective to lead the person from a subjective trying state to a more sensing state. As discussed in the introduction section, this transition belongs to the trying-sensing continuum discussed by Davelaar and colleagues (E. J. Davelaar et al., 2018).

These methodological approaches follow the NFT guidelines from (Enriquez-Geppert et al., 2017; Sitaram et al., 2017).

These changes in the experimental design are reflected in Figure 35, but one can also go to Figure 41 with an entire session GUI representation. In the following sections, similar to chapter **4**, we detail each part of the E2 design.

5.3.1 Questionnaires & Self-report measures

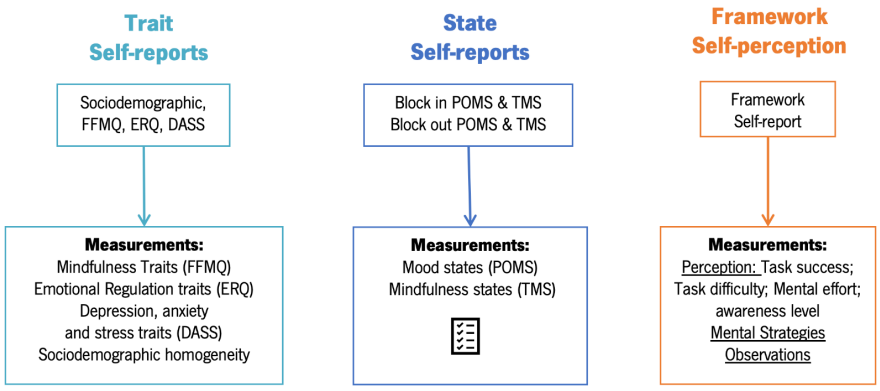


Figure 36 - Self-reports of E2. This diagram represents the three types of self-reports used: traits, states, and framework self-perception.

In this section, we break down the self-reports used (Figure 36) in the E2.

Traits

For descriptive baseline purposes, participants completed first a sociodemographic questionnaire (SOC), then standard, well-validated scales. For mindfulness-related traits, we used the Five Facet Mindfulness Questionnaire, FFMQ, which assesses five mindfulness dimensions (Baer et al., 2008; Gregório & Gouveia, 2011): observing. *"I notice the smells and aromas of things"*; describing. *"I am good at finding words to describe my feelings."*; acting with awareness, *"I find myself doing things without paying awareness attention.";* nonjudging of inner emotions, "*I think some of my emotions are bad or experience inappropriate, and I should not feel them."*; nonreactivity to inner emotions. *"I perceive my feelings and emotions experience without having to react to them."*. For assessing symptoms of depression, anxiety, and stress, we used the Depression Anxiety Stress Scale, DASS (Crawford & Henry, 2003; Pais-Ribeiro et al., 2004). For emotional regulation, we used the Emotion Regulation Questionnaire, ERQ, which assesses two dimensions (Lovibond & Lovibond, 1995; Vaz et al., 2014): cognitive reappraisal, where a person attempts to change how he or she thinks about a situation in order to change its emotional impact; expressive suppression, *"I keep my emotions to myself"* - where a person attempts to inhibit the behavioural expression of his or her emotions.

Sample States

In order to assess the immediate outcomes of the interventions on mood and state mindfulness, participants also completed the Profile of Mood States-Short Form, POMS (Faro Viana et al., 2012) and

the Toronto Mindfulness Scale, TMS (Lau et al., 2006), which assesses the degree to which participants' experience mindful curiosity (e.g., *"I was curious to see what my mind was up to from moment to moment"*) and mindful decentering (e.g., *"I experienced myself as separate from my changing thoughts and feelings"*).

NF combined with the sample states offers a way to relate the phenomenological structure of subjective experience with a real-time characterization of large-scale neural operations throughout the experiment.

Framework self-perception

In order to assess the perceived outcome of the framework, we developed a simple questionnaire to measure the participant self-perception (subjective experience), and we used the acronym NFT for the questionnaire. It is similar to the one used in E1 but has a more straightforward layout with only closed questions and has a complete checkup. To view the differences, go to **Appendix II – Self-reports**.

This questionnaire addresses the following (check **Appendix II – Self-reports** section **E2 self-report**):

- Experiment perception: task success, task difficulty, mental effort, awareness level, experiment duration, intensity/quality of focus in the mental strategies, among others.
- Mental Strategies.
- Observations.

Specific characteristics

These self-reports were copied to digital form using open-source Google Forms software. The participant used a tablet to complete them. This enables a tidier, resource-friendly, and faster acquisition of data. Also, the digital form proved not a hindrance for this population (age:18-43, Education level: above high school education).

The questionnaires are available in digital forms at the following links:

1st questionnaire: https://forms.gle/2uT7f7oH3pd4c9FD9

2nd questionnaire: https://forms.gle/nQNRQkBWEVtbKySo8

3rd questionnaire: https://forms.gle/k1zVwzwVacu7hBYRA

These self-reports are also included in **Appendix II – Self-reports**.

5.3.2 Training session baseline & block in/out

The Block in (Bin) serves as the baseline block for our framework. Also, it helps to test the user understanding, i.e., at the end of Bin, the researcher/technician asks if the participant understood what was expected from him/her during the tasks. Bin is composed of 3 tasks (see Figure 35): 90 s rest eyes closed (REST_EC), 90 s rest eyes open (REST_EO), and 3 min NFT eyes open (NFT_EO). The tasks REST_EC and REST_EO are used to compute the threshold for all blocks of NFT with eyes closed (NFT_EC) and NFT_EO, respectively. The threshold calculation will be demonstrated in the following sections.

The Block out (Bout) serves as the outcome block, assessing the learning outcome by comparison with the Bin. This training design is based on the pre-post NFT design explained in the guidelines of Enriquez-Geppert et al. (Enriquez-Geppert et al., 2017). Bout has the same layout as Bin (see in Figure 35). It is essential to mention that Bin and Bout are equal in the EG and CG. The groups only diverge from blocks 1 to 4, with the difference being priming tasks for EG and rest tasks for CG.

The implementation of EO and EC in the same session came from literature and E1, where we found that we could not compare priming with eyes closed with rest or NFT with eyes open. From the literature, the alpha amplitude is generally seen as a function of reduced sensory input from the thalamic nuclei to the cortex (Chow et al., 2017; D. Vernon et al., 2009). Keeping the EO will suppress alpha amplitude relative to an EC condition, providing a lower baseline from which to attempt to increase the alpha amplitude, thereby presumably more amenable to intervention effects via NF (for more detail on the usage of EO and EC conditions, please go back to section **2.4**). As such, the baseline and the dynamics of PSD in EO and EC conditions are very distinct. Also, performing similar tasks with EO and EC have distinct effects on EEG activity and behavioural performance (Reichert et al., 2015), as one will see in the results section **5.5**. Considering this, we selected both conditions to ensure comparability between tasks and between conditions.

In E2, each task at the beginning of the block has a pre-task screen. Unlike E1, this pre-task screen is present at the beginning of each block because we want a seamless transition between tasks inside the block. The pre-task screen is necessary for several reasons: user's own pace; relaxation and resting of the previous block; signal artefacts control; adjustments that may be needed. For more on instructions, go to **Appendix III – Instructions.** In the following sections, we discussed each task instruction individually.

5.3.3 Rest state task & trying state control condition (REST)

Rest state task (REST) is a standard task in NFT protocols. Standardly used to evaluate the subject baseline and compute the initial NFT threshold to find the individual rest state baseline (Enriquez-Geppert et al., 2017). The simple version is to give the instruction *"try to relax/rest during the task"*.

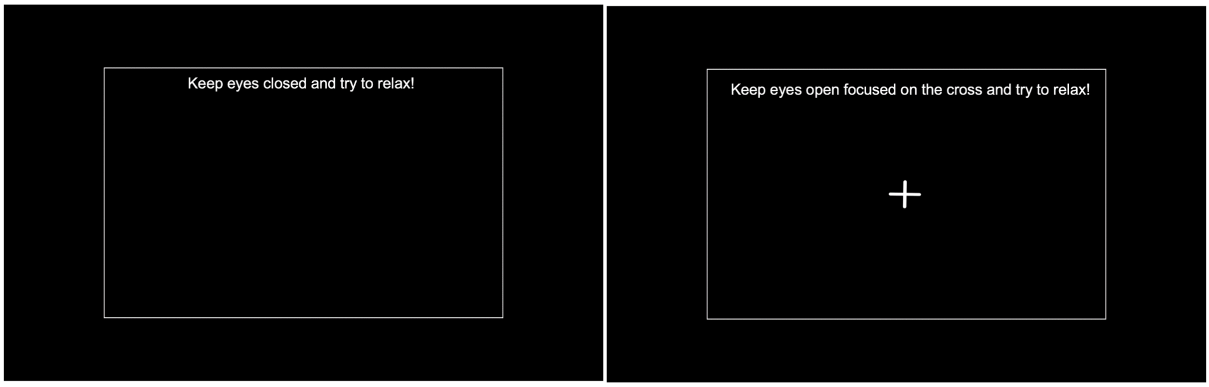


Figure 37 - GUI representation of the rest task screen. The eyes closed is represented on the left, and the eyes open on the right.

In E2, REST has a pre-task and task screen with instructions. In the REST pre-task screen, the subject is introduced to the task and is instructed to focus and relax before using the key *"Enter"* to start the task. In the task screen, REST is only instructed with *"try to relax"*, and the difference is only in the interface. With EO, the participant needs to focus on the cross in the centre of the screen, while with EC, he/she needs to relax and wait for the ending auditory cue, a bell. Figure 37 shows the GUI used for each task with instructions translated from Portuguese. In addition, the text instructions for EO and EC are in **Appendix III – Instructions** section **E2 REST task instructions**.

Contextually, in E1 was possible to observe not only dynamic PSD shifts from the REST task during the session (from the first block to the last, please refer to **Appendix IV – Additional results**), but also self-reports hinting that the participant was trying to rest and with difficulties in sensing relaxation. It suggests that the participants were closer to a *"trying"* state than a resting state. Therefore, while in E1, we had an ABA design to account for trying versus sensing conditions, in E2, we used the REST task as the trying no-priming control condition, while the priming tasks are for the sensing condition. The priming tasks are further developed in the next section.

5.3.4 Pre-training Priming Protocol (PRIME)

The pre-training priming protocol (PRIME) is our innovation to answer the questions: Does priming support NFT SR learning? Can we implicitly prime the target brain state and help explicitly control the target brain

state in NFT? Are MM focused attention stimuli able to prime in the intended direction? Is this the stimulus category that needs to be used in the future (in development) machine learning framework?

Below we discuss the training design and the methodology basis of PRIME and describe the MM stimuli used.

Training Design

The basis for PRIME is a brain state-dependent stimulation experimental method to investigate the causal role of MM stimulus versus REST stimulus.

As already referred, in BSDS designs, the use of an active control group is not necessary to study the functional role of brain states guiding stimulation. However, in the current framework, priming is not a close-loop stimulator but instead a fixed randomization of two MM stimuli. Therefore control conditions and an active control group are necessary to compare with the target conditions. This is the same methodological basis that was used for the E1. However, because E1 had a complex ABA design (A: target condition, B: control condition) to see brain states fluctuations, we decide in E2 to simplify the design assuming the hypothesis that REST leads the subject to a more trying and self-related thinking state. Therefore, to simplify the analysis of stimulus-response oscillations, priming with MM guided stimuli is the target condition while REST is the control condition. The hypothesis is that the attentional focus will wander around during the control condition when the technician only instructs the subject to *"try to relax"*, while the MM task will promote attentional focus, awareness, and less self-related thinking. In this way, we have two groups, one with priming target conditions, the EG, and the control group with the REST control condition.

In fact, Davelaar et al. found some surprising evidence that the typical instruction *"try to relax and focus on the task"* that is used in NFT and REST can be detrimental to the learning success (E. J. Davelaar et al., 2018). In this way, a pure implicit instruction like guiding the person toward the desired subjective experience can possibly have better effects on short NFT sessions.

This simple design makes possible the study of linear feature changes within-session and between-group in the REST and MM tasks and NFT.

Mindfulness Meditation Intervention (MM)

As already discussed in section **2.2**, mindfulness meditation techniques comprise training an individual to more efficiently sustain their attention toward an intended object (e.g., bodily sensations, like respiration, tingling on fingers) and away from external (e.g., external stimulus like sounds, visual cues) or internal sources of distraction (e.g., thoughts, mind wandering), resembling the hypothesized *"optimal"* state of NFT SR learning. As such, like E1, MM was chosen as the basis to develop the two stimuli used in this framework. One focuses on breathing (BM), and the other focuses on an imaginary thought of a calm place (IM). Also, we hypothesize that the internal focus of IM could have a more significant correlation to the form of focused attention the subject presents when focusing on the mental strategies to up-regulate the NF.

In E2, participants were primed with new audio-guided MM instructions (updated based on the observations of E1), and like E1, the instructions were reviewed/transcript to Portuguese by a specialized mindfulness psychologist and recorded by a hospital Nurse on macOS using Garageband® software. The new audio-guided instructions were adapted considering the experimental design of 3 minutes long priming task per block. These short and repeated tasks are based on the following hypothesis that stems from the observations of E1:

- Short blocks, repetition of same stimuli per block, and more blocks (instead of ABA design per block and fewer blocks) seem to be a better and more straightforward approach for naïve populations:
    - They do not have experience focusing their attention on the target, revealing that it *"is difficult to focus on the target while the audio guide is talking"*.
    - They do not have the experience to recall their attention to the focus target after mind wandering: *"after losing focus because of a distraction, I was not able to focus again"*.
    - Their subjective experience with a longer block and repetition of the same task (ABA design) is not satisfying. They used adjectives to describe their experience like *"bored"* and *"fatigue"*.
- The repeated audio guide per block can serve as a mantra between the blocks, something that the participant can cling to and bring him back to the focus target.
- In E2 design, 3 min tasks per block are repeated for a straightforward between-group comparison of REST and MM tasks.

This short stimuli design probably has limitations in the level of mastery of mindfulness states achieved per task - typically, audio guide meditations take 15 min (P. A. Frewen et al., 2014). Nonetheless, it seems suitable for naïve populations, and it is an evolution of E1 design based on participants experience.

Bodily focused attention on breathing (BM)

Like E1, in the BM task, participants were primed with audio-guided MM instructions, with the focused attentional target being on bodily breathing sensations. As referenced above, the focus was to simplify the audio instructions based on the E1 participant's subjective experience. As such, some of the audio instructions in E1 passed to the pre-task screen in E2 and were also simplified to obtain an objective dialogue with more *"silence"* between instructions. While in E1, we had 7 lines of dialogue with lines reaching a max of 41 words, in E2, we had 5 lines with a maximum of 22 words per line. To compare the two, please refer to **Appendix III – Instructions** section **E2 BM instructions** with the manuscript for the text instructions in Portuguese, used in each of the screens, and the audio instructions with the time marker.

Imagery focused attention on a calm place (IM)

Similarly, the participants were primed with the same procedure as BM, but the focus of attention was on a mental image of a calm place, like E1. While in E1, we had 8 lines of dialogue with lines reaching a max of 41 words, in E2, we have 6 lines with a maximum of 22 words per line. To compare the two, please refer to **Appendix III – Instructions** section **E2 IM instructions** with the manuscript for the text instructions in Portuguese, used in each of the screens, and the audio instructions with the time marker.

5.3.5 Alpha Neurofeedback training protocol (NFT)

Training Design

Alpha NFT protocol was based on guidelines from Enriquez-Geppert et al., Sitaram et al. and Lubianiker et al. (Enriquez-Geppert et al., 2017; Lubianiker et al., 2019; Sitaram et al., 2017). It consists of a pre-post training design to investigate single-session SR performance of alpha upregulation (8-12Hz).

The EEG-alpha protocol aimed to investigate the trainability of alpha after priming versus no-priming the subject and assess subjective experience during the training. Therefore, a protocol was set up, including

a no-priming active control group (CG). Participants of the control group were pseudo-randomly matched to the experimental group. They received NFT without the pre-training PRIME tasks.

As already referred to in section **4.3**, SPC is the core of the training protocol. It uses the input data acquired for online feature extraction, threshold and feedback calculation of feature changes, online artefact rejection, online feedback generation and outputs the feedback to the presentation. As such, we dedicate the subsequent sections to define the methods used for SPC and how they interact from one side with SA and from the other with SP.

Online feature extraction

In this training protocol, feature extraction is driven by the hypothesis[21] that up-regulation of alpha has some relation to the *"optimal"* state and alpha is the most validated protocol in MM practice, reviewed by (Aftanas & Golosheikin, 2003; Cahn & Polich, 2006; Chiesa & Serretti, 2010; Lomas et al., 2015).

Concerning NFT specificity (please refer to **1.3.7** for more detail), evidence is most in favour of band non-specificity within and across sessions. However, there is some evidence of specificity across session baselines (John H. Gruzelier, 2014a, 2014b; van Lutterveld et al., 2017), which is important to justify the implementation of an equal pre-training block (Bin) and a post-training block (Bout) to find differences in baseline values. Regarding topographical non-specificity, topography plays a minor role, so choosing the electrode location Pz comes down to where alpha is generally maximal recorded with average amplitudes ranging 30-50 μV (Ergenoglu et al., 2004; D. Vernon et al., 2009) and which location is more recurrent in the literature (Dempster & Vernon, 2009; John H. Gruzelier, 2014b; D. Vernon et al., 2009). Another topic is outcome specificity. Behavioural gains can be stronger for the training protocol and not correlate directly with the training band, indicative of specificity of behavioural outcome even where frequency non-specificity rules (John H. Gruzelier, 2014b). As we already discussed in section **2.1.3- Neuroimaging targets**, concerning the *"optimal"* state, the literature reveals an amplitude increase in alpha and SMR range and a decrease in the other bands in frontal, central, and posterior sites. Therefore, exists evidence supporting alpha training behavioural outcome from comparative protocol studies.

From all the specificity evidence, the expected ideal training protocol would be an NF interface to neuromodulate the whole dynamics of the power spectrum of each individual, not only one specific band. Training effects are likely to be more generalized (not specific to one band), in keeping with a functional system perspective. However, the simplistic strict localization view is embedded in scientific consciousness, in contrast to the realistic but complicated functional system perspective (John H.

Gruzelier, 2014b). Therefore, modulating alpha in posterior sites, even if it is not the complete picture it is the most valid and straightforward at the moment to have correlations with the *"optimal"* state behavioural outcome, coupled with a fine-grained analysis of the various learning parameters when aligned with the entire spectral bands and the behavioural tasks.

The band to extract the NF was a fixed-frequency band. The present study opted to define the alpha band using the traditional 8–12-Hz frequency range, following the majority of meditation literature which has generally investigated effects on the 8–12-Hz band (Aftanas & Golosheikin, 2003; Cahn & Polich, 2006; Chiesa & Serretti, 2010; Chow et al., 2017; J. Gruzelier et al., 2010; Silvia E. Kober et al., 2017; Lagopoulos et al., 2009; Lomas et al., 2015; Navarro Gil et al., 2018; Tang et al., 2015; Tang, 2017). As such, we acknowledge the exclusion of implementing IAF to establish individual band range as a potential study limitation, and future trials would do well to compare our results with IAF-informed studies, largely because previous studies noted a high inter-individual variability in the alpha rhythm. Thus, using a fixed frequency band like the 8-12 Hz can introduce bias against certain subjects, especially those with an IAF beyond this band (Haegens et al., 2014; D. Vernon et al., 2009).

Threshold & feedback calculation of feature changes

The sampling rate of the EEG amplifier was 1kHz. Therefore, Pz EEG spectral densities were estimated online from 1,024 s (≈1 s) segments containing 1024 samples, updated every ≈200 ms. While in E1, we had updates every 1 s with entirely new data, in E2, we managed to obtain a sliding window of ≈1 s updated every ≈200 ms (for a smoother feedback experience even using the RDA server, please go back to section **3.1** for more detail in the signal acquisition software), meaning ≈800 ms of old data plus ≈200 ms of new data. As such, spectral densities were estimated from 1024 ms epoch data using a discrete Fourier transform with Hamming windows (WELCH method with n_fft=1024, n_per_seg=1024, n_overlap=256)[22].

Though in E1, we used SMR (12-15Hz) as a reward band and theta (4-8Hz) and beta (15-35Hz) as inhibit bands. In E2, we simplified the feedback and only calculated the reward band alpha (8-12 Hz) - mean power of Pz without SD.

For each subject, the initial threshold was set such that the EEG-alpha amplitude of the subject, in the initial baseline REST task of 90 s (at Bin), would be 65% of the time above the threshold. Therefore, considering a normal distribution, the formula to extract the threshold from the REST task was mean-

0.38*SD. The initial threshold was only recalculated after each NFT block in case of extreme situations (i.e., adaptation of the threshold for positive feedback based on perceived task difficulty):

- If the ratio between the number of feedbacks above the threshold and the total number of feedback presented was above 90%, then threshold=threshold+0.1*threshold.
- If the ratio between the number of feedbacks above the threshold and the total number of feedback presented was below 10%, then threshold=threshold-0.1*threshold.

Amplitude changes of alpha activity during training were then compared to this threshold in order to present the feedback.

For more details on data processing, please go to data analysis in section **5.4**.

Online artefact rejection & confounders

Remembering what we discussed in the last chapter (section **4.3.4**), signal activity during an experiment can be biased or correlated with non-neuronal artefacts that can be technical (experimental setup), physiological, and demographic, acting to increase within-group variability (confounders). Therefore, various artefacts generate activity that affects the whole EEG frequency spectrum, including those frequencies that are usually the focus of NFT. For example, in the worst case, when ignoring eye artefacts, the participants may falsely learn to modulate their eye movements rather than their brain activity.

Nonetheless, the best artefact rejection is to prevent artefacts from appearing in the first place, especially in the technical side of things (e.g., minimize artefacts during data collection and train/instruct subjects to minimize artefacts). Therefore, the preferred approach was preventing and implementing a simple but effective NFT algorithm to automate artefact rejection.

Technically speaking, in E2, we used Cz as a common reference instead of an average reference online (like E1) because this reference configuration could be visually inspected with Pycorder (see Figure 38) to make sure that there were no relevant artefacts in the channels of interest before starting the training. The same can be said for the choice of using Actichamp default mode versus shielding mode[23]. While shielding mode can help experimental environments with electrical noise, it is also an irreversible correction of noise in the signal that can create artefacts (as occurred in E1). This way, we were able to obtain a more robust configuration in E2.

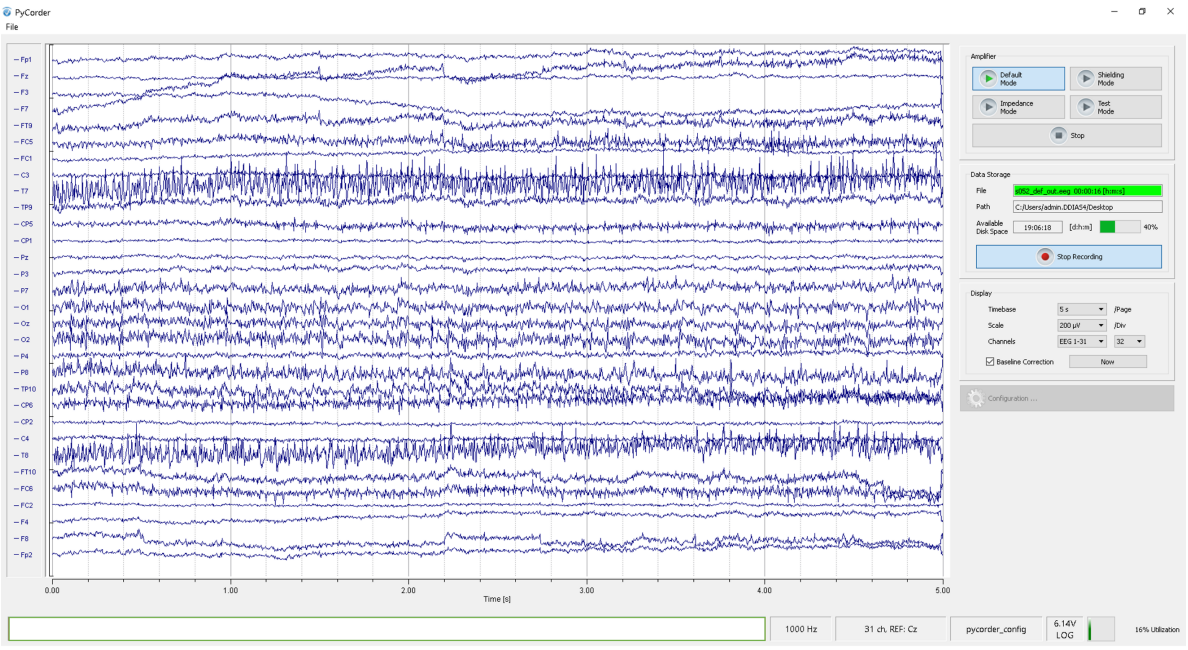


Figure 38 - Pycorder signal representation with Cz as a common reference. Channels in the temporal and occipital region show a higher signal-to-noise ratio.

To reject possible physiological artefacts, we used some target channels to automate epoch rejection. These channels were Fp1, Fp2, Fz, and Pz (see Figure 39). Furthermore, we enumerate why we only choose these four channels. We used four channels for faster processing. These four channels, including Pz, were selected to remove epochs that had noise common to these channels. The noise in other channels was not considered significant for this study. For example, noise in temporal regions that are not common to the Cz reference (like headphones touching the electrodes) will not appear in the four channels. Fp1 and Fp2 were chosen for their relationship with eyes artefacts. Fz and Pz were used because of the probability of having artefacts lower than their neighbour channels, and they represent most of the noise topography.

Additionally, participants were verbally instructed (see **Appendix III – Instructions**) about the possible physiological artefacts in real-time, how these artefacts would influence the feedback presentation, and trained on how to avoid them.

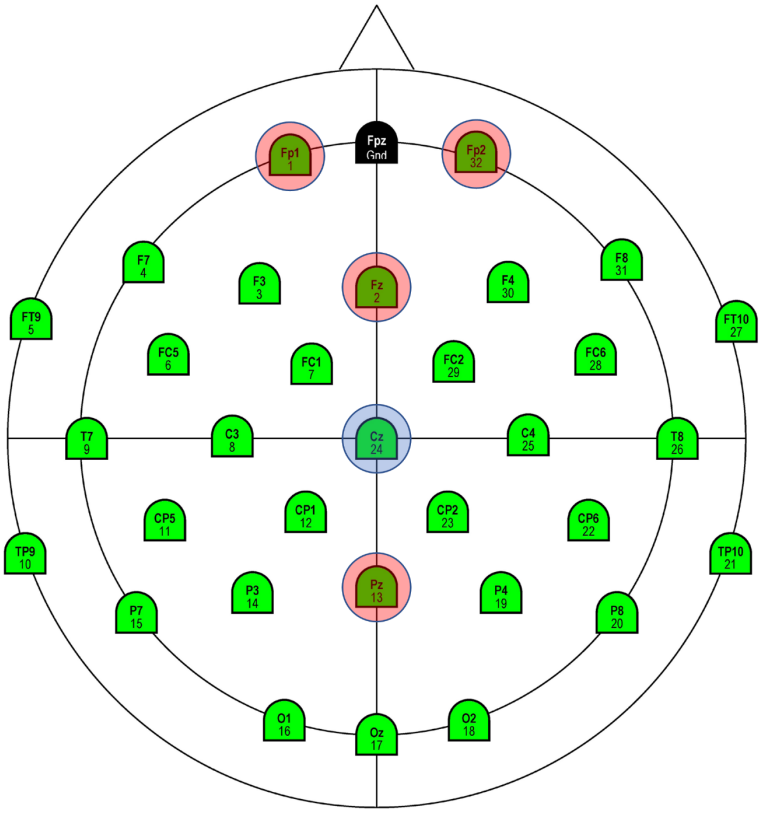


Figure 39 – E2 Ch selection for feature extraction. The channels Fp1, Fp2, Fz, and Pz, were selected from the unified optimized layout based on an international 10-20 localization system (Brain Products GmbH).

Online Feedback-generation

Because of the implementation of blocks with EO and EC, we implemented multimodal audiovisual feedback. We also strive to make both feedbacks (audio and visual) affectively neutral, not intrusive, and one-dimensional, i.e., a visual bar and an audio pitch that only showed positive and negative neurofeedback.

We used the same reward function for each modality: positive feedback when rewarding frequency above threshold (mean alpha power/threshold >1) and negative feedback when below threshold (mean alpha power /threshold <1).

In E1, three vertically moving bars represented the power changes in 3 different bands (please go back to Figure 26). In E2, we decided to take a step back in the visual complexity, considering that all the subjects in E1 referred that the three moving bars were *"distracting"*. Therefore, we opted only to show the alpha as a reward band. As reward cues, we used a point system and visual colour change. For the point system, the participant was rewarded with an extra point for each new reward epoch (updated every

200 ms for a smoother experience), while the visual cue consisted of a change in the bar from red to green. See this in the following Figure 40.

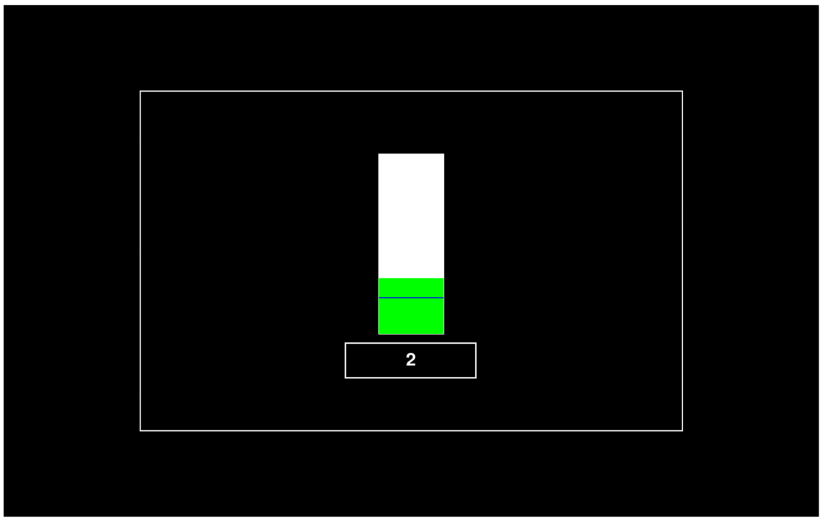


Figure 40 – E2 neurofeedback presentation GUI. This image shows successful regulation when the alpha amplitude is above the respective threshold (blue line), with the sum of the points in the box below the bar.

The decision to implement audio feedback came firstly from the implementation of the EC blocks. Then, we noticed that the audio complemented the visual because the bar can be visually distractive and stimulates specific responses that can interfere with the neural target objective (trying and controlling seems to be detrimental). Also, for the subject to get to the neural target, the first objective is to focus on a neuromodulation strategy, and the audio seems not to interfere as much as the visual signal, as speculated by (D. Vernon et al., 2009). Therefore, even in EO blocks, the subject can focus on the neuromodulation strategy without the visual distraction. Also, we strive to make the reward sound affectively neutral and one-dimensional (only 1 type of sound and constant volume) to not interfere with the NFT performance. These choices are inline with the majority of NF studies that have used simple forms of interfaces solely to indicate the level of neural activity change. These interfaces are usually one-dimensional (size or height; volume or pitch), unimodal (visual or auditory), and affectively neutral (Lubianiker et al., 2019).

For the auditory feedback, we used Mac OS Garageband® piano synthesizer, Outer Lands Synth, to create a reward and an inhibit sound, simplifying the auditory piano feedback from (Meir-Hasson et al., 2016). The reward was a low pitch piano C1 note (≈33 Hz), while the inhibit sound was a higher pitch C2 note (2*C1≈66 Hz), both one-dimensional and constant volume. One can go online and play the sounds located inside the NeuroPrime package, folder *"stimulus"* (N. M. C. da Costa, 2020). We choose the lower frequency to be the reward target as it is the lower pitch with the most neutral sound, while the

higher frequency pitch is more intrusive. However, some participants can link the higher pitch (more energy) to the reward while the lower to the inhibition. Thus, subjects were instructed otherwise during pre-training. Additionally, because the sounds were sought to be affectively neutral, they were similar, and only during pre-training by comparison and repetition of the sound made subjects understand their difference. Additionally, the literature in Neurofeedback is vague in audio design (E. Davelaar, 2017; Enriquez-Geppert et al., 2017; John H. Gruzelier, 2014b; Reichert et al., 2015; Rogala et al., 2016). As such, our audio design choices can be accounted as limitations, and we suggest, in future experiments, to test different sounds and pitches and infer the best audio feedback.

The NF was presented continuously. However, during artefact epoch rejection, if, for example, the person blinked or contracted any muscle, the NF stopped being presented for that epoch, maintaining the same feedback of the previous epoch: visually, the bar would stop, and the sound would maintain the pitch. As such, EO blocks (with more blinks and muscle contractions) were more prone to artefacts, while EC blocks were less sensitive to artefacts.

5.3.6 Additional Framework Training Characteristics

Provision of neuromodulation strategies

The investigator was in the room with the participant during the entire experiment.

Because participants were naïve to MM and NFT, they received verbally, for example, a collection of possible strategies on how to self-regulate alpha (e.g., *"Explore Mental strategies: like focus on something on the screen; positive thoughts, negative thoughts, neutral, and others"*). They were instructed to test these as well as strategies by themselves in order to select the best working mental operation to change their brain activity in the intended direction.

They were explicitly instructed that the primary objective was to pass the bar above the threshold or the audio to the positive low pitch sound and get the highest sum of points possible. The secondary objective, more challenging, was to maintain the bar above the threshold (positive rewarding state) for extended periods.

Each NFT task lasted 3 min per block. Therefore, the participants were instructed to try a maximum of 3 strategies per block, to take at least 1 min per strategy (this is an approximation as subjects had no

timer), respecting the time they need to focus on something and that focus to change their mental state (e.g., *"Explore and take your time!"*).

Another suggestion was to explore from simple to complex strategies. Simple, for example, tingling on the finger or thinking in a black background. While complex, for example, thinking about a music piece and the different sounds that the instruments make.

As discussed in the previous section, participants were also instructed about the artefacts and how they interfere with the NFT interface. In fact, because EEG signal amplitude is in the range of the μV while muscle contraction is in the mV range, any muscle contraction above the neck appears as an artefact in the signal, e.g., smile. This means that when these artefacts occurred, the NF could not be presented. As such, visually, the participant saw the bar stopping whenever an artefact occurred. However, they were instructed not to look at it as a problem because the main objective was to focus entirely on the neuromodulation strategy while only using the NF to check if the brain activity is going in the intended target direction.

The text for all these instructions can be found in **Appendix III – Instructions** section **Pre-training verbal Instructions**.

Number of sessions

The single session within-subject[24] design was used to compare behavioural effects when different stimuli were presented during the same session. Also, it is a between-group design for comparisons between priming and no-priming.

Just as a side note, Gruzelier commented: *"The within-subject methodology is to be commended, assuming there is no carry over influences from one band to another"* (John H. Gruzelier, 2014b). In our case, one limitation can be the carry over influences between block tasks conditions: EO or EC and different priming stimuli. Randomization accounted for this fact.

Figure 41 shows a GUI representation of an entire session constituted by:

- 6 blocks with 14 tasks (T#):
    - Bin:
        - REST_EC (90 s, T1) + REST_EO (90 s, T2) + NFT_EO (3 min, T3) + State Self-report questionnaire (≈3min)
    - B1 (EO|EC):

- CG: REST (3 min, T4) + NFT (3 min, T5);
- EG: PRIME (BM | IM, 3 min, T4) + NFT (3 min, T5);

○ B2 (EC | EO):

- CG: REST (3 min, T6) + NFT (3 min, T7);
- EG: PRIME (IM | BM, 3 min, T6) + NFT (3 min, T7);

○ B3 (EC | EO):

- CG: REST (3 min, T8) + NFT (3 min, T9);
- EG: PRIME (BM | IM, 3 min, T8) + NFT (3 min, T9);

○ B4 (EO | EC):

- CG: REST (3 min, T10) + NFT (3 min, T11);
- EG: PRIME (IM | BM, 3 min, T10) + NFT (3 min, T11);

○ Bout:

- REST_EC (90 s, T12) + REST_EO (90s, T13) + NFT_EO (3 min, T14) + State Self-report questionnaire (≈3min) + NFT self-perception report(≈3min)

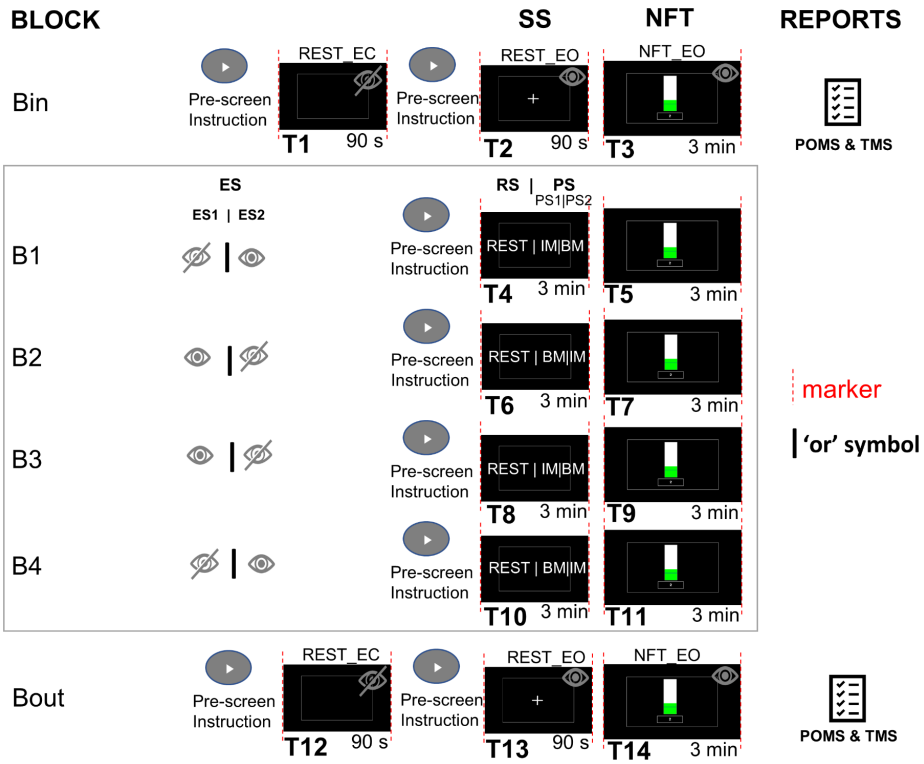


Figure 41 – E2 GUI representation of the entire session. The marker for the start and the stop of the task is represented as red dashed lines. The "or" symbol is represented as "|". SS is the stimuli sequence. ES is the eyes sequence. RS is the REST sequence. PS is the PRIME sequence.

The list and Figure 41 display the randomization of the four blocks (EO | EC and BM | IM) after Bin and before Bout. As already explained and defined in section **5.1**, ES was randomized between two

sequences: ES1) EO, EC, EC, EO; ES2) EC, EO, EO, EC. PS was also randomized between two sequences: PS1) BM, IM, BM, IM; PS2) IM, BM, IM, BM. While the CG had only one RS: RS) REST, REST, REST, REST. Totalizing into 4 different randomization groups: 1) BM_EO, IM_EC, BM_EC, IM_EO; 2) BM_EC, IM_EO, BM_EO, IM_EC; 3) IM_EO, BM_EC, IM_EC, BM_EO; 4) IM_EC, BM_EO, IM_EO, BM_EC. Simply put, these combinations were chosen to achieve randomization of PRIME stimuli between the two ES protocols, i.e.:

- EO: IM | BM, BM | IM.
- EC: IM | BM, BM | IM.

Comparing this block structure with E1, we can see the simplification of the block task structure and the addition of more blocks for multiple comparisons within and between subjects. However, there is a tradeoff in complexity. While the block structure is simple, the within-subject variables and their randomization are more complex than E1.

Study blinding

As previously discussed in the above section and section **5.1**, PRIME stimulus (BM | IM) and the ES protocol (EO | EC) were randomized and double-blinded, i.e., neither the subject nor the researcher knew the group. The main groups (EG | CG) were randomized and single-blinded to the subject. The main criteria for the two randomizations were to balance the groups in number and sex. In Table 2, the group sample combinations resultant for each randomization are detailed.

Table 2 - Samples according to the different group randomizations. In red is the number of remaining subjects for analysis after EEG data inspection.

	CG	**EG**	**EO**	**EC**	**IM**	**BM**	**F**	**M**
CG	31(30)	-	15	16(15)	-	-	19	12(11)
EG	-	31(30)	17(16)	14	16(15)	15	18	13(12)
EO	15	17(16)	32(31)	62(60)	9(8)	8	18	14(13)
EC	16(15)	14	62(60)	30(29)	7	7	19	11(10)
IM	-	16(15)	9(8)	8	16(15)	31(30)	10	6(5)
BM	-	15	8	7	31(30)	15	8	7
F	19	18	18	19	10	8	37	-
M	12(11)	13(12)	14(13)	11(10)	6(5)	7	-	25(23)

EG, experimental group; CG, control group; EC, eyes closed; EO, eyes open; IM, imagery mind PRIME stimuli; BM, breathing meditation PRIME stimuli; F, female; M, Male.

Control group conditions from a process-based perspective

In order to determine MM priming effects in NFT intervention, the effects resulting from MM neuromodulation on the specific NFT target process (alpha neuromodulation) must be differentiated from the general processes (control, learning, reward) of NFT practice (Lubianiker et al., 2019). To this end, we chose to implement a no-priming REST task control condition. This is not quite the ideal control condition because the REST task can also alter the MM general processes (attention control, emotional regulation, and self-awareness). However, it is the most relevant to answer the question: does priming with MM tasks provide more NFT efficiency than REST tasks? This is important because many protocols use rest tasks right before the NFT.

Ideally, the NFT target processes should also be differentiated from NFT general processes to find the baseline for the target processes, e.g., randomizing different targets (Lubianiker et al., 2019). This way, it would also be possible to evaluate the NFT treatment specificity. However, this would require an additional group, which was not possible in this experiment due to the number of participants. Figure 42 summarizes this information.

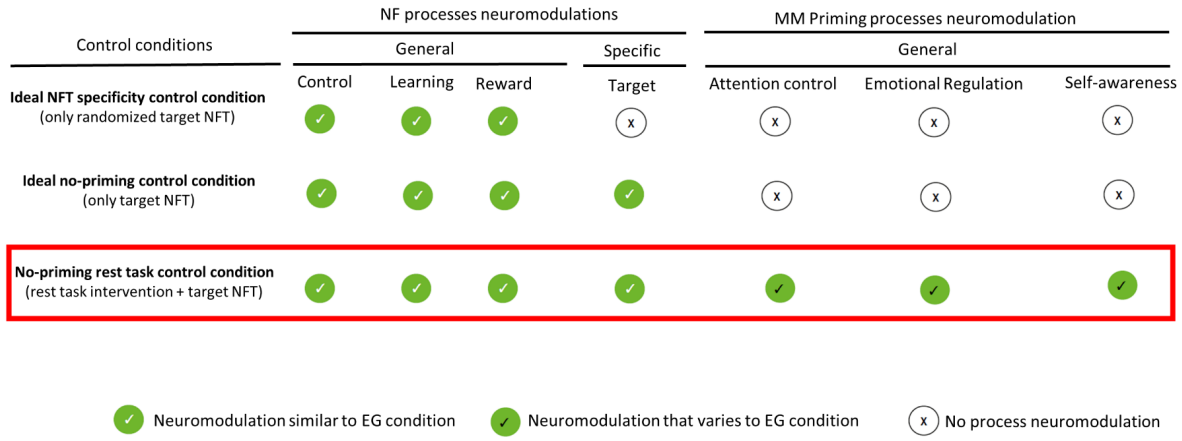


Figure 42 - Control condition for E2 based on (Lubianiker et al., 2019). The control condition selected was the no-priming rest task control condition.

GSR & HRV

Tonic and phasic GSR, biomarkers for sympathetic system responses (Boucsein et al., 2012; Critchley, 2002; Posada-Quintero & Chon, 2020), and HRV signals, biomarkers for vagal parasympathetic system responses (Beauchaine, 2001; Graziano & Derefinko, 2013; Malik et al., 1996; Montano et al., 2009; Zahn et al., 2016)), were continuously acquired to monitor the participant during the session.

As such, a new biosignals device was introduced in E2, James One from MindProber Portugal, with a built-in GSR sensor and a PPG sensor that allows HRV measurements (Correia et al., 2020; Moreira et al., 2019). Each signal was acquired at a sample rate of 100 Hz, and feature extraction was calculated at a 1 s interval. The biodevices were placed in the left hand of all the participants, even if they were left-handed, see Figure 43.

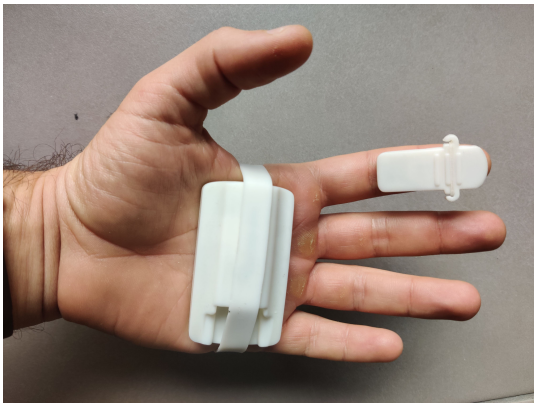


Figure 43 - James One GSR & HRV. In the finger is placed the HRV, while In the hand is located the GSR.

The subjects were instructed to rest the hand on top of the table or rest their hand on the lap with the sensors facing upwards. Also, they were adverted to move it as little as possible.

5.4 Data analysis

EEG online and offline processing algorithms are very similar but with different objectives. While online analysis is made to correctly represent the real-time alpha brain activity from the Pz electrode, in the offline analysis, we aimed to assess the effects of priming in NFT. Thus, some parts of these pipelines are very different and will be discussed.

Our pipeline is divided into the following intertwined processes: input data, pre-processing, processing, and output data.

5.4.1 EEG input data

In the online loop, the data updates at an average rate of 200 ms in each iteration, then it is concatenated in an epoch buffer of ≈1 s (1024 ms, a pylsl definition), which means that the epoch is made from ≈800 ms of the previous data plus the new ≈200 ms data (for more on threshold and feedback calculation, please go back to section **5.3.5-Threshold & feedback calculation of feature changes**). To this

end, in E2, we used a 50 ms block buffer for a more robust online sampling buffer because the RDA data server returns a minimum chunk size of 50 ms (for 1KHz returns 50 samples). This way, the chunks are blocked to multiples of 50 ms (100 ms, 200 ms). Nonetheless, each iteration of the online loop takes on average 200 ms of new data. Therefore, the block buffer will hold 200 ms of data to be appended to a ring buffer. As such, in E2, we also implemented a ring buffer, this way, we always get the last 1024 ms of the acquired data to perform the classification on, even if the update rate is lower or higher than 200 ms. For more detail in the block buffer and ring buffer, see section **3.2-Wyrm**.

In offline, there is no real-time loop. Instead, the entire length of each task is analyzed. To reduce the data into epochs of 1 s, the data is segmented then each segment is processed during pre-processing.

5.4.2 EEG pre-processing

After importing the data, the offline data was thoroughly inspected for movement artefacts using the visual tools from Brain Vision Analyzer (Brain Products GmbH). First, the data before the task and after the task was removed. Then, the data was checked for noisy channels, which were rejected, so they are not included in the next processing steps. This step was not performed online, and pre-processing started with filtering with a caveat: when filtering the data chunk-wise in an online loop, we used a Butterworth filter with filter delay values to receive the same results as if we were filtering offline the whole data set at once (using Scipy function lfilter[25]). For both pipelines, continuous EEG measurements were filtered with first a lowpass filter with a high cutoff value of 40 Hz (remove high frequency artefacts and unnecessary frequencies for our study), then a highpass filter with a low cutoff value of 1 Hz (remove low frequency artefacts and direct current offset). The filter used was a finite impulse response filter (FIR) of 5th order. The original sampling of 1KHz was maintained (no subsample) for a better resolution on the fast Fourier transform (FFT). Afterwards, offline rejected channels were interpolated, then an average of EEG activity at every electrode site was used as a reference, thereby removing noise common to all sites using an average reference. When online, as referred to in section **5.3.5-Online artefact rejection & confounders**, the common reference Cz selected in pycorder was maintained because visual inspection of the signal quality can only be done before the training session. Then, as also justified in the same section, the artefact rejection was performed for offline and online EEG data on 1 s epochs (offline data segmented to 1 s epochs) of the four selected channels Fp1, Fp2, Fz, and Pz. In both online and offline pipelines, we selected to exclude epochs with abnormally large amplitudes with a maximum peak-to-peak of over ±100 μV for online and ±150 μV for offline (we selected to constrict more the detection online to

make sure the data was without artefacts, as visual inspection is not possible), and also based on the flatness of the signal epochs were excluded with a minimum peak acceptance of ±0.5 μV. After a visual inspection in all subjects of E1 and pilot subjects of E2, these peak-to-peak thresholds proved sufficient to reject most epochs with artefacts. Nonetheless, this is *"one size fits all"*, and as demonstrated by Jas et al. (Jas et al., 2017), the thresholds are subject dependent, so future trials would do well to use more personalized automated artefact detection methods. Additionally, offline epochs contaminated by spurious gross-movement and other non-stereotyped artefacts were also identified by visual inspection and rejected.

Finally, to simplify the inspection and rejection of subjects after pre-processing, we implemented the same classification as in E1 with the exclusion criteria to be less than 40 % of epochs per task (see section **4.4.3**). From the first 62 subjects, 61 are good, 0 are noisy, and 1 is bad (missing data). The bad subject was removed from the study (N=61).

5.4.3 EEG processing

EEG power spectrum was calculated using Welch's PSD estimate, applying the *"pwelch()"* function from MNE.

Continuous EEG was transformed using an FFT and averaged in the frequency domain using 1024 points of FFT length, 1024 points hamming window segment, and 256 points of overlapping (n_fft=1024, n_per_seg=1024, n_overlap=256)[22]. In E2, the delay of computing the FFT overlap online is compensated by a faster update of data (while E1 updated at 1 s rate, E2 updated at 200 ms). As such, we used the overlapping because it enables a better FFT resolution

The PSD from the selected channels were then grouped into different bands, with a standard alpha peak (AP) of 10 Hz instead of a personalized IAF: delta (2 to 4 Hz, AP - 8 to AP - 6), theta (4 to 8 Hz, AP - 6 to AP - 2), lower alpha (8 to 10 Hz, AP - 2, AP), upper alpha (10 to 12 Hz, AP to AP + 2), overall alpha (8 to 12 Hz, AP - 2 to AP + 2), SMR (12-15 Hz, AP + 2 to AP + 5), beta (15 to 35 Hz, AP + 5 to 35) and gamma (35 to 100 Hz).

With the feature extraction finished, we addressed feature changes during the NFT session. For the purposes of E2, we only analyze the features changes of the Pz channel. The other three channels were not analyzed (for more on the selected channels, please go back to **5.3.5-Online artefact rejection & confounders**).

5.4.4 EEG output data

Online NFT feedback and threshold feature changes were already addressed before in section **5.3.5**. Therefore, we will focus on offline feature changes.

In this study, the EEG band measure assessing NFT successful control is also based on the suggested measures from Dempster and Vernon (Dempster & Vernon, 2009) that can be used to assess feature changes of brain activity during NF. We choose to study the changes in absolute alpha amplitude of the Pz channel, reflecting brief and temporally unstable increases over time from the learner. Then, this power spectra measure was $\log_{10}$-transformed to obtain normally distributed data. Based on this measure, we assessed feature changes within the session by using the Bin REST task as the reference and each block NFT task as the target. This way, we observed the changes from block-to-block. Additionally, this methodology enables the evaluation of the task specificity (see section **1.3.7** for more detail in NFT specificity), assessing whether the target feature or frequency of interest has been predominantly modulated in the REST, PRIME, and NFT tasks.

5.4.5 GSR & HRV

GSR and HRV were continuously monitored for all the participants during the session. Each signal was acquired at a sample rate of 100 Hz, and features were extracted at 1 s intervals. GSR tonic (skin conductance level - SCL) and phasic components (skin conductance responses - SCR) were extracted offline from each 1 s interval, with an exosomatic direct current sensor (Moreira et al., 2019). HRV time domain, frequency domain, and non-linear domain features were also extracted from the PPG RR-intervals (Correia et al., 2020). For a list of descriptions of all the features, please go to **Appendix V – E2 feature** section **GSR features** and **HRV features**.

5.4.6 Self-reports

The traits, states, and framework self-perception reports were exported to a database, and the scores for each dimension were summed before doing statistical analysis. For a list of descriptions of all the features extracted, please go to **Appendix V – E2 features** section **Self-Reports features**.

5.4.7 Group domains

Apart from the intervention groups (EG, CG) and EEG measures, the additional multivariate data is grouped in four domains, two belonging to qualitative data while the other two are quantitative. Qualitative data are the subject traits groups domain (TG = SOC, FFMQ, DASS, ERQ) and emotional states group domain (SG = TMS, POMS, NFT). Quantitative emotional states are divided into the skin response (GSR) domain and the heart rate variability domain (HRV). These domains and their respective features are detailed in **Appendix V – E2 features**.

5.4.8 Statistical analysis

Statistical analysis was performed using the R language. Significance was assumed if $p < .05$ (two-tailed). Demographic data at Pre-intervention (T0, referring to the moment right before starting the training session) were compared between-groups with one-way ANOVA or $\chi 2$ test with Fisher exact correction. Significant group effects at Bin EC and EO baseline tasks were further explored to locate group differences in band profile using one-way ANOVA. RM ANOVAs were calculated for each condition (REST EC, REST EO, and NFT EO) and frequency band (theta, alpha, SMR, beta) with time (Bin versus Bout) as within-subject factors, and the intervention group (EG versus CG) as between-subject factor. Only time effects, group main effects, and interactions with a group are reported. For the main outcomes, mean difference and 95% confidence interval [95% *CI*] are reported. Effect sizes are reported as partial eta-squared (η_{p2}), with effects interpreted as small (.01), medium (.06), or large (.14).

Afterwards, to perform single session analysis, individual NFT performance was quantified by regression slopes of the trained alpha feedback frequency across the intervention blocks B1 to B4 (regression slopes have a mathematical component of within and between tasks). For that, B1 to B4 were further break down in EO only tasks and EC only tasks, culminating in 3 tasks per subject: *"restBin",* the baseline REST task to get the initial threshold at Bin; *"nft1"*, the first NFT task preceded by priming (in the EG) or no-priming (in the CG) and *"nft2"*, the second block of NFT preceded by priming or no-priming. Regression slopes were estimated individually (predictor variable = feedback task number; dependent variable = z-transformed power of alpha) and subsequently averaged per group domain (based on (Silvia E. Kober et al., 2017)).

Additionally, to verify the existence of group domain effects on NF learning apart from priming (EG) and no-priming (CG), the same alpha regression analysis was performed on two subgroups of participants

according to the features in each domain. Each feature (qualitative or quantitative variable) was converted into a dichotomous variable: high value (HV) and low value (LV), representing the groups above and below the best central measure, respectively. We found that the best central measure was mean=(maximum+minimum)/2 for the quantitative regression slopes (slopes obtained from the regression of GSR and HRV values) and the qualitative data of the 60 participants. As such, the statistical hypothesis testing was centred on comparing the regression slopes from each group of HV with LV, HV with zero, and LV with zero. When considering the grouped frequency distribution of HV in the different domains (represent how frequent each HV value occurred within each domain), we selected features with similar HV frequencies in both EG and CG and with nine or more subjects (at least ≈ 1/3 of the EG and CG sample) for balanced comparisons because we are not only comparing with zero slopes but also HV versus LV. One-sample *t*-tests were calculated for each group to test whether the regression slope is different from zero and between-groups to test whether the two regression slopes are different. Only features with significant time effects, group main effects, and interactions with groups are reported.

5.5 Results

5.5.1 Group characteristics

At pre-intervention before the training session starts, T0, there were no differences between the intervention groups in age, gender, and education, as described in Table 3. There were no baseline differences at Bin between-groups in alpha and SMR power during EO and EC tasks in the Pz electrode (using the $\log_{10}$ transformation). However, there were some baseline differences between-groups in theta EC ($p < .05$) and beta EC ($p < .01$) and EO ($p < .05$). Additionally, EEG epoch results showed that artefact-free segments were correctly maintained above 40 % of the total task segments.

Table 3 - Group characteristics at pre-intervention T0 (for *N* = 60).

	EG (*N* = 30)		**CG** (*N* = 30)		***p-value***	
	M	*SD*	*M*	*SD*	*F*	*p*
Demographic						
Age (years)	28.87	7.40	27.50	6.38	0.587	ns
Gender (F/M)	18/12		19/11		0.00[a]	ns
Education (9/12/15/17/21)	0/3/10/12/5		0/8/8/11/3		5.01[b]	ns
Conditions						
ES (ES1/ES2)	16/14		15/15		0.0[a]	ns
SS (RS/PS1/PS2)	0/15/15		30/0/0		-[c]	-[c]
Baseline Bands						
theta (EC/EO)	-0.02/-0.16	0.28/0.2	0.27/-0.05	0.42/0.24	9.75/3.92	**/ns
alpha (EC/EO)	0.52/-0.015	0.61/0.47	0.82/0.19	0.56/0.45	3.90/3.04	ns/ns
SMR (EC/EO)	-0.15/-0.35	0.55/0.40	-0.07/-0.28	0.55/0.38	0.23/0.53	ns/ns
beta (EC/EO)	-0.75/-0.94	0.27/0.23	-0.56/-0.79	0.28/0.22	7.31/6.30	**/*

EG, experimental group; CG, control group; M, mean; SD, standard deviation; EC, eyes closed; EO, eyes open; F, female; M, Male; ES, eyes sequence; ES1 and ES2, eyes sequence 1 and 2; SS, stimuli sequence; RS, REST sequence; PS1 and PS2, PRIME sequence 1 and 2.
Education level values refer to the number of participants reporting the number of years completed in one of the following five-category: (1) *N*>=9, ninth grade; (2) *N*>=12, Secondary; (3) *N*>=15, Bachelor's degree; (4) *N*>=17, Master's degree; (5) *N*>=21, Ph.D.
Significant tests are marked with asterisks (* $p < 0.05$, ** $p < 0.01$).

[a] $\chi 2(df=1)$

[b] $\chi 2(df=5)$

[c] Stimuli sequence (SS) is intended to be different for the CG and the EG.

5.5.2 EEG power spectrum at pre and post priming intervention

Repeated measures ANOVA results for each condition and frequency band, and the difference (Bout-Bin) between $\log_{10}$ means from the 60 subjects are shown in Table 4. Log_{10}-transformed EEG power spectra of theta, alpha, SMR, and beta frequency bands at pre- (Bin) and post- (Bout) priming intervention are shown in Figure 44.

Table 4 – RM ANOVA of pre-(Bin) and postintervention (Bout) power spectra for three conditions: REST EC, REST EO, and NFT EO.

Task		*T*			*T x G*	
		F	η_{p2}	*Bout-Bin*	*F*	η_{p2}
REST EC	theta	3.98	0.06	-0.050	4.86*	0.08
	alpha	5.04*	0.08	-0.061	0.01	<0.001
	SMR	4.67*	0.09	0.054	<0.001	<0.001
	beta	4.45*	0.07	-0.033	2.13	0.04
REST EO	theta	8.89**	0.13	0.056	0.64	0.01
	alpha	18.17***	0.24	0.096	0.07	0.001
	SMR	33.62***	0.38	0.015	0.61	0.01
	beta	5.21*	0.08	0.033	0.01	<0.001
NFT EO	theta	4.41*	0.07	0.039	0.77	0.01
	alpha	20.67***	0.26	0.109	0.65	0.01
	SMR	0.02	<0.001	0.015	0.02	<0.001
	beta	0.79	0.01	0.012	0.17	0.003

REST, the rest task; NFT, the alpha neurofeedback training; EC, eyes closed, EO, eyes open; T, time; G, group. Bout-Bin, the difference between $\log_{10}$ means from the 60 subjects.

Significant tests are marked with asterisks (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

Looking at Table 4, the main findings in all the population were a significant decrease between Bin and Bout for the REST EC condition in alpha and beta and an increase in SMR, while for the REST EO, a significant increase in theta, alpha, SMR, and beta. As for the NFT EO, a significant increase in theta and alpha was observed. A significant interaction *T x G* (time × group) was found for theta value on the REST EC task, while the value of theta in the CG group decreases from Bin to Bout. In the EG group, this value is slightly increased. This last result can be confirmed in Figure 44, as well as the similar behaviour of the EG and the CG between the Bin and the Bout.

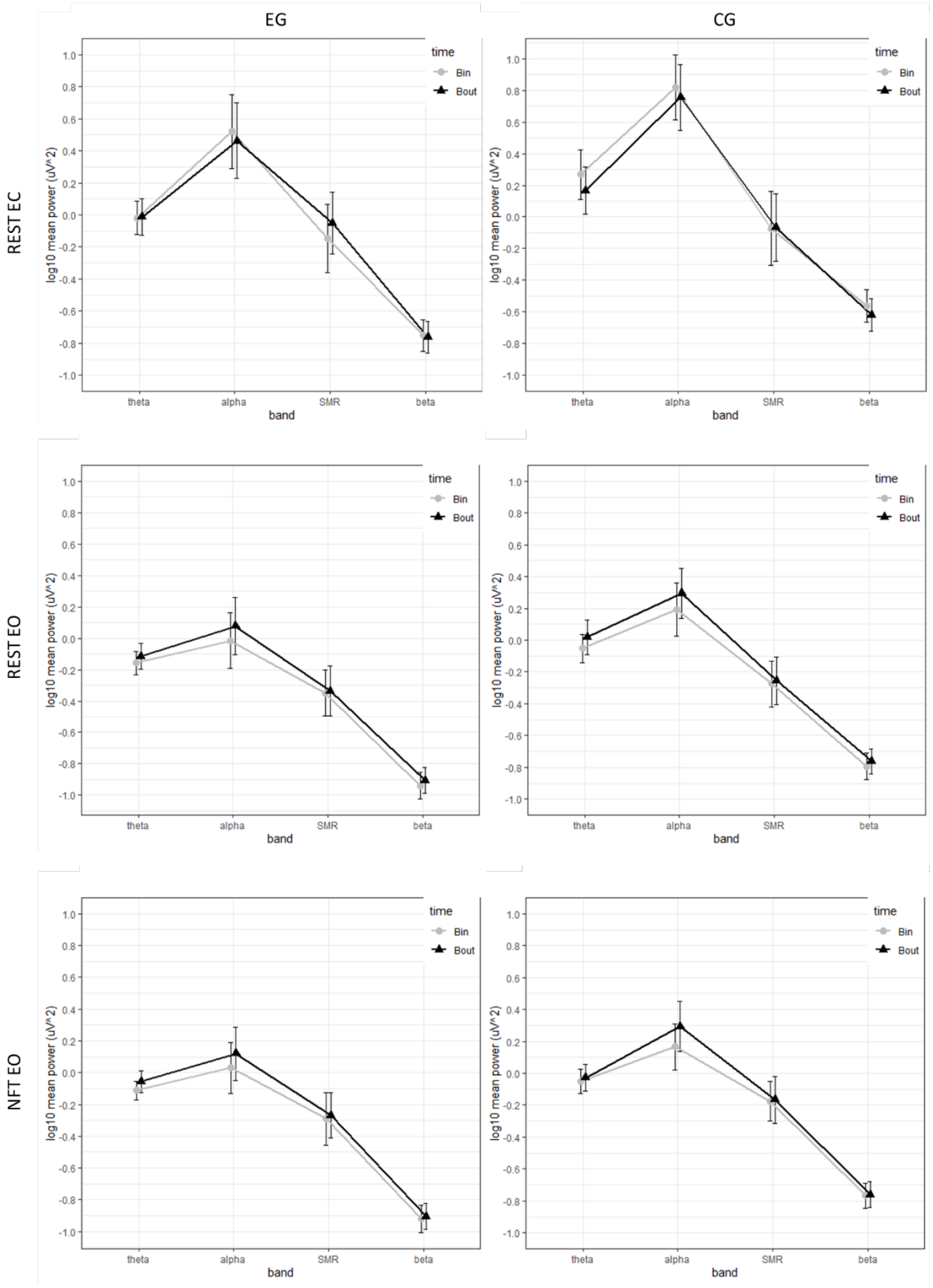


Figure 44 - EEG power spectrum at Bin and Bout. Estimated marginal means are log-transformed absolute power (μV^2) with 95% confidence intervals. During REST EC, both groups show reductions in alpha, CG also has reductions in theta, while EG increases SMR. Whereas for the REST EO, both groups show up-regulation of alpha, similarly to the NFT EO task.

5.5.3 NFT performance in different group domains at intervention blocks

As demonstrated in the previous section, results from EO tasks require a different analysis from EC tasks. Therefore, the tasks were analysed separately at the intervention blocks (*"nft1"* and *"nft2"*), as described in section **5.4.8**. Regarding the analysis of no-priming (CG) and the priming (EG) results, both groups were able to voluntary increase their alpha during intervention blocks on EO and decrease during EC after a single session of NF training (Figure 45). These changes were reflected by linear increase and decrease of the power, respectively, matching the results discussed in the previous section at pre- and post-intervention (Figure 44). When individual alpha was regressed on EO NFT tasks, 24 out of 30 EG (80%) participants and 17 out of 30 CG (57%) participants were able to linearly increase their alpha, as suggested by positive individual regression slopes. Checking further, considering half of the maximal slope as the threshold (0.80 = 45.83°) instead of a zero slope, 12 out of 24 (50%) EG participants and 6 out of 17 CG (35%) were able to increase above this slope. One sample *t*-tests revealed that regression slopes in the EG ($t(29) = 4.38$, $p < .001$) were significantly larger than zero, while the CG were not ($t(29) = 1.18$, $p > .1$).

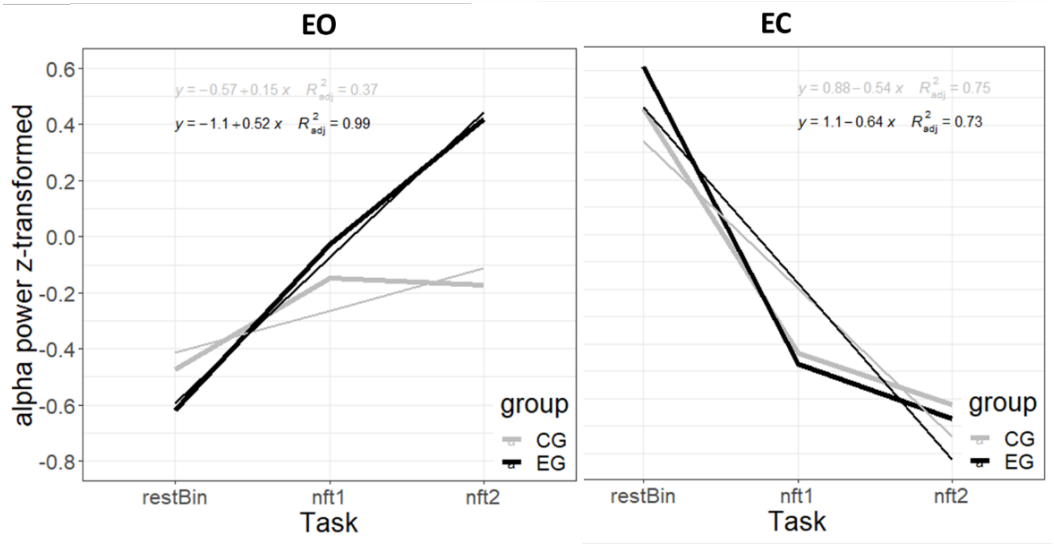


Figure 45 - Z-transformed EEG power at intervention blocks. Alpha z-transformed power over the baseline (restBin) and NFT tasks for EO condition and EC at intervention blocks (nft1 and nft2). The regression slopes are presented separately for CG and EG. Additionally, the regression equations are depicted as well as the regression lines for each group are indicated by thinner lines. The regression slopes at intervention blocks show a significant alpha increase for the EG in the EO condition. In contrast, the EC condition shows a similar downregulation of alpha in both groups.

We also directly compared the slopes between groups. A *t*-test revealed a significant difference between the slopes of the EG and CG ($t(58) = -2.10$, $p < .05$). For the EC NFT tasks, we have comparable results between the two groups, as 24 out of 30 EG participants and 24 out of 30 CG participants had negative

regression slopes. From these, 17 out of 24 EG and 16 out of 24 CG (≈70%) participants had greater negative slopes than half the minimal slope (-0.72 = -41.14°). One sample *t*-tests revealed that regression slopes in the EG ($t(29) = -5.53$, $p < .000001$) and CG ($t(29) = -4.50$, $p < .001$) were significantly smaller than zero. A *t*-test revealed no difference between the negative slopes of the EG and CG ($t(58) = 0.62$, $p > .05$). To verify the group domain effects, the first column of Table 5 depicts the HV frequency distribution of each significant domain feature (according to the methodology described in section **5.4.8**). The subsequent columns represent the average alpha power slope for the HV and LV groups and their *t*-test's. Considering the alpha regression slope, in the TG domain, the EG subjects with LV of "actware" (those acting with less awareness) at T0 (pre-intervention) were the most effective on increasing alpha power in the EO condition. At the same time, the CG subjects with HV of *"expressive suppression"* (where a person attempts to inhibit the behavioural expression of his or her emotions) during EC had the larger downregulation of alpha during the intervention blocks. For the SG domain, LV of reported *"vigour"* at Bout in the EG led to the most significant EO NFT performance in this domain, followed by HV of *"decentering"* at Bin and HV of *"tension"* changes (as the difference Bout-Bin). While for the CG, LV of *"fatigue"* changes (as the difference Bout-Bin) led to the most significant EO NFT performance, followed by LV *"confusion"* changes. Considering the GSR regression slopes at intervention blocks, the EG participants with LV of *"scl std"* (standard deviation of the tonic baseline skin conductance level), as well as those with LV of *"scr sumResp"* slope (sum of the amplitudes of phasic event skin conductance responses) had better efficacy on increasing alpha power during EO NFT performance. LV of *"scr meanResp"* slope (mean of the amplitudes of phasic event skin conductance responses) led to the greatest downregulation of alpha during EC. While for the CG participants, those with HV of *"scl mean"* (mean of the tonic baseline skin conductance level) led to the significant increase of alpha slopes during EO NFT. Considering the HRV domain, the alpha power slopes (55 subjects because of missing HRV values) during the EO NFT performance were most significant for the EG participants with LV of *"rmssd"* (it reflects high-frequency influences on HRV - fast or parasympathetic, those influencing larger changes from one beat to the next), and downregulation of alpha was greatest with LV of *"sdnn"* slope (the standard deviation of the time interval between successive normal heart beats - i.e., the RR-intervals). In contrast, the CG participants with HV of *"sdnn"* significantly decreased alpha during EO NFT performance and participants with HV of *"vlf"* (variance in HRV in the very low Frequency - .003 to .04 Hz by default, reflecting an intrinsic rhythm produced by the heart which is modulated primarily by sympathetic activity) led to the most downregulation of EC alpha during NFT.

Table 5 – Significant multi-feature domains. Alpha z-transformed regression slopes over the baseline (restBin) and NFT tasks for EO condition and EC at intervention blocks (nft1 and nft2).

Domain	Feature	HV frequencies (EG/CG)	EO All [HV^{p1}/ LV^{p2}]^{p3}	EO EG [HV^{p1}/ LV^{p2}]^{p3}	EO CG [HV^{p1}/ LV^{p2}]^{p3}	EC All [HV^{p1}/ LV^{p2}]^{p3}	EC EG [HV^{p1}/ LV^{p2}]^{p3}	EC CG [HV^{p1}/ LV^{p2}]^{p3}
TG	**FFMQ actaware**	13/16	[0.27*/0.4**]	**[0.16/0.79***]$^{++}$**	[0.35/-0.08]	[-0.51***/-0.67***]	[-0.57**/-0.7***]	[-0.46*/-0.64**]
	ERQ expressive suppression	17/13	[0.4**/0.27*]	[0.55**/0.48*]	[0.21/0.1]	**[-0.76***/-0.43**]$^{+}$**	[-0.73***/-0.54**]	**[-0.8***/-0.35]$^{+}$**
SG	**TMS decentering (Bin)**	18/19	**[0.37**/0.28]**	**[0.69***/0.27]**	[0.07/0.29]	[-0.65***/-0.5**]	[-0.72***/-0.53*]	[-0.58***/-0.47]
	POMS Vigour (Bout)	13/15	**[0.21/0.44**]**	**[0.2/0.76***]$^{+}$**	[0.22/0.09]	[-0.47**/-0.7***]	[-0.62**/-0.67***]	[-0.34/-0.74***]
	POMS confusion (Bout-Bin)	12/13	**[0.19/0.44***]**	[0.64**/0.44*]	**[-0.23/ 0.44*]$^{++}$**	[-0.56***/-0.61***]	[-0.56*/-0.7***]	[-0.57**/-0.52**]
	POMS fatigue (Bout-Bin)	18/21	**[0.19/0.6***]$^{+}$**	[0.48**/0.58*]	**[-0.06/0.63*]$^{+}$**	[-0.62***/-0.54**]	[-0.63***/-0.66*]	[-0.61***/-0.38]
	POMS tension (Bout_Bin)	17/20	[0.34**/0.34*]	**[0.69***/0.3]**	[0.04/0.38]	[-0.59***/-0.6**]	[-0.65***/-0.64*]	[-0.54***/-0.54]
GSR	**GSR scl_mean**	19/15	**[0.42***/0.22]**	[0.39*/0.74**]	**[0.46**/-0.15]$^{+}$**	[-0.53***/-0.81***]	[-0.61***/-0.88]	[-0.42*/-0.78***]
	GSR scl_std	15/17	**[0.22/0.46***]**	**[0.36/0.68***]**	[0.1/0.22]	[-0.55***/-0.66***]	[-0.71***/-0.53*]	[-0.4*/-0.79***]
	GSR scr_meanResp	19/19	[0.37**/0.27]	[0.46*/0.61**]	[0.28/-0.08]	[-0.44**/-0.72***]	**[-0.32/-0.86***]$^{+}$**	[-0.54**/-0.54*]
	GSR scr_sumResp	11/10	**[0.32/0.34**]**	**[0.4/0.59***]**	[0.24/0.11]	[-0.61***/-0.57***]	[-0.63***/-0.68*]	[-0.57*/-0.52**]
HRV	**HRV sdnn**	15/15	**[0.46***/0.23]**	[0.48*/0.56*]	**[0.44*/-0.12]$^{+}$**	[-0.53***/-0.57***]	**[-0.45*/-0.95***]$^{+}$**	[-0.7**/-0.38*]
	HRV rmssd	14/9	[0.3*/0.4**]	**[0.35/0.69***]**	[0.23/0.17]	[-0.6***/-0.52***]	[-0.58**/-0.7**]	[-0.64**/-0.41*]
	HRV vlf	12/9	[0.57**/0.22]	[0.66**/0.41*]	[0.46/0.06]	[-0.73***/-0.4**]	[-0.69***/-0.54*]	**[-0.81***/-0.31]$^{+}$**

HV, high value. LV, low value. All, EG and CG subjects . EO, eyes open. EC, eyes closed. EG, experimental priming group. CG, control no-priming group. Total sample = 60, EG=30 and CG=30 subjects. Total HV = EG HV + CG HV, Total LV = 60 – Total HV. EG LV = 30 - EG HV. CG LV = 30 – CG HV. Note for HRV data: Total = 55, EG=28 and CG=27 subjects. Statistically significant non-zero regression slopes, *p1* and *p2*, marked with an asterisk (*$p < 0.05$, ** $p < 0.01$, ***$p < 0.001$) Statistically significant differences between the two regression slopes from HV and LV, *p3*, groups are marked with a cross (+$p < 0.05$, ++ $p < 0.01$, +++$p < 0.001$). Green, significant upregulation. Red, significant downregulation.

5.6 Insights from Experiment 2

Participants

In E2, we doubled the number of participants to 62 and extended the age range from 18 to 43 years.

Hardware and software setup

Hardware and software were reviewed to meet the requirements. In the hardware, Bluetooth headphones were used for sound stimulation that does not interfere with the electrodes. Straps were used to pull the cap tight against the scalp. Self-reports were translated to google forms, and a tablet was used to complete them. Additionally, EEG, GSR, and HRV devices (Moreira et al., 2019) were used for a broader psychophysiological approach. In the software, Pycorder Actichamp APP was used for the remote data access (RDA) server with the LSL RDA APP to connect with pylsl because, as referred to in E1, the LSL Actichamp APP had problems. This RDA method has a more significant delay, 50-200 ms, while the LSL Actichamp APP has a delay of only 2 ms (Brain Products GmbH, 2017). However, this delay is within the acceptable range of Neurofeedback real-time applications. Relying on Pycorder as the main app for starting/stopping the signal streaming enables a smoother and more integrated configuration. During the configuration, Pycorder enables visual inspection of the channels facilitating its calibration, and at the same time, we can instruct the subject of possible artefacts and trained how to avoid them (see Figure 38). We also selected default mode instead of shielding mode (which can cause noise problems that cannot be solved) because we were certain of our meticulous preparation with this method. In future trials, as a new LSL Actichamp APP is available (Brain Products GmbH, 2020), we will be able to use Pycorder for configuration, and after the configuration, use LSL Actichamp APP to start/stop the streaming independently, we will lose on the smoothness of the configuration but gain on a lower streaming delay.

Experimental Design

The experimental environment was more isolated than E1 but did not have a Faraday cage. However, we took some measures to diminish electric noise, such as having a room with more distance to hallways, thicker walls, and asking participants to put their phones in flight mode.

Another note, to further understand E2 within-subject alpha dynamics during the session, please go to **Appendix IV – Additional results** section **E2 within-subject session profiles**).

PRIME

The priming in E2 has a more straightforward design where the control condition is the REST task of the CG. From the results obtained, this control condition assumption seems reasonable. The EG during the EO priming intervention blocks showed an improved ability to control their own brain activity compared to the CG, while for the EC blocks, a downregulation on both groups was evident and physiologically plausible due to the saturation of alpha in EC condition (Barry et al., 2007; Chow et al., 2017; Nan et al., 2018).

MM updates & future proposals

From E1, we learned quite a lot about how to adapt the instructions better. For example, the recall instruction, where the user is reminded to come back to the breathing gently, was passed to the instruction's pre-task screen. In fact, in E1, from the 33 participants, 14 said that this instruction on the guided audio distracted them. Instructions were also simplified and better timed than E1 (for the instructions, please go to **Appendix III – Instructions**).

Additionally, because in E1, we had no way to quantify MM performance, as such, we searched for a mindfulness performance score (MPS) in the literature. Although several surveys of mindfulness-related traits have been validated (e.g., FFMQ and TMS), few standardized methods exist for measuring experiences related to the practice of mindfulness meditation states. This is problematic because mindfulness, as currently defined, represents a state rather than a trait variable, specifically, a state of attention, awareness, and being that is open and non-judgemental (Bishop et al., 2004; Kabat-Zinn, 2003; Sierpina, 2005; Williams & Kabat-Zinn, 2011).

Nonetheless, we found that Frewen and colleagues (P. A. Frewen et al., 2008, 2014) have investigated a method called mindfulness breath attention score (MBAS). MBAS can be interpreted as a way to index participants' ability to sustain their attention toward the breathing process during meditation practice and, accordingly, their capacity to disengage from mind wandering. MBAS are calculated as the sum of the self-reported frequency with which persons can maintain their attention toward their breathing as queried quasi-randomly approximately every 3 min (meditation bell) during the practice of meditation of at least 10 min duration (e.g., three times during a 10 min meditation or five times during a 15 min meditation).

MBAS was tested by Frewen and Colleagues and correlated positively with the mindful trait *"actware"*, *"Acting with Awareness"*. The *"actware"* dimension is a reverse-scored subscale of the FFMQ that assesses the trait of persons to focus their attention and be consciously aware of their thoughts, feelings, and behaviour. It is the reverse from mind wandering or running on *"automatic pilot"*, i.e., the reverse of having one's attention frequently divided, and/or being distractible - e.g., the reverse of these affirmations *"When I do things, my mind wanders off, and I'm easily distracted"*, *"It seems I am running on automatic without much awareness of what I'm doing"* (Baer et al., 2008). Nonetheless, MBAS was independent of TMS mindful curiosity and decentering (situational awareness) and other FFMQ subscales in previous studies (P. Frewen et al., 2011; P. A. Frewen et al., 2014). As such, MBAS can complement the analysis of mindfulness states.

MBAS was tested but not implemented in the final E2 due to the complexity required and bias (as it can affect the mental state) that could bring to the experiment. Our short and repeated mindfulness task structure was already built around the probability of mind wandering and how we could maintain the focus target right before the NFT. For example, in naïve populations, 3 min short mindfulness tasks structure can be sufficient to enable a focused attention state before the mind starts to wander (Frewen also uses 3 min to test mind wandering). Also, guided audio was adjusted, so the person maintains the attention on the object of focus, e.g., at 2min30s the person is reminded to come back by the instruction *"maintain attention in the focus target"*. Using MBAS could lead to loss of attention to the object of focus because the person needs to do the classification. In a 10 min task, the measurement of MBAS seems feasible, but during a 3 min task, it can become an unnecessary complexity. In fact, our first objective is not to make the person more mindful (trait) but to be mindful right now (state), which is the rationale of the short task structure that leaves little room for mind wandering. This approach has clear limitations of how to measure mindfulness state performance but has the first step to test stimulus-response (PRIME stimuli versus NFT response) seemed the most reliable at the time.

Nonetheless, after E2, a closer analysis made us realize that an alternative to a quasi-random bell interval keypress would be a keypress when the participant subjectively disengages from mind wandering and returns the attention to the focused object (subjective recall). This would be a significant marker to study the individual mindfulness capacity and could be implemented in our single-session short block design. However, subjects had to be trained to remember to press. In addition, we also think that MBAS is not yet complete for 10 min structure tasks, and we propose a mixed approach of the quasi-random bell intervals with the possibility of subjective recall (while the fixed bells can remind the person to recall, the subjective recall is more proximal of the subjective experience). We propose that the number of keypress

ticks in a keyboard would subjectively account for the time the subject thought he was in mind wandering, for example, from a scale from 0 ticks to 5 ticks. So, every time the subject recalls (disengage mind wandering) or ears the bell, he should evaluate the mind wandering. These, in our view, will enable a more precise and complete mindfulness score. Also, depending on the experiment's goal, a keyboard or a sheet of paper can be used to place the tick mark. The advantage of the keyboard, in this case, is that the subjective recall time markers are placed automatically and synchronized with the acquisition.

REST

REST task was with EO and EC, enabling the analysis to find if the eyes closed rest state had some connection to the responders, as studied in (Nan et al., 2018). Additionally, REST, PRIME, and NFT had the same eyes protocol for brain state-dependent stimulation comparisons. These will be further explored in the future.

NFT

The number of blocks per session in E2 was extended. EO condition with four blocks, whereas EC with two blocks. The initial instructions were more specific and were provided with real-time examples. These changes offered a more robust training design - both groups did significantly synchronize alpha between Bin and Bout.

EO and EC conditions were used to find the contrast of one another (during PRIME and NFT). With eyes open, we saw a significant alpha synchronization (the objective of the NFT), with the priming protocol population being more capable of getting the brain activity above the threshold than the no-priming control group. Furthermore, when individual alpha was regressed on EO NFT tasks, 24 out of 30 EG (80%) participants and 17 out of 30 CG (57%) participants were able to linearly increase their alpha, as suggested by positive individual regression slopes. Nonetheless, this was in the context of a single session, and we still need testing if the same results can be replicated or deepened in a multiple-session design. In the EC protocol, using the same analysis, we saw a significant decrease of alpha activity from *"restBin"* to *"nft1"* and *"nft2"*. This desynchronization in both groups can mean a neurophysiological response to the eyes being closed. As physiologically expected, a saturation reflex occurs in the Pz channel after closing the eyes in the initial resting task at Bin – i.e., during an eyes-closed resting condition, alpha activity is dominant and may represent an optimal level of alpha activity that maybe is not possible to up-regulate beyond, whereas attending to visual stimulation has an inhibiting effect on alpha (Barry et al., 2007; Chow et al., 2017; Nan et al., 2018; D. Vernon et al., 2009). During the subsequent NFT tasks, the participants have lower alpha activity. Thus, in Figure 45, we obtain a steep negative regression slope.

This seems comparable to the results from the single-session design from Chow et al. (Chow et al., 2017). Their results show parietal alpha (8-12 Hz) decreasing in the first three NFT tasks (each task is a 3 min alpha NFT protocol with EC, with a total of 5 tasks), and only increasing in the fourth and fifth. As we only have two NFT EC tasks, we only see a decrease in alpha. Nonetheless, in Table 5, some groups show steeper downregulation slopes. Such behaviour changes in these groups can be connected to task engagement. Hence, we need to extract this information from the data in future analysis, probably by removing the initial baseline from the analysis and only looking at the two NFT EC tasks. Another unlikely hypothesis for this behaviour can be a technical artefact. Even with training instructions, the audio feedback pitch for reward and inhibition could have been too similar for most people, and they were downregulating instead of regulating. Considering these reasons, if one wants to study EC in a similar single session context, our advice is to use more than two NFT training tasks and lower the initial threshold (below mean-0.38*SD), as the EC resting baseline threshold may represent an optimal level of alpha activity that is difficult to up-regulate beyond. Use other bands or band ratios to avoid saturation (like SMR in the Cz channel) and extensively test audio pitches for positive and negative feedback. Additionally, the profile of theta power is always lower than alpha (see Figure 44). This result is generally the case in adults during normal wakefulness and, in this case, focus on tasks (Louis et al., 2016)

For these reasons, EO PRIME intervention seems to increase subsequent NFT performance, while the CG REST intervention does not seem to. Nonetheless, a more extensive analysis of PRIME versus REST dynamics is needed.

Domains: Self-reports, GSR and HRV

For qualitative measures of traits supplementing the FFMQ, we added the scales ERQ and DASS for descriptive purposes. For states, POMS and TMS were added at the Bin and Bout to have a more rigorous understanding of the fluctuations of subjective experience and qualitatively the emotional state. At the same time, GSR and HRV were introduced in E2 for the possibility of finding biomarkers that indirectly quantify the emotional state.

In Table 5, the most significant results of the five domains are presented for the intervention block tasks (*"restBin"*, *"nft1",* and *"nft2"*).

In this study, sociodemographic and framework self-perception selected features (see **Appendix V – E2 features**) had no group domain effects on NF learning in priming (EG) and no-priming (CG).

In the TG domain, the EG participants with low values of *"actware"* at T0 were the most capable of increasing alpha power in the EO condition. As such, persons with low levels of acting with awareness

traits, probably naïve to the concept of mindfulness or meditation practice, were more stimulated by the priming intervention. In comparison, the CG participants with higher values of ERQ *"expressive suppression"* during EC had the most downregulation of alpha. This result needs to be guided by the possibility of being a neurophysiological phenomenon since mainly all the subjects downregulate alpha during the intervention, i.e., 24 out of 30 EG participants and 24 out of 30 CG participants had negative regression slopes. After further individual inspection, only 1 out of 30 EG and 3 out of 30 CG participants had a positive regression slope. From another perspective, after within-session analysis, the steeper downregulation in EC appears between the first initial REST baseline and the other blocks. This change can be due to task engagement, and as we already discussed in the section above, further analysis needs to be conducted to explore this hypothesis.

For the SG domain, low values of reported *"vigour"* at Bout led to the most successful EO NFT performance in the EG, followed by higher values of *"decentering"* at Bin and higher *"tension"* changes (Bout-Bin). As such, subjects with decreased state of energy and increased tension (connected to subject effort), probably due to the demand for focused attention on internal sensations in the guided audio, had better performance. Another distinctive EG feature is the higher *"decentering"* state at Bin, which is connected to the learner's "optimal" state (section **1.3.3)**. It reflects an increase of situational self-awareness (self-regulated awareness of thoughts and feelings), i.e., an increase in the capacity of non-judgement by avoiding distractive task-unrelated thoughts - "awareness of one's experience with some distance and disidentification rather than being carried away by one's thoughts and feelings" (Lau et al., 2006). For the CG, lower *"fatigue"* changes (Bout-Bin) led to the most successful EO NFT performance, followed by lower *"confusion"* changes (Bout-Bin).

Concerning the GSR biomarkers, the EG participants with lower slope values (slope between *"baseline", "nft1"* and *"nft2"*) of SCL standard deviation and SCR sum seem to perform the best. This finding appears to be in line with the literature, since lower values of SCL standard deviation and SCR sum during task performance usually reflect less arousal (diminished stimulation of the sympathetic nervous system) and perhaps, explaining a less stressful, relaxed, and non-judgement attitude (towards stimuli, thoughts or feelings) during task performance (Boucsein et al., 2012; Posada-Quintero & Chon, 2020).

Concerning the HRV metrics, the EG participants with lower HRV slopes of *"rmssd"* performed better (i.e., lower high-frequency variations of vagal parasympathetic components during the tasks), and it might show a more effective task engagement of the subject during the NFT task (Malik et al., 1996; Zahn et al., 2016). In contrast, the CG performers had high slope values of SCL mean and HRV *"sdnn"*. In the

case of HRV, the literature suggests that a higher baseline HRV is related to concomitants of better self-control and higher vagal withdrawal scores to better attention control and emotional regulation (Beauchaine, 2001; Graziano & Derefinko, 2013; Zahn et al., 2016).

As such, the biomarker results seem to suggest that mindfulness priming stimulates engagement and a relaxed and non-judgement attitude in alpha NFT performers, and the trait and state self-reports results seem to corroborate these behavioural correlations.

Session additional characteristics

A more continuous experience per block was achieved. The participant only paused mainly at the beginning of each block to rest, drink water or adjust himself to be more comfortable.

Summary

In this single session design, as initially predicted, the behaviour at pre- and post-priming intervention are similar between the EG and CG. Nonetheless, the EG during the EO intervention blocks showed an improved ability to control their brain activity compared to the CG. While for the EC blocks, a significant decrease of alpha activity in the NFT tasks in relation to the initial resting baseline on both groups was evident. As such, in the EC condition, we need further analysis to separate intervention feature changes from this possible downregulation occurring in the Pz channel during the NFT tasks. Alpha activity is dominant during an eyes-closed resting task and may represent an optimal alpha activity level that is impossible or very difficult to up-regulate beyond (Barry et al., 2007; Chow et al., 2017; Nan et al., 2018; D. Vernon et al., 2009). As such, a different analysis should be conducted to subtract the effects of the initial resting baseline. Additionally, the profile of theta power is always lower than alpha (see Figure 44). This result is generally the case in adults during normal wakefulness and, in this case, focus on tasks (Louis et al., 2016). In more detail, within the EG, the best performers in the EO condition had low values of awareness as a trait and reported stronger signs of built-up tension and less vigour at Bout. As such, subjects which reported a low capacity of acting with awareness seem to have benefited the most from priming, and the demand for focused attention on internal sensations through guiding audio seemed to enhance the subject's emotional states of tension and lack of vigour at the end of the protocol. In contrast, the CG participants were not guided (staring only to cross on the screen) and did not express these emotional states. Another distinctive characteristic of EG best performers in the EO condition is a higher situational awareness (decentering) at Bin, which is connected to the learner *"optimal"* state, i.e., the

capacity of non-judgement and avoiding distractive task-unrelated thoughts. Regarding the EC condition, both group results seem to indicate a neurophysiological decrease of alpha. However, in this regression slope analysis, intervention feature changes (like task engagement) are probably obscured by the steep slope between *"restBin"* and the subsequent tasks *"nft1"* and *"nft2"* – i.e., *"restbin"* may represent the optimal level of alpha activity and it should be very difficult to get close to this level or up-regulate beyond (D. Vernon et al., 2009). Thus, we need to attempt to extract this information from the data in future analysis, probably by removing the initial baseline *"restBin"* (similar to removing an offset). Additionally, since EC condition is less amenable to intervention effects via NFT (Barry et al., 2007; Chow et al., 2017; Nan et al., 2018; D. Vernon et al., 2009), maybe more than two NFT tasks are needed to extract up-regulation effects in a single session design, like the 5 NFT tasks in (Chow et al., 2017). Concerning the biomarkers, low GSR activity in the intervention blocks, seen both at the tonic (slopes of SCL standard deviation) and phasic level (slopes of the total sum of SCR), seems necessary to have better NFT performance. It appears to indicate that priming led to less sympathetic arousal on the EG participants, and perhaps, it explains the less stressful, relaxed, and non-judgement attitude task performance (Boucsein et al., 2012; Posada-Quintero & Chon, 2020). Concerning the HRV, the EG subjects with lower high-frequency variations of vagal parasympathetic components seem to had better performance on NFT, which might reflect a more effective task-engagement of the subject during the NFT task (Malik et al., 1996; Zahn et al., 2016). While on the CG, subjects with a higher standard deviation of the N-N intervals appeared to have improved performance. Accordingly, previous works in the literature claim that a higher baseline HRV is related to better self-control and higher vagal withdrawal scores to better attention control and emotional regulation (Beauchaine, 2001; Graziano & Derefinko, 2013; Zahn et al., 2016).

As such, in E2, we met most of the requirements laid out by E1. It was possible to significantly distinguish the priming versus no-priming effects in EEG and subjective experience measurements. Nonetheless, future work should address the limitations of E2 to find the ideal design to maximize SR performance. Nevertheless, more importantly, E2 clarifies the requirements moving forward. Priming with MM external neurostimulation seems to lead to more effective NFT sessions than REST no-priming interventions. Therefore, the MM category of stimuli seems a good starting point for the virtual machine controller.

CHAPTER 6

General discussion & future proposals

6. CHAPTER 6 – GENERAL DISCUSSION & FUTURE PROPOSALS

The following sections start by discussing the limitations and advantages of the final framework. Then, a general discussion and future proposals.

6.1 Advantages

Voluntary recruitment without any monetary encouragement was advantageous for involvement, excitement, and study interest. Only people with a state of curiosity and a state of necessity came to the study. However, this kind of recruitment was challenging to conduct and achieve the desired sample, being in sample number or diversity of participant background.

Positive feedback was provided as a low-frequency auditory tone trying to make the sound affectively neutral and not intrinsically rewarding, providing less bias in the NFT protocol (Sulzer et al., 2013).

As a proof of concept, we primed healthy individuals, and subjects with low values of the trait acting with awareness showed better NFT performance. We hypothesize this to be advantageous, as we presume this approach can also work in non-healthy populations with deficits in self-regulation, like Attention deficit hyperactivity disorder (ADHD).

Single-session design has limitations, as we explain in the next section. However, it is also advantageous to recruit a significant sample number of subjects to facilitate the test of the priming versus no-priming hypothesis (John H. Gruzelier, 2014b; T. Ros et al., 2014).

Open-source framework design enables reusability and testability by the neuroscientific community.

6.2 Limitations

Before training, no behavioural tests were performed to quantify traits (like Stroop test, *N*-back, and others) for attention control, emotional regulation, and self-awareness. Instead, we used self-reports to describe those traits qualitatively. This choice was due to EEG experimental design: session time constraints and session complexity.

Due to the single-session design nature of the protocol, transfer effects (intervention side effects, like relaxation, habituation, among other behaviours) could not be evaluated. As explained in the section above, the single-session design was chosen due to the advantage in recruiting subjects, but also because it is enough to investigate the stimuli response of specific features of oscillations and their association with NFT performance, between and within groups (for more detail go to section **2.4**). Our objective was to research NFT learning ability performance and not the behavioural outcome of NFT. This objective also justifies why no sham group was added to test NFT outcome specificity and why we chose a single-session design. Nonetheless, a single-session design training of naïve populations has the limitation of generally providing data distributions with more variance and not showing the complete learning curve effects neither in the priming nor in the NFT. A future study must consider a multi-session design to understand the complete effects of priming versus no-priming.

In E2, the emotional states were only measured in Bin and Bout. This choice was taken because changes between subsequent blocks would be too similar in a single-session design. As such, because the *"walking"* and transition of states are an essential measure, we at least measure the *"in-state"* (Bin) and *"out-state"*(Bout) of the experiment. Future experiment designs with multi-session need to account for this limitation of the single-session design.

The Neurofeedback online experiment was developed in-house using NeuroPrime (see chapter **3**). Various tests were performed and demonstrated consistency. Nonetheless, the two experiments discussed in this thesis are the initial case studies for the present framework. NeuroPrime is an open-source framework. Thus, future studies from our and other research groups will allow further improvements. We invite other groups to use the framework and contribute to its progress.

Positive feedback was presented to be non-intrusive, intrinsically not rewarding, and affectively neutral (in E2, only one bar and low-frequency audio). This choice was to constrain the intervention effects to the priming versus no-priming condition instead of dealing with the effects of feedback itself. However, we need to stress that, because it is not intrinsically rewarding, it must be assumed that participants are motivated by their self-efficacy and/or the intrinsically rewarding properties of the targeted neurophysiological state.

The present study did not take note of participants' IAF. The use of the IAF, defined as the frequency exhibiting the higher EEG amplitude within the extended alpha range, has become increasingly popular as an estimate of alpha activity (Hanslmayr et al., 2005; Klimesch et al., 2007). Nevertheless, the present study started by defining the alpha band using the traditional 8–12-Hz frequency range. Primarily in

keeping with most meditation literature (for literature detail, please go back to section **2.2**) and secondly because IAF adds extra complexity to online and offline processing (the comparison of priming and the no-priming response of specific features of oscillations and their association with NFT performance). This way, we are testing the effects in the same band frequency range in all subjects. Nonetheless, it will be necessary to incorporate IAF online and offline in future trials for comparison with no-IAF results.

It has been previously demonstrated that performing similar tasks with EO and EC can significantly change EEG activity and behavioural performance (Reichert et al., 2015). In the present experimental design, the control implemented in E2 was to separate the eye protocols between distinct blocks into two randomized sequences (see Figure 41). Also, this was our choice to test the same subject in the two conditions due to the population sample. However, we still need to account that some of the neuromodulations may be related to having blocks of EO and EC in the same session. For them not to happen, a separate group for each condition is required in future trials.

There was no test to score attentional focus performance during priming, like meditation performance scores (P. A. Frewen et al., 2014). We only had, after the priming, subjective experience states (POMS and TMS) to score emotional priming. MBAS score was tested but not implemented in the final E2 due to the complexity required and bias (which can affect the mental state) that could bring to the experiment. Our short (3 min) and repeated mindfulness task (4 blocks) structure already was built around the probability of mind wandering and how we could maintain the focus target right before the NFT (for a more detailed discussion, go back to section **5.6-PRIME**).

Our neurophenomenological approach is limited to neuropsychological scales due to time and human resources constraints. However, an interview approach similar to the one implemented by Davelaar et al. (E. J. Davelaar et al., 2018) instead of only self-reports should probably be met in further studies.

Working with real-time decoding of EEG signals has multiple limitations, such as noise and movement-related artefacts (M. X. Cohen, 2019). For example, small movements above the neck, such as eye blinks or muscle contractions, can add artefacts to the signal. Attempts were made to prevent and detect such artefacts in real-time and not include those samples when calculating the Neurofeedback. This process is not perfect and can sometimes lead to false positives leading to variations in the number of epochs per subject task (see **Appendix IV – Additional results**). As such, we need to include this as a limitation.

Temporal limitations and team limitations conditioned data mining. An example of this is the number of statistical tests, multivariate analysis, and *"big data"* approaches to be implemented in future publications.

6.3 General discussion & future proposals

From the pilot E1 implementation, we observed the dynamic shifts from the rest state between blocks during the session (please refer to **Appendix IV – Additional results**). In fact, with self-reports, it seemed the participants were *"trying"* to rest and possibly not *"sensing"* relaxation, probably meaning that the person is closer to a trying state than a rest state. Additionally, even if not significant, the E1 analysis tendency pointed against the null hypothesis: priming seemed to affect the NFT SMR protocol developed. The error range presented in this analysis was still considerable. Even so, this pilot evaluation provided a steppingstone for E2.

With all the changes implemented in E2, we observed a more robust and significant effect in priming versus no-priming in the EO condition. While the current priming protocol needs more research and is not yet ready to be implemented on final products, e.g., SR serious games applications (Israsena et al., 2021; Manuel Ninaus, Witte, et al., 2013), it potentially provides an essential layer of personalization and mutual intervention-participant (game-player) adaptation.

To optimize SR learning, future work will address the use of neural networks (e.g., using reinforcement learning, deep learning for time series forecasting with long short-term memory networks, multilayer perceptron's, convolutional neural networks, among others) to learn the sequence of stimuli that leads the subject towards the desired *"optimal"* state (as theorized in chapter **2**). The framework should adapt to the user's own pace (even slow down user pace if needed) and regulate/control the user's brain state according to the target. As such, the basis developed during this Ph.D. project will evolve to a closed-loop BSDS similar to the closed-loop NFT, where the monitoring of brain activity with machine learning algorithms can guide the application of brain stimulation (please go back to section **2.1.4** for more detail) - making the actual stimulation personalized and dependent on specific brain states (Enriquez-Geppert et al., 2017; Hartmann et al., 2011).

In the current single-session context and during the EO condition, we found that priming increases NFT performance and change the percentage of responders in a training population (80% of EG participants and only 57% of CG participants could increase their alpha linearly). Because the difference between the groups lies in the NFT preceding task (PRIME task versus REST task), we can also conclude that the REST task does not seem to be the best primer for this type of research protocol. We found it imperative to discuss baseline priming tasks and improve instructions since the instruction *"try to relax"* and even *"focus on the cross"* are probably insufficient to diminish self-related mental processes and target a

relaxed or/and attentive state (E. J. Davelaar et al., 2018) - leading to uncertain brain states that can decrease the learning outcome during the NFT. Reversely, depending on the context, the learning phase of the subject, and the learning outcome, we can even test if the REST task can be a good priming task or a good baseline task. For example, like our E2 or in a clinical setup where the subject needs to control their brainwaves, the REST task probably simulates a better day-to-day baseline (the initial threshold), from which the subject should improve. Also, the initial REST baseline can be used as a predictor of NFT performance (Nan et al., 2015, 2018; Reichert et al., 2015; Wan et al., 2014). Nevertheless, we demonstrate that during our EO intervention blocks (in a single-session naïve population context), a mindfulness instructional approach was superior at priming NFT performance than the REST task, which is a step further in a better neurofeedback operant. As such, future research on this topic is necessary.

We should also not forget that this type of framework will not substitute other SR mind-body training techniques, like physical exercise, musical training, meditation, among others. We consider this framework a possible mechanistic approach[4] to these techniques, a researching tool for priming SR. Our vision is to assist novices in controlling their brain states and support experts to quantify which stimuli target their *"optimal"* homeostatic brain states. Additionally, in the future, more immersive and personalized setups where the user can use movement as a priming stimulus (e.g., trying to balance in a gymnastic beam, chi-gong breathing, dancing, virtual or augmented reality simulations) can prove more informative than just sitting on a chair looking at tasks on a screen.

To summarize, we answered part of the proposed questions relative to the EO condition in the following paragraphs. In contrast, the EC condition seems mainly governed by neurophysiological processes of eyes closing. The resting baseline activity level seems to obscure the alpha activity changes on the NFT tasks – i.e., the resting baseline activity may represent the optimal level of alpha activity, and it should be challenging to get close to this level or up-regulate beyond (D. Vernon et al., 2009). Additionally, since EC condition is less amenable to intervention effects via NFT (Barry et al., 2007; Chow et al., 2017; Nan et al., 2018; D. Vernon et al., 2009), maybe more than two NFT tasks are needed to extract up-regulation effects in a single session design, like the 5 NFT tasks in (Chow et al., 2017). Nonetheless, further data mining is needed to clarify if there are also alpha activity changes in the NFT tasks under the predominant dow when removing the resting baseline.

Considering the fundamental question, does priming with external stimulation increase the SR of NF? Priming increases the number of subjects with higher NFT performance during intervention blocks. As such, some implicit factors in priming were affecting the explicit control of NFT, especially in subjects

with a trait of low capacity to act with awareness. However, can these priming effects transfer to a multi-session design, or are they only crucial in the first session of NFT?

Questioning the targets, which mental/brain states can be *"optimal"* for learning self-regulation of brain activity? Analyzing the EEG, MM priming seems to assist alpha neuromodulation to constantly increase the number of epochs above threshold tasks, considering half of the maximal regression slope (0.80 = 45.83°), 12 out of 24 (50%) EG participants and only 6 out of 17 CG (35%) were able to increase above it. Therefore, the hypothesized *"optimal"* target state seems to correspond to the actual state needed for the learner to self-regulate brain activity (i.e., irrelevant associations between internal states and external reward need to be avoided, and the learner needs to stay engaged, focused, and undistracted). Considering the self-reports, the subjects that seem to be more affected by priming have higher values of decentering at Bin (situational awareness, a non-judgement attitude), show lower values of acting with awareness and show greater changes in tension and less vigour at Bout. Analyzing the biomarkers, the best performers on priming EG and the no-priming CG revealed different results. Lower GSR activity in the intervention blocks, seen both at the tonic (SCL standard deviation slopes) and phasic level (total sum of SCR slopes), should explain a less stressful, relaxed, and non-judgement attitude task performance (Boucsein et al., 2012; Posada-Quintero & Chon, 2020). The EG subjects with lower HRV activity (i.e., lower high-frequency variations of vagal parasympathetic components, measured by *"rmssd"* slopes) at the intervention blocks might show a more effective task-engagement of the subject during the NFT task (Malik et al., 1996; Zahn et al., 2016). While on the CG, subjects with higher HRV (i.e., a higher increase of standard deviation of the N-N intervals, *"sdnn"* slopes) seems related to better self-control and emotional regulation (Beauchaine, 2001; Graziano & Derefinko, 2013; Zahn et al., 2016). As such, based on the analysis of EEG, GSR, HRV, and self-reports between the EG and CG, the hypothesized *"optimal"* target state seems to correspond to the actual state needed for the learner to self-regulate brain activity - i.e., the learner needs to stay engaged and show situational awareness with a non-judgement attitude.

Questioning the stimulus, how can we non-invasively stimulate the *"optimal"* state? In this thesis, we used audio-guided practices based on MM techniques, so the more appropriate question is: are MM stimuli a good self-regulation primer to reach the *"optimal"* state, compared with the standard rest baseline tasks used in Neurofeedback? In this experimental study context, MM priming in the EG significantly assists alpha neuromodulation compared with only CG rest tasks. However, in what regards MM stimuli is a good primer to reach the *"optimal"* state, the only way to answer with the current results is by comparing group domain effects on EO NF learning apart from priming (EG) and no-priming (CG). The best EG performers had a lower capacity to act with awareness at pre-intervention and higher situational awareness

(decentering) at Bin. As such, the priming seems to stimulate these subjects with more intensity. In turn, this relates to the learner's *"optimal"* state of being aware without judgement and avoid task-unrelated thoughts. On the contrary, the only information that we can extract from the CG is that subjects with fewer changes in confusion and fatigue perform better. Also, in the EG, subjects with low values of variance of GSR and HRV performed better, while in the CG, that was not the case. This difference seems correlated with MM priming, as low changes of SCL and SCR should explain less stressful, relaxed, and stimuli-insensitive (non-judgement attitude) task performance.

Questioning the measurements, how can we measure each individual's target performance (learning and behavioural outcomes)? Considering the EEG, all the three measurements from (Dempster & Vernon, 2009) were tested, amplitude and tBAT helped us compare changes within-session and across the blocks, while the *"integrated change"* is hard to track significant average changes but shows variance changes across blocks. However, due to the complexity of the analysis in E2, we chose only to present the amplitude (future publications will consider tBAT and the integrated change). Regarding the trait self-reports, the *"actware"* dimension of FFMQ seems to predict that users with lower values (lower acting with awareness in day-to-day life) will significantly benefit from this priming intervention. In the subjective experience, it seems essential to target the decentering dimension of the TMS scale, and the POMS scores seem to correctly quantify the moods relative to the intervention. Also, HRV and GSR features seem to correctly separate some of the emotional states (relaxation, non-judgement attitude, task-engagement) from the EG best performers versus CG best performers.

Relative to the framework experimental temporal Design, what is the best temporal design to implement the framework? The short block design successfully stimulated the NFT in E2, using simple priming stimuli followed by NFT in each block. In E1, with the complex ABA design, we could not find significance. However, other factors such as methodological and technical limitations already discussed also interfered with these results, making it difficult to determine the causes for this lack of effect. More experiment designs need to be tested to answer this question. In conclusion, although two designs are described in this thesis, there are many other ways to design a session with the priming attributes of our framework. That being said, we invite groups to use our open-source framework (chapter **3**) in experiments and help us improve it.

Considering the open-source software, was it possible to develop open-source software for fast and straightforward integration of advanced closed-loop applications? An open-source Python framework was developed to tackle the aforementioned questions (see chapter **3**).

To summarize, what was gained by developing this type of framework? To develop groundwork and propose a solution to the priming design to maximize self-regulation and discover its fundamentals/methodologies.

Nonetheless, with our research, we were unable to answer the following question: Do non-responders exist in NFT or do the problems in personalization designs need to be overcome for each individual to self-regulate their brain activity? For this, we need to implement a pre-screening score of NF learning capabilities in future research, then train the subjects with the priming framework and inspect if it correlates with the score. As we already pointed out in section **1.2.3**, it is known that participants vary in their ability to regulate brain activation. However, these individual differences in NF learning capabilities are still difficult to be predicted (Alkoby et al., 2018). Research is growing in predictors via behavioural scores (Eva Maria Hammer et al., 2012; Kadosh & Staunton, 2019), functional (Blankertz et al., 2010; Nan et al., 2015; Reichert et al., 2015; Scheinost et al., 2014; E. Weber et al., 2011), or anatomical (Halder et al., 2013; M. Ninaus et al., 2015) indices. This should be considered when allocating participants to study groups (Lubianiker et al., 2019).

Finally, MM priming seems to target mechanisms that scaffold the subject into a superior NF operant. In the future, such mechanisms still need to be discriminated from NF-specific (related to training a target neurophysiological variable), NF non-specific (dependent on the NF context, but independent from the act of controlling a particular brain signal), or general-non-specific mechanisms (including the common benefits of cognitive training as well as psychosocial influences) (Tomas Ros et al., 2020). That being said, we can *"walk"* with higher confidence to the next step, i.e., automate the framework and optimize priming personalization by adapting convolutional neural networks to learn the sequence of stimuli that leads the subject towards the desired *"optimal"* state.

6.4 Concluding remarks

Throughout the two case studies presented in this thesis, we developed a human-computer framework to assist the SR of NF, aiming to decrease the number of unsuccessful practitioners (non-responders/non-learners) of SR tasks. The assistance was done by priming the subject with mindfulness guided instructions right before the explicit NFT. This intervention was the first step to demonstrate that priming with external stimulation assists NFT performance and potentially turns NFT non-responders into responders. The main results showed that priming with mindfulness stimuli enables higher significance

of EEG target self-regulation during the EO intervention blocks in a single session design. Additionally, from the self-reports and biomarkers, the most significant priming performers had low values of acting with awareness trait at pre-intervention, also showed higher *"decentering"* at the first block (situational awareness, non-judgement attitude towards thoughts, feelings or external stimuli), and reported signs of built-up *"tension"* and less *"vigour"* at the end of the experiment protocol (Bout). As such, especially on subjects with low capacity to act with awareness, the demand for focused attention on internal sensations through guiding audio seems likely to implicitly support the subject's emotional regulation capacity. In turn, it should increase NFT task engagement and target situational awareness.

Nonetheless, there are remaining questions to be solved that should be addressed in further experiments. In the future, we should be able to: experiment with the priming effects in a multi-session design and check if they are only crucial for the first session of the NFT or if they support the subject throughout the multi-session; test different temporal designs to find the best design for this type of framework; find the *"optimal"* mechanisms that should be primed and validate stimuli able to prime them; test if MM audio-guided is the *"optimal"* stimuli at priming NF SR mechanisms or if other categories of stimuli targeting different mechanisms or stimuli personalization have the same or better efficacy in leading the subject into the *"optimal"* learning state; evaluate the hypothesis that non-responders/non-learners depend on the priming protocol personalization, i.e., that non-responders/non-learners can be turned into a responders/learners. In this way, we are trying to answer whether brain activity self-regulation can be scaffolded by implicitly priming the *"optimal"* state at pre-NFT, limiting the number of non-optimal mechanisms, and potentiating optimal mechanisms that improve NF SR performance.

Scaling up this priming assistance research, we envision a machine controller that uses neural networks to classify and select the required neurostimulation to arrive at the desired target—this way, outsourcing the difficulty of sensing the correct mental strategies. Moreover, the machine controller should assist the participant to gravitate/walk towards the desired mental state by implicit neurostimulation, which should increase explicit self-neuromodulation.

In conclusion, we took the first steps towards a better NF operant. Showing that priming with mindfulness stimuli enables higher significance of EEG target self-regulation in a single session. In this way, we find necessary further research of priming right before NFT for a more precise methodology in this field.

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APPENDIX I – ETHICS

University of Minho SECVS project ethical approval for good practices with human subjects.



Universidade do Minho

SECVS

Subcomissão de Ética para as Ciências da Vida e da Saúde

Identificação do documento: SECVS 011/2018

Título do projeto: *Capacidade Individual de Aprendizagem (da Auto-Regulação da Actividade Cerebral) no Treino de Neurofeedback (Individual Learning Ability (of Brain Activity Self-regulation) in Neurofeedback Training)*

Investigador(a) responsável: Nuno Sérgio Dias, Instituto de Investigação em Ciências em Vida e Saúde, Escola de Medicina (EM), Universidade do Minho, e ICVS/3B's - Laboratório Associado, Universidade do Minho; Estela Guerreiro Silva Bicho Erlhagen, Departamento de Eletrónica Industrial, Escola de Engenharia (EE), Universidade do Minho, e ICVS/3B's - Laboratório Associado, Universidade do Minho; e o aluno de doutoramento Nuno Miguel Cerqueira da Costa, do ICVS e do Centro ALGORITMI, Universidade do Minho

Subunidade orgânica: Escola de Medicina, Universidade do Minho

PARECER

A Subcomissão de Ética para as Ciências da Vida e da Saúde (SECVS) analisou o processo relativo ao projeto intitulado *Capacidade Individual de Aprendizagem (da Auto-Regulação da Actividade Cerebral) no Treino de Neurofeedback (Individual Learning Ability (of Brain Activity Self-regulation) in Neurofeedback Training).*

Os documentos apresentados revelam que o projeto obedece aos requisitos exigidos para as boas práticas na experimentação com humanos, em conformidade com o Guião para submissão de processos a apreciar pela Subcomissão de Ética para as Ciências da Vida e da Saúde.

Face ao exposto, a SECVS nada tem a opor à realização do projeto.

Braga, 8 de maio de 2018.

A Presidente

Maria Cecília de Lemos Pinto Estrela Leão

APPENDIX II – SELF-REPORTS

Traits self-reports

To check our version of the sociodemographic, FFMQ (Gregório & Gouveia, 2011)., DASS (EADS-21) (Pais-Ribeiro et al., 2004) and ERQ (Vaz et al., 2014) go to the 1st questionnaire: https://forms.gle/2uT7f7oH3pd4c9FD9

States self-reports

To check our version of POMS and TMS go to the 2nd questionnaire: https://forms.gle/nQNRQkBWEVtbKySo8

Custom framework self-reports

E1 self-report

Questionário pós-neurofeedback

Este questionário pretende avaliar a sua perceção da tarefa de neurofeedback.
*Obrigatório

1. Código do(a) participante
(a preencher pelo investigador)

2. Data

Exemplo: 7 de janeiro de 2019

3. Qual pensa ter sido o seu grau de sucesso durante a tarefa? *

Marcar tudo o que for aplicável.

	Não sei	Nada ou ligeiramente	Um pouco	Moderado	Bastante	Extremo
Escolha um:	☐	☐	☐	☐	☐	☐

4. Qual foi o nível de dificuldade da tarefa? *

Marcar tudo o que for aplicável.

	Não sei	Nada ou ligeiramente	Um pouco	Moderado	Bastante	Extremo
Escolha um:	☐	☐	☐	☐	☐	☐

5. Qual foi o nível de esforço mental? *

Marcar tudo o que for aplicável.

	Não sei	Nada ou ligeiramente	Um pouco	Moderado	Bastante	Extremo
Escolha um:	☐	☐	☐	☐	☐	☐

6. Leia cada palavra e marque a resposta adequada no espaço correspondente à palavra. Indique em que medida sentiu cada uma das seguintes expressões, durante a tarefa? *

Marcar tudo o que for aplicável.

	Não sei	Nada ou ligeiramente	Um pouco	Moderadamente	Bastante	Extremamente
Motivado	☐	☐	☐	☐	☐	☐
Relaxado	☐	☐	☐	☐	☐	☐
Concentrado	☐	☐	☐	☐	☐	☐
Cansado	☐	☐	☐	☐	☐	☐
Frustrado	☐	☐	☐	☐	☐	☐
Pensativo	☐	☐	☐	☐	☐	☐

7. Quão consciente estava do que surgia, na sua percepção momentânea, durante a tarefa (por exemplo, poderia estar muito consciente de que estava concentrado, relaxado,...)? *

Marcar tudo o que for aplicável.

	Não sei	Nada ou ligeiramente	Um pouco	Moderadamente	Bastante	Extremamente
Escolha um:	☐	☐	☐	☐	☐	☐

8. Pensa que o feedback apresentado através da(s) barra(s) correspondeu à sua atividade cerebral em algum momento? *

Marcar tudo o que for aplicável.

- [ ] Sim
- [ ] Não

9. Quais foram as estratégias de regulação que usou durante a tarefa? Destas estratégias, alguma se correlacionou positiva, ou negativamente com o feedback apresentado pela barra?
(escreva o nome da estratégia)

Marcar tudo o que for aplicável.

	Positivamente	Neutra (sem correlação)	Negativamente
_____	☐	☐	☐
_____	☐	☐	☐
_____	☐	☐	☐
_____	☐	☐	☐
_____	☐	☐	☐

10. Mudou de estratégia de regulação ao longo da tarefa?

Marcar tudo o que for aplicável.

- [ ] Sim
- [ ] Não
- [ ] Se sim, sabe a quantidade de vezes?_____

11. Pensa que a técnica de neurofeedback o(a) poderá ajudar?

Marcar tudo o que for aplicável.

- [ ] Sim
- [ ] Não
- [ ] Se sim, de que forma?_____

12. Indique outras informações ou comentários que achar necessários sobre a tarefa de neurofeedback, por favor.

E2 self-report

NFT_1 *

Indique em que medida sentiu cada uma das seguintes expressões:

	0:Nada	1:Um pouco	2:Moderado	3:Bastante	4:Extremo
1:Qual pensa ter sido o seu grau de sucesso durante o treino?	○	○	○	○	○
2:Qual foi o nível de dificuldade do treino?	○	○	○	○	○
3:Qual foi o nível de esforço mental durante o treino?	○	○	○	○	○
4:Quão consciente estava do que surgia, na sua percepção momentânea, durante o treino (por exemplo, poderia estar muito consciente de que estava concentrado, relaxado,...)?	○	○	○	○	○
5:Sentiu-se entusiasmado quando conseguiu controlar o neurofeedback?	○	○	○	○	○
6:Sentiu-se frustrado quando não conseguiu controlar o neurofeedback	○	○	○	○	○

7:Sentiu que a experiência demorou demasiado tempo?	○	○	○	○	○
8:Sentiu que a experiência demorou pouco tempo?	○	○	○	○	○
9:Sentiu algum formigueiro no corpo?	○	○	○	○	○
10:Sentiu a cabeça leve, ou como se tivesse a ter uma tontura?	○	○	○	○	○
11:Pensa que o tipo de estratégia mental teve influência no seu Neurofeedback?	○	○	○	○	○
12:Pensa que a intensidade/qualidade da sua atenção sobre a estratégia mental teve influência na regulação do seu Neurofeedback?	○	○	○	○	○

NFT_2: Pensa que o feedback apresentado durante a tarefa correspondeu à sua atividade cerebral em algum momento? *

- ○ 1:Sim
- ○ 2:Não

NFT_3 *

Quais foram as estratégias de regulação que usou durante a tarefa? Destas estratégias, alguma se correlacionou positiva, ou negativamente com o feedback apresentado pela barra?

	0:Não usei.	1:Positivamente	2:Neutra (sem correlação)	3:Negativamente
1:Relembrar memórias positivas(momentos bons, musicas que evocam sentimentos positivos, ...)	○	○	○	○
2:Relembrar memórias negativas(momentos negativos, traumas, ...)	○	○	○	○
3:Imaginação positiva (lugar calmo, sons calmos, felicidade, amor,...)	○	○	○	○
4:Imaginação negativa (dor, lugar triste/traumático, raiva, rancor...)	○	○	○	○
5:Focar na respiração	○	○	○	○
6:Focar em algo no ecrã	○	○	○	○
7:Focar num dos sentidos(visão, tacto, olfacto,...)	○	○	○	○
8:Sentir sensações corporais (formigueiro, contração muscular,...)	○	○	○	○
9:Sentir sensações positivas (sentir relaxado, calmo, em paz,...)	○	○	○	○
10:Sentir sensações negativas (sentir stressado, nervoso,...)	○	○	○	○
11:Tentar ficar	○	○	○	○

positivo(calmo, relaxado,...				
12:Tentar ficar negativo(raiva, stress, ansiedade)	○	○	○	○
13:Pensar no futuro	○	○	○	○
14:Pensamentos neutros(imaginar uma pedra, fundo branco, fundo preto,...)	○	○	○	○
15:Não dar importância ao neurofeedback	○	○	○	○
16:Motivar-me a conseguir alterar o Neurofeedback(Imaginar a barra verde,...)	○	○	○	○
17:Tarefas cognitivas (calculo matemático, contar ovelhas,...)	○	○	○	○

NFT_4: Quantas vezes mudou de estratégia de regulação ao longo da tarefa? *

(Responda o numero de estratégias que utilizou)

A sua resposta

NFT_5: Pensa que a técnica de neurofeedback o(a) ajudou ou poderá ajudar? *

- ○ 1:Sim
- ○ 2:Não

NFT_6: Indique outras informações ou comentários que achar necessários sobre a tarefa de neurofeedback.

(Por Exemplo, outras estratégias mentais que usou e tiveram efeitos.)

A sua resposta

APPENDIX III – INSTRUCTIONS

Pre-training verbal Instructions

Verbal instructions translated from Portuguese to English. The following Verbal instructions are given to the subject after finishing the trait self-reports:

1. Ask for the motivation to do this experience;
2. Ask about current background;
3. Ask about meditation and neurofeedback knowledge
4. Use a powerpoint to explain NFT and Experiment:

    1. NFT Verbal instructions:

        1. Analogy with physical training: "if I ask you to contract the left bicep with more force, you can sense that, we call that biofeedback. Additionally, if I'm your trainer and see that you can improve the movement, I can give instructions to do so. Now imagine that I want you to train a part of your brain for example, the somatosensory cortex and elevate electric frequency in that zone, can you do it? No, correct? We don't have internal feedback, that is why we use instruments like the EEG and fMRI to extract the data from those areas and present them as Neurofeedback through technology."
        2. Objectives (showing a replay from a NFT GUI):
            1. 1st objective: By passing the bar above the threshold, or the audio to the positive low pitch sound, you get points. Your main objective is to do the more points possible
            2. 2nd objective: Is to maintain more time possible the Neurofeedback in the positive state.
        3. How do you modulate your Neurofeedback, you ask?
            1. Explore Mental strategies: like focus on something on the screen; positive thought, negative thoughts, neutral, ...
            2. I can't give you the right instructions, contrary to physical exercise, because each person is different and each one will get more intense or focused with different types of strategies.
            3. Therefore the main focus is to go on a quest and explore which mental strategies can you focus more and then see if that has any effect on your neurofeedback. So you don't need to always be looking to the Neurofeedback, each time that you find yourSelf fully engaged with your mental state that is when you should look to your Neurofeedback.

Also, very important, the artefacts (showing real-time EEG signal, see Figure 38)

        4. Has you can see, this are the 32 channels;
        5. From Fp1 to Oz, left side channels; From Oz to Fp2, right lobe channels;
        6. Fp1 and Fp2 are the ones in close to your eyebrows; For example, if you blink, you see blink artefacts.

7. In fact, because EEG signal is around the μV while muscle contraction is around the mV, any muscle that you contract from the neck up will appear as an artefact in the signal, e.g., smile.
8. What is important for you to note is that when these artefacts occur, I can't present these signals as your Neurofeedback. As such, visually you will see the bar stopping, whenever an artefact occurs. However, that should not bother or be a problem for you, as said before, you main objective is to be fully focused on your neuromodulation strategy then see if the brain activity is going in the intended target direction.

4. Two modalities (specific to E2):
    1. Vision and audio, because you will have to regulate with eyes open and eyes closed
5. Try to do maximum 3 strategies per block (specific to E2):
    1. You will have 6 blocks with 3 minutes each., because you need time to focus on the mental strategies and see if it works or not, it is a good idea to let at least one minute per strategy, if you see It does not work, then you can change it. Also, as you should already be aware, focusing takes some time.
6. Strategy complexity:
    1. Another tip is to explore from simple to complex strategies. Simple for example, tingling on the finger, or think in black. While complex, for example, think about music piece and the different sounds that the instruments make.
7. Behaviour target:
    1. After the experiment you will know the behaviour target that you are trying to modulate.

2. REST Verbal Instructions:

1. In this task you only need to try to relax. You will have rest tasks with eyes open and eyes closed.
2. With eyes closed a bell will signal the end of the task.

3. PRIMING Verbal Instructions:

1. For the EG pay attention and follow along the audio-guided instructions.

E1 REST task instructions

The text instructions with translation are described in the next list:

- "TAREFA: ESTADO DE REPOUSO"
    - TASK: REST STATE
- "Aproveite para respirar, beber água ou chamar o investigador caso necessite de ajuda para ficar mais confortável"
    - Rest and breath, you can drink some water or call the technician if you need some help to get more comfortable.
- "Durante as tarefas, mantenha os olhos abertos focados na cruz que aparece no ecrã."
    - During Tasks, keep eyes open focused on the point on the screen

- "Coloque-se confortavelmente e tente relaxar."
    - Adjust for more comfort and try to relax.
- "Carregue ENTER para começar."
    - Push ENTER to start the task.

Note that, after the participant finished the traits self-report and before the training session, similar pre-training verbal instructions were conveyed by the investigator, as follows:

- "In this task you only need to try to relax with your eyes open focused on the point on the screen."

E1 BM instructions

Below is the manuscript for the text instructions in Portuguese, used in each of the screens, and the audio instructions with the time marker.

Instructions pre-task screen

"TAREFA: ESTÍMULO AUDITIVO.

PRATICA GUIADA DE RESPIRAÇÂO.

Por favor coloque auscultadores.

Permaneça com os olhos fechados e atento ao audio, durante a tarefa.

Carregue ENTER para começar!"

Instructions task screen

"Mantenha os olhos fechados!"

Audio guided instructions

00:00 – "Coloque-se confortavelmente e feche os olhos (não necessário – se estiver nas instruções de texto antes de começar a tarefa)"

00:10 – "Preste atenção à sua respiração, notando cada inspiração/ expiração."

00:28 – "Foque-se no local do corpo onde esta sensação é mais forte: será mais no peito, no abdómen, ou na zona das narinas...?!."

00:54 – "Siga o movimento natural da respiração, não o tente alterar nem controlar, apenas preste atenção e observe."

01:18 – "Se perceber que a sua mente divaga, e notar que começou a pensar noutra coisa, saiba que é normal, divagar faz parte da natureza da mente, apenas observe a distração, e gentilmente volte a sua atenção para as sensações da respiração."

02:06 – "Explore, não tenha pressa."

02:50 – "Assim que ouvir o som para terminar, abra os olhos lentamente."

E1 IM instructions

Below is the manuscript for the text instructions in Portuguese, used in each of the screens, and the audio instructions with the time marker.

Instructions pre-task screen

"TAREFA: ESTÍMULO AUDITIVO.

PRATICA GUIADA DE IMAGINAÇÂO.

Por favor coloque auscultadores.

Permaneça com os olhos fechados e atento ao audio, durante a tarefa.

Carregue ENTER para começar!"

Instructions task screen

"Mantenha os olhos fechados!"

Audio guided instructions

00:00 – "Coloque-se confortavelmente e feche os olhos

00:06 – "Pense num lugar especial à sua escolha.

00:15 – "Pode ser um lugar onde já esteve, mas também pode ser um lugar imaginário!

00:31 – "Um lugar onde nada nem ninguém o incomoda, onde se sente calmo e em segurança, longe de todas as preocupações e inquietações.

00:59 – "Use a sua imaginação para ver..., ouvir..., sentir..., saborear... e cheirar todos os pormenores nesse lugar, como se estivesse lá agora

01:27 – "Se perceber que a sua mente divaga, e notar que começou a pensar noutra coisa, saiba que é normal, divagar faz parte da natureza da mente, apenas observe a distração, e gentilmente volte a sua atenção para o seu lugar especial.

02:06 – "Explore, não tenha pressa.

02:50 – "Assim que ouvir o som para terminar, abra os olhos lentamente."

E2 REST task instructions

Below is the text instructions for EO (in EC, the "eyes open" sentence is replaced by "eyes closed") with translation. In the pre-task screen the task title indicates if the REST task will be followed by NFT.

- "TAREFA: ESTADO DE REPOUSO OLHOS ABERTOS "
    - TASK: REST STATE EYES OPEN ("followed by NEUROFEEDBACK" is added if true)
- "Durante as tarefas, mantenha os OLHOS ABERTOS focados no ecrã."
    - During Tasks, keep EYES OPEN focused on the screen
- "Tente não mexer a cabeça ou piscar os olhos!"
    - Try not to move your head or blink!
- "Coloque-se confortavelmente e TENTE RELAXAR."
    - Adjust for more comfort and TRY TO RELAX
- "Carregue ENTER para começar."
    - Push ENTER to start the task.

Note that, after the participant finished the traits self-report and before the training session, similar pre-training verbal instructions were conveyed by the investigator, as follows:

- "In this task you only need to try to relax. You will have rest tasks with eyes open and eyes closed."
- "With eyes closed a bell will signal the end of the task."

E2 BM instructions

Below is the manuscript for the text instructions in Portuguese, used in each of the screens, and the audio instructions. In the pre-task screen the task title indicates if the task will be followed by NFT.

Instructions pre-task screen

"TAREFA: PRÁTICA DE RESPIRAÇÃO GUIADA seguida por NEUROFEEDBACK.

BLOCO: 1 / 6

Durante a PRÁTICA GUIADA se perceber que começou a pensar noutra coisa, saiba que é normal, divagar faz parte da natureza da mente, apenas observe a distração, e gentilmente volte a sua atenção para a tarefa.

Tente não mexer a cabeça ou piscar os olhos!

Coloque-se confortavelmente.

Durante as tarefas, mantenha os OLHOS ABERTOS|OLHOS FECHADOS focados no ecrã, atento ao audio.

Carregue ENTER para começar!"

Instructions task screen

Eyes open: "Mantenha os OLHOS ABERTOS focados na cruz, atento às instruções auditivas!"

Eyes closed: "Mantenha os OLHOS FECHADOS, atento às instruções auditivas!"

Audio guided instructions

00:00 – "Preste atenção à sua respiração, notando cada inspiração/ expiração."

00:23 – "Foque-se no local do corpo onde esta sensação é mais forte: será mais no peito, no abdómen, ou na zona das narinas..."

00:50 – "Siga o movimento natural da respiração, não o tente alterar nem controlar, apenas preste atenção e observe."

01:20 – "Explore não tenha pressa."

02:25 – "Mantenha a sua atenção na respiração."

E2 IM instructions

Below is the manuscript for the text instructions in Portuguese, used in each of the screens, and the audio instructions.

Instructions pre-task screen

"TAREFA: PRÁTICA DE IMAGINAÇÃO GUIADA seguida por NEUROFEEDBACK.

BLOCO: 1 / 6

Durante a PRÁTICA GUIADA se perceber que começou a pensar noutra coisa, saiba que é normal, divagar faz parte da natureza da mente, apenas observe a distração, e gentilmente volte a sua atenção para a tarefa.

Tente não mexer a cabeça ou piscar os olhos!

Coloque-se confortavelmente.

Durante as tarefas, mantenha os OLHOS ABERTOS|OLHOS FECHADOS focados no ecrã, atento ao audio.

Carregue ENTER para começar!"

Instructions task screen

Eyes open: "Mantenha os OLHOS ABERTOS focados na cruz, atento às instruções auditivas!"

Eyes closed: "Mantenha os OLHOS FECHADOS, atento às instruções auditivas!"

Audio guided instructions

00:00 – "Pense num lugar especial à sua escolha."

00:05 – "Pode ser um lugar onde já esteve, mas também pode ser um lugar imaginário!

00:08 – "Um lugar onde nada nem ninguém o incomoda, onde se sente calmo e em segurança, longe de todas as preocupações e inquietações.

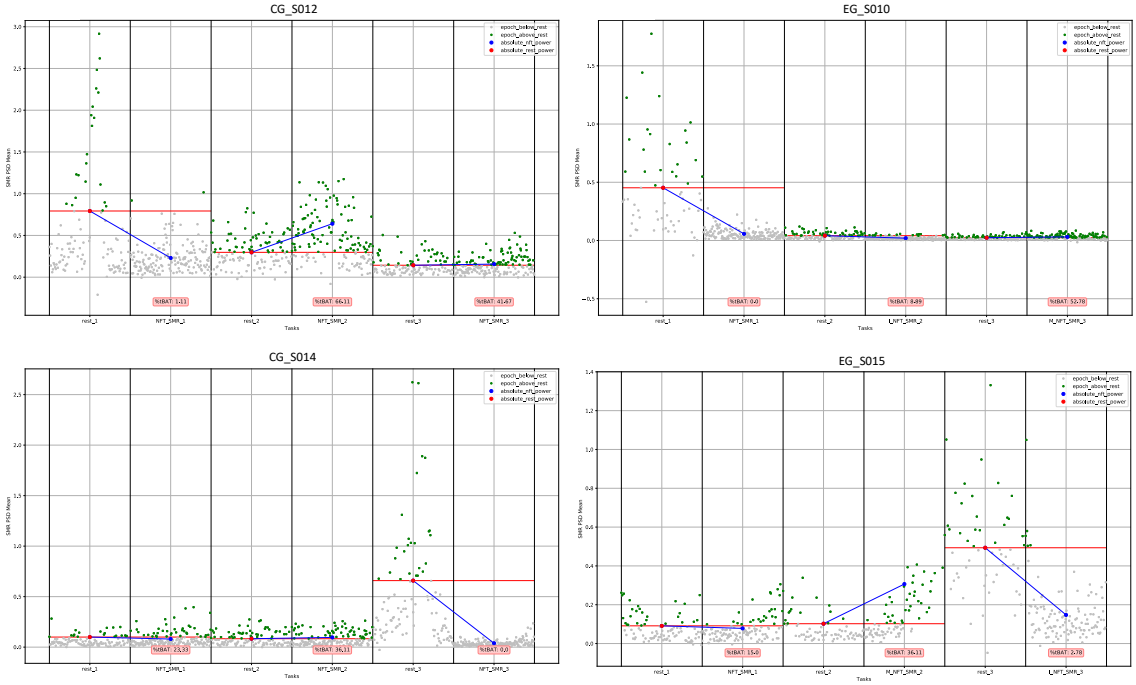
00:24 – "Use a sua imaginação para ver..., ouvir..., sentir..., saborear... e cheirar todos os pormenores nesse lugar, como se estivesse lá agora.

01:20 – "Explore não tenha pressa."

02:25 – "Mantenha a sua atenção no lugar especial."

APPENDIX IV – ADDITIONAL RESULTS

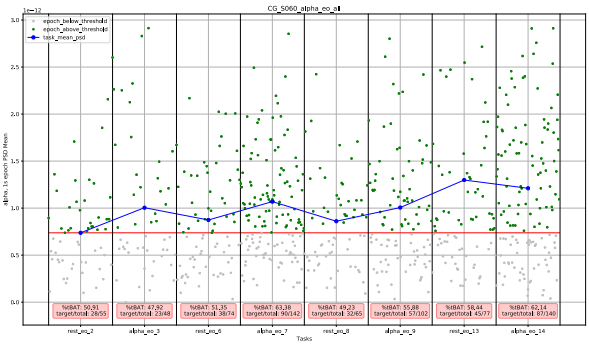
E1 within-subject session profiles



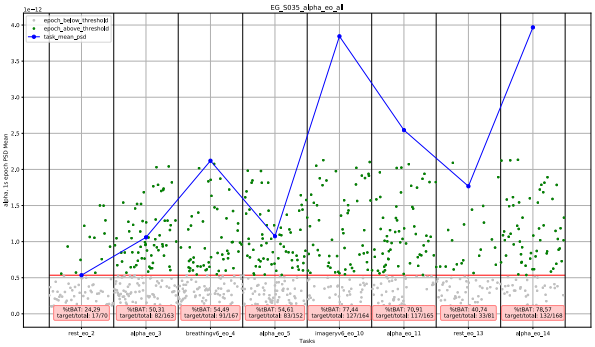
E2 within-subject session profiles

Positive response

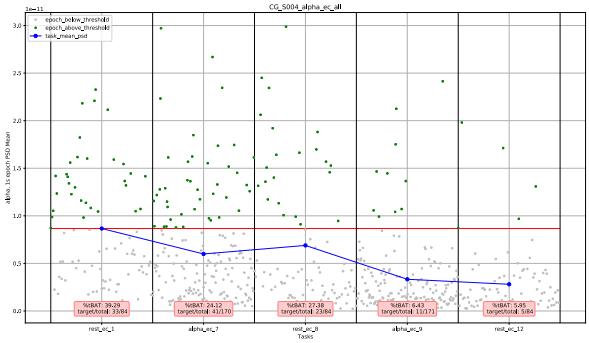
CG

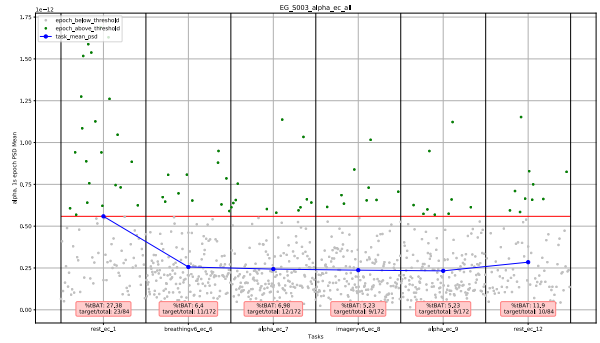


EG

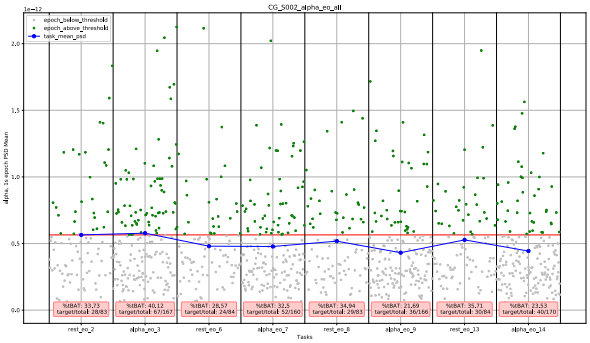


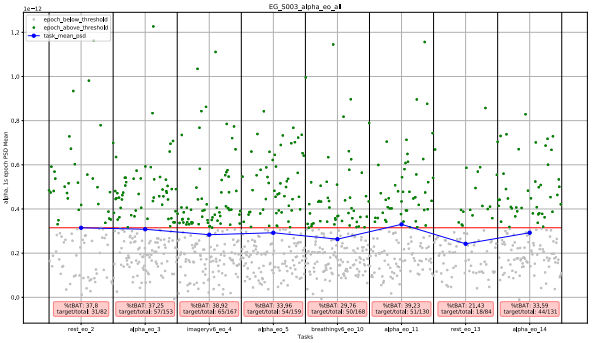
Negative response





Non responders





APPENDIX V – E2 FEATURES

EEG features

Sample rate: 1000 Hz

Feature region of interest (ROI): Pz

Features extracted per subject:

- [theta,alpha,SMR,beta]: list of bands extracted
- epoch_a: epochs array of each task = [[band PSD mean, standard deviation]..., [*N*-epoch]]. Each epoch band PSD is calculated from 1000 samples per second.

Measure used to detect brain activity changes due to neurofeedback (Dempster & Vernon, 2009):

- mean: changes in absolute values of frequency band mean amplitude (power spectra measures were $\log_{10}$-transformed to obtain normally distributed data), reflecting brief and temporally unstable increases over time from the learner.

GSR features

Sample rate: 100 Hz

Features extracted per subject :

- epoch_a: epochs array of each task = [[TIMESTAMP,SAMPLE_COUNTER, GSR_VALUE,], ... ,[*N*-epoch]]. Each epoch is 1 sample of GSR value, calculated from the 100 samples per second.

Tonic GSR Features, skin conductance level (scl) (Boucsein et al., 2012; Posada-Quintero & Chon, 2020):

- scl_mean: GSR mean per task.
- scl_std: GSR standard deviation per task.

Phasic GSR Features, skin conductance responses (scr) (Boucsein et al., 2012; Posada-Quintero & Chon, 2020):

- scr_nResp: the number of responses per task.
- scr_meanResp: mean of response amplitude per task.
- scr_sumResp: sum of response amplitude per task.

HRV features

Sample rate: 100 Hz

Features extracted per subject:

- epoch_a: epochs array of each task = [[TIMESTAMP,SAMPLE_COUNTER, BPM_VALUE,RR_VALUE], ... ,[*N*-epoch]]. Each epoch is 1 sample of RR value, calculated from the 100 samples per second.

Time Domain Features (Champseix, 2018; Malik et al., 1996):

Mostly used on long term recordings (24h) but some studies use some of those features on short term recordings like in our case, from 1 to 5 minutes window.

- mean_nni: The mean of RR-intervals.

- sdnn: The standard deviation of the time interval between successive normal heart beats (i.e., the RR-intervals).
- sdsd: The standard deviation of differences between adjacent RR-intervals
- rmssd: The square root of the mean of the sum of the squares of differences between adjacent NN-intervals. Reflects high frequency (fast or parasympathetic) influences on hrV (i.e., those influencing larger changes from one beat to the next).
- median_nni: Median Absolute values of the successive differences between the RR-intervals.
- nni_50: Number of interval differences of successive RR-intervals greater than 50 ms.
- pnni_50: The proportion derived by dividing nni_50 (The number of interval differences of successive RR-intervals greater than 50 ms) by the total number of RR-intervals.
- nni_20: Number of interval differences of successive RR-intervals greater than 20 ms.
- pnni_20: The proportion derived by dividing nni_20 (The number of interval differences of successive RR-intervals greater than 20 ms) by the total number of RR-intervals.
- range_nni: difference between the maximum and minimum nn_interval.
- cvsd: Coefficient of variation of successive differences equal to the rmssd divided by mean_nni.
- cvnni: Coefficient of variation equal to the ratio of sdnn divided by mean_nni.
- mean_hr: The mean Heart Rate.
- max_hr: Max heart rate.
- min_hr: Min heart rate.
- std_hr: Standard deviation of heart rate.

Frequency Domain Features (Champseix, 2018; Clifford, 2002; Malik et al., 1996):

Mostly used on short term recordings, from 1 to 5 minutes window.

- total_power: Total power density spectral
- vlf: variance (= power) in HRV in the Very low Frequency (.003 to .04 Hz by default). Reflect an intrinsic rhythm produced by the heart which is modulated primarily by sympathetic activity.
- lf: variance (= power) in HRV in the low Frequency (.04 to .15 Hz). Reflects a mixture of sympathetic and parasympathetic activity, but in long-term recordings, it reflects sympathetic activity and can be reduced by the beta-adrenergic antagonist propanolol.
- hf: variance (= power) in HRV in the High Frequency (.15 to .40 Hz by default). Reflects fast changes in beat-to-beat variability due to parasympathetic (vagal) activity. Sometimes called the respiratory band because it corresponds to HRV changes related to the respiratory cycle and can be increased by slow, deep breathing (about 6 or 7 breaths per minute) and decreased by anticholinergic drugs or vagal blockade.
- lf_hf_ratio: lf/hf ratio is sometimes used by some investigators as a quantitative mirror of the sympatho/vagal balance.
- lfnu: normalized lf power.
- hfnu: normalized hf power.

Self-Reports features

The reader can check out the digital forms in the following links:

- 1st questionnaire at T0 (pre-intervention): https://forms.gle/2uT7f7oH3pd4c9FD9

- 2nd questionnaire at Bin: https://forms.gle/nQNRQkBWEVtbKySo8
- 3rd questionnaire at Bout: https://forms.gle/k1zVwzwVacu7hBYRA

Traits (*TG)*

See the form online (1st questionnaire).

Sociodemographic

First, we converted options:

- a: 0h, b: 1-3h, c: 4-8h, d: 9-18h, e: >18h [hours per week]
- a: 0h, b: 1-3, c: 4-7, d: 8-14, e: >14 [frequency per week]

To points:

- a: 0, b: 1, c: 5, d: 15, e: 25

Then, summed each question score of the same domain.

Selected features for analysis:

- SOC_10: physical activity,
- SOC_11: physical exercise,
- SOC_12: games,
- SOC_13: technology,
- SOC_14: hobbies,
- SOC_15: emotional regulation,
- SOC_16: medication,
- SOC_17: addictions.

FFMQ

5 dimensions obtained by summing the items (describe, observe, nonjudge, actaware, nonreact) (Baer et al., 2008; Gregório & Gouveia, 2011):

(R) = reverse item

- Observe. "I notice the smells and aromas of things.".
- Describe. "I am good at finding words to describe my feelings."
- Actaware (acting with awareness). "I find myself doing things without paying awareness attention." (R)
- Nonjudge (nonjudging of inner emotions). "I think some of my emotions are bad or experience inappropriate and I should not feel them."(R)
- Nonreact (nonreactivity to inner emotions). "I perceive my feelings and emotions experience without having to react to them."

ERQ

2 dimensions obtained by summing the items (cognitive reappraisal, expressive suppression) (Lovibond & Lovibond, 1995; Vaz et al., 2014):

- Cognitive reappraisal. Where a person attempts to change how he or she thinks about a situation in order to change its emotional impact.
- Expressive suppression. “I keep my emotions to myself.” - where a person attempts to inhibit the behavioural expression of his or her emotions.

DASS

3 dimensions obtained by summing the items (stress, anxiety, depression) (Crawford & Henry, 2003; Pais-Ribeiro et al., 2004).

Sates (*SG)*

See the form online (2nd questionnaire).

TMS

2 dimensions obtained by summing the items (curiosity, decentering) (Lau et al., 2006):

- Decentreing: awareness of one’s experience with some distance and disidentification rather than being

carried away by one's thoughts and feelings.

- Curiosity: reflect awareness of present moment experience with a quality of curiosity.

POMS

4 dimensions obtained by summing the items (tension, fatigue, vigour, confusion) (Faro Viana et al., 2012):

- Tension: state of preoccupation and muscle tension.
- Fatigue: state of tiredness, inertia, boredom.
- Confusion: state of confusion.
- Vigour: state of energy, physical vigour and psychological. vigour

Framework self-perception (NFT)

See the form online (3rd questionnaire).

Selected features for analysis:

- NFT_1_1: success perception,
- NFT_1_2: difficulty perception,
- NFT_1_3: mental effort,
- NFT_1_5: success excitment,
- NFT_1_6: failure frustation,
- NFT_1_11: mental strategy influence,
- NFT_1_12: attention on mental strategy influence.

NOTES

[1] Endnotes example. These are important endnotes and definitions that can help the reader. These endnotes are referenced in the thesis by a superscript number.

[2] Homeostasis. Homeostasis is the range in each life is possible, i.e., the regulation of internal states aimed at maintaining conditions compatible with life (Man & Damasio, 2019). The processes of the Self (e.g., what we designate as valuable in terms of goods and actions) are directly or indirectly related to the possibility of maintaining a homeostatic range in our interior. Moreover, certain configurations of these processes within the homeostatic range are associated with "optimal" life regulation, while others are less efficient, and others are closer to the danger zone (which disease and death can set in). Humans diagnose these configurations through the detection system known as feelings, considered by Damasio the fundamental processes of consciousness: *"optimal ranges express themselves in the conscious mind as pleasurable feelings; dangerous ranges, as not-so-pleasant or even painful feelings"*. That is why feelings not only serve as somatic mind stream markers but also as barometers of homeostatic self-regulation (Damasio, 2010).

[3] Self-regulation/self-control: two terms that are used in literature related to the capacity of voluntary control and/or regulate the Self. For example, (Wood et al., 2014) uses self-control while (Tomas Ros et al., 2014) uses self-regulation.

[4] Mechanistic theory. The assumption that psychological processes and behaviours ultimately can be understood in the same way that mechanical or physiological processes are understood. Its explanations of human behaviour are based on the model or metaphor of a machine and invoke mechanical causality, reducing complex psychological phenomena to simpler physical phenomena. Also called mechanistic approach (APA, 2020).

[5] Attention control. Attention control is a core mechanism subdivided in: alerting (vigilance), orienting (selection) & conflict monitoring (executive): alerting, readiness in preparation for an impending stimulus, which includes tonic effects that result from spending time on a task (vigilance) and phasic effects that are due to brain changes induced by warning signals or targets; orienting, the selection of specific information from multiple sensory stimuli; conflict monitoring, monitoring and resolution of conflict between computations in different neural areas, also referred to as executive attention. Sustained attention: refers to the sense of vigilance during long continued tasks and may involve both tonic alerting and orienting. Selective attention: may involve either orienting (when a stimulus is present) or executive function (when stored information is involved) (Tang et al., 2015).

[6] Self-awareness. Awareness span refers to the variability of the contents available to attention and conscious processing. Awareness span ranges from narrow, focused attention directed at a singular content (e.g., in an intense mental activity) to broad, extended awareness embracing "all the things" in a single grasp (e.g., contemplating the horizon) (Vaitl et al., 2005). There exist different types of awareness (being conscious of something, making something into an object of conscious attention), like body awareness (body as an object of conscious attention), awareness of present-moment experiences, meta-awareness (making awareness itself an object of conscious attention), amongst others (Tang et al., 2015). Self-awareness (self as an object of conscious attention) refers to the self–world structure of human experience. In a reflective attitude, all experience is "mine," that is, related to the subject's self. In the flow of immediate experience, however, the degree of self-reference may largely vary from "forgetting oneself" in absorption or exaltation to an intensified feeling of one's unique being, "I,here and now." (Vaitl et al., 2005).

[7] Emotion regulation. Emotion regulation pertains to the processes involved in different aspects of the emotional processing, such as initiation, maintenance, modification, intensity or duration (Gross, 2014). The ability to regulate emotions is relevant for the maintenance of physical and mental well-being. Evidence has demonstrated that impaired emotion regulation is a attribute of multiple psychopathological conditions, particularly of internalizing disorders, such as anxiety or depression (Aldao et al., 2010).

[8] Priming. In cognitive psychology, the effect in which recent experience of a stimulus facilitates or inhibits later processing of the same or a similar stimulus. In repetition priming, presentation of a particular sensory stimulus increases the likelihood that participants will identify the same or a similar stimulus later in the test. In semantic priming, presentation of a word or sign influences the way in which participants interpret a subsequent word or sign (APA, 2020). The conjugations prime and primer are used to reflect the same concecpt.

[9] Theoretical Framework. Theories are formulated to explain, predict, and understand phenomena and, in many cases, to challenge and extend existing knowledge within the limits of critical bounding assumptions. The theoretical framework is the structure that can hold or support a theory of a research study. The theoretical framework introduces and describes the theory that explains why the research problem under study exists (Swanson & Chermack, 2014). Unless the scale is large enough, most theories are just hypotheses, however in this thesis we address more complex brain hypothetical components that need to be articulated (Damasio, 2010). Therefore, what we address can't be accounted only by a single hypothesis or a single mechanism, therefore the right term to designate our effort is the framework.

[10] Neurophenomenology: rigorous collection of first-person accounts of subjective experience through careful guiding and questioning from a researcher (Bagdasaryan & Le Van Quyen, 2013; E. Davelaar et al., 2016; E. J. Davelaar et al., 2018).

[11] Neuromodulation Strategy. Mental strategy, brain strategy or training strategy in this thesis are a synonym of neuromodulation strategy – a more appropriate term, because mental or even brain is somewhat limiting what voluntary neuromodulation can be, while neuromodulation is a more generic term that can encapsulate the entire spectrum of possible modulation strategies and also encapsulate trying-sensing processes.

[12] Online and offline BCI experiment. In a BCI setup, online refers to a real-time experiment where the data is processed piece-by-piece in a serial fashion (like an online algorithm) and can also be in a closed-loop design where the data is feedback to the system and updates it (e.g., NFT experiment). Offline, all the data from the experiment is processed in one chunk (e.g., calculate the baseline of an NFT experiment from a rest state task) (Nan et al., 2018).

[13] Self-referential processes. Self-referential processes are self-control mechanisms, such as attention to inner states, agency, cognitive control and self-awareness play an important role in gaining control over brain activity. Therefore, brain regions supporting interoceptive attention such as cingulate cortex, supplementary motor area, dorsomedial and lateral prefrontal areas and especially the insula, as a hub for self-referential processes, can be relevant for NF training because they are involved in the regulation of neuronal activity in many other regions of the brain, which may both favor or hinder NF learning (Manuel Ninaus, Kober, et al., 2013). Findings from a few recent studies seem to suggest that brain structures supporting self-referential processing might be affected

by mindfulness meditation. Evaluative self-referential processing is assumed to decrease as an effect of mindfulness meditation, whereas awareness of present-moment experiences is thought to be enhanced.(Tang et al., 2015).

[14] Locus of control (LOC). This concept was developed in Rotter's theory of social learning. The fundamental idea is that a specific behaviour in a specific situation can be explained by subjective reinforcement of performance results, and by subjective expectations, that a specific result will appear as an action result. Persons with an external LOC perceive the results of their actions not as a result of their own performance but as a result of good or bad luck, coincidence, destiny, not predictable or dependent by other people. Persons with an internal LOC perceive reinforcement and events, that follow ones owns actions, as dependent to their own performance or personality. For a detailed assessment of the LOC characteristics of a person there exist several different questionnaires that allow to quantify the LOC with respect to various aspects (Burde & Blankertz, 2006; Manuel Ninaus, Kober, et al., 2013).

[15] Mental & brain state: Mental State(psychological): pattern of behaviour activity (thinking, mind wandering, rumination). Brain State(neurophysiological): reliable pattern of activity and/or connectivity in multiple large–scale networks. Brain System is the hardware. While the mental system is more the software (J. Gruzelier et al., 2010; Haynes & Rees, 2006; Lotte et al., 2013).

[16] Agency. When participants believe to have control over a NF protocol, they refer to the feeling of causing the action, meaning that the participants believe they are able to control the NF in an appropriate way. In the literature this phenomenon is called agency. Agency plays an important role in self-consciousness and tells us whether an action is caused by ourselves or other entities (Manuel Ninaus, Kober, et al., 2013).

[17] Type I processes reflect the automatic, capacity-free, effortless and context- specific information processing such as for instance trying to open the office door with the home key because one has been thinking about dinner. Moreover, type I processes are usually unconscious and difficult to control by self-instruction. Type II processes reflect the activity of a supervisory attention system, specialized in monitoring and regulating the activity in other cognitive systems. Type II processes are usually in the centre of our focus of attention, are regulated mainly by self-instruction and are fundamental for executive functions and metacognitive abilities. Accordingly, control beliefs are much more related to the function of the type II processes while the heuristics regulating most of our cognitive activity and behaviour are type I processes (Wood et al., 2014).

[18] Tonic and phasic oscillations: Oscillations are differentiated according to whether they are measured during rest, in which case they are labeled tonic oscillations (topography diffuse), or whether they are related to specific task-conditions or stimuli, under which condition they are referred to as phasic oscillations (topography regionally-specific). Tonic changes occur over the life cycle in response to circadian rhythms, fatigue, distress, neurological disorders. Phasic oscillations reflect changes in oscillatory activity in response to an event and exhibit a specific topography (Enriquez-Geppert et al., 2017).

[19] Control theory: Interdisciplinary branch of engineering that deals with the behaviour of dynamical systems with inputs, and how their behaviour is modified by feedback. The cornerstone of control theory is the feedback loop (Tomas Ros et al., 2014).

[20] Interoception. Interoception is the body-to-brain axis of sensations that originates from the internal body and visceral organs. It plays a unique role in ensuring homeostasis, allowing human beings to experience and perceive the state of their bodies at any one time. The sense of the internal state of the body. This can be both conscious and non-conscious. This is important for maintaining homeostatic conditions in the body and, potentially, aiding in self-awareness (Craig, 2003; Vaitl, 1996).

[21] Data-driven and hypothesis-driven feature extraction. In general, feature extraction can be performed in a data-driven manner, for instance with BCI aiming at the control of specific devices. However, with neurofeedback as a method to alleviate symptoms or enhance cognitive and behavioural performance, feature selection is usually based on hypothesis/evidence for an association between oscillations and cognition or symptoms.

[22] Power spectrum density calculated using Welch's method. Calculates periodograms for a sliding window over the time dimension, then averages them together for each channel/epoch. n_fft: The length of FFT used. n_overlap: The number of points of overlap between segments. n_per_seg Length of each Welch segment (windowed with a Hamming window). Note that n_overlap <= n_per_seg<=n_ftt.

[23] Actichamp shielding mode: actiCHamp supports two modes of recording: The default mode and the active shielding mode. The shielding mode is available in Recorder and can be activated in PyCorder in the source code. It can be used with the referential and reference-free montage, and depending on the combination, the shielding mode suppresses the environmental electrical noise slightly differently Environmental noise can have different characteristics depending on their source (AC power lines, computers, displays, wireless equipment). The critical distinctive features are the mode (normal mode and common mode) and the distribution across the EEG channels. AC line noise usually is common mode noise but shows a large variation regarding the topographical distribution: The frontal positions are often more affected than occipital channels (by facing a computer screen, for example). As a rule of thumb, the better the noise fulfills the common mode characteristics and the more uniform the distribution is, the better shielding mode works. In contrast, for channels that are less affected by common mode noise, shielding mode can cause an over-compensation, which results in more noisy signals, since the assumptions of the noise characteristics are not fulfilled. In any case the data are modified: Either reversible (referencing) or irreversible (active shielding). Thus, for using a reference channel (i.e., referencing) together with the active shielding mode, the characteristics of the noise and the environment have to be considered. The best way of selecting the appropriate strategy is to careentirey evaluate the recorded pilot data in both time and frequency domain. Even though actiCHamp is highly immune to environmental electrical noise due to the flexible handling of referencing and shielding mode, the best way is to eliminate electrical noise at the source (Brain Products GmbH, 2019).

[24] Study designs. Within-subjects (or repeated-measures) study design: the same person tests all the conditions (i.e., all the user interfaces). Between-subjects (or between-groups) study design: different people test each condition, so that each person is only exposed to a single user interface.

[25] Ifilter, is a causal forward-in-time filtering only, similar to a real-life electronic filter. It can't be zero-phase. It can be linear-phase (symmetrical FIR), but usually isn't. Usually it adds different amounts of delay at different frequencies. It filters data along one-dimension with an IIR or FIR filter. This works for many fundamental data types (including Object type). The filter is a direct form transposed implementation of the standard difference equation.