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A subject-specific neurofeedback approach for cognitive enhancement

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Thesis submitted in fulfillment of the requirements for the degree of Doctor of Philosophy in Computer Science and Systems Engineering

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Resumen

La técnica de neurofeedback (NF) permite el aprendizaje de la auto-regulación de la actividad cerebral, por la cual los usuarios pueden aprender a modificar (hasta un cierto grado) patrones de la actividad cerebral. Un punto clave del NF en la práctica es la técnica de registro de la actividad cerebral, donde el electroencefalograma (EEG) es la más usada debido a que es no invasiva, portátil y tiene una buena resolución temporal.

La investigación en neurociencia ha reportado en repetidas ocasiones la relación de determinadas funciones cognitivas y desórdenes psiquiátricos con las oscilaciones del EEG. Por lo tanto, no es sorprendente que la regulación de estas oscilaciones conlleve efectos en comportamiento. Por ejemplo, muchos estudios han aplicado esta técnica de NF para aumentar funciones cognitivas como memoria de trabajo, atención y habilidades visuoespaciales, usualmente evaluadas en usuarios sanos. Además se ha aplicado NF para el tratamiento de desórdenes psiquiátricos tales como el trastorno por déficit de atención con hiperactividad (TDAH), depresión, epilepsia y tinitus, entre otros.

El EEG es una señal no estacionaria que presenta una variabilidad inherente entre usuarios en los correlatos de procesos mentales. Sin embargo, la gran mayoría de técnicas de NF desarrolladas hasta el momento son genéricas en el sentido de que no se adaptan a los patrones individuales de EEG de cada usuario. En este sentido ha habido una tendencia en los últimos años hacia el uso de técnicas de NF específicas por medio de la adaptación de algunos métodos involucrados en el procedimiento. Esta tesis aborda el diseño de una técnica de NF dentro de un framework unificado, y muestra su viabilidad por medio de la implementación de tres estudios de NF consistentes en el incremento de la actividad en alpha superior para mejora cognitiva, evaluada en usuarios sanos, pacientes con depresión mayor y niños con TDAH.

Una disciplina que viene a la mente cuando pensamos en cómo individualizar la técnica de NF son las interfaces cerebro-computador (BCIs). Las BCIs es una tecnología reciente cuyo objetivo es abrir un canal de comunicación entre un humano y un dispositivo usando únicamente la actividad cerebral para mejor la calidad de vida de personas con graves deficiencias mo-

toras. Un punto clave de las BCIs es que los métodos de procesamiento de la señal se adaptan a cada usuario y momento de utilización de la tecnología. Esto se logra usualmente por medio de una fase de calibración ejecutada antes de la operación en línea. En esta fase de calibración los usuarios realizan tareas mentales que permiten medir algunos correlatos de EEG que son usados para calcular filtros individualizados, por ejemplo en términos de filtrado de artefactos y detección de tareas mentales. Después estos filtros se aplican en línea al EEG para decodificar las tareas mentales, accionando en consecuencia el dispositivo.

Tomando el framework de BCI como referencia, proponemos los siguientes métodos individualizados: (1) un método de filtrado de artefactos en tiempo real (usando separación ciega de fuentes) para eliminar los artefactos de los patrones cerebrales de interés; (2) un método novedoso para la individualización de los patrones cerebrales de acuerdo a la combinación de registros de EEG en dos condiciones (estado de reposo y tarea activa); (3) un método para calcular el nivel de trabajo de los patrones cerebrales (baseline) por sujeto y sesión; y (4) una variedad de métodos y métricas para evaluar los efectos del NF en los patrones cerebrales (post-análisis).

Para evaluar la viabilidad y validez experimental de esta técnica de NF, llevamos a cabo una implementación de un protocolo de NF basado en el incremento de la actividad en alpha superior para mejora cognitiva, evaluada en tres estudios distintos de NF involucrando usuarios sanos, pacientes con depresión y niños con TDAH. Estos estudios investigaron si individuos sanos, con depresión y ADHD son capaces de incrementar la potencia en alpha superior por medio de NF y, si es así, si estos efectos están relacionados con efectos en comportamiento (rendimiento cognitivo o escalas clínicas).

1. El primer estudio investigó los efectos de una única sesión de NF en usuarios sanos (N = 19) en un diseño experimental con falso feedback. Este estudio mostró un incremento en la potencia en alpha superior en la tarea activa (inmediatamente después del NF) así como un incremento en potencia en alpha superior durante la tarea de rotación mental (intervalo pre-estímulo), únicamente para el grupo experimental. Ambos grupos mejoraron en rendimiento cognitivo, con una mejora superior para el grupo experimental. Sin embargo una única sesión parece insuficiente para producir diferencias significativas entre grupos.

2. El segundo estudio investigó los efectos de ocho sesiones de NF en pacientes con depresión (N = 60) en un estudio controlado. Este estudio mostró un incremento en la potencia en alpha superior en la tarea activa (pre-post estudio) para el grupo experimental. Estos efectos no

estuvieron restringidos espacialmente o espectralmente al parámetro de NF. Se encontró un incremento de actividad a nivel de las fuentes cerebrales en alpha para el grupo experimental, localizado en el giro cingulado anterior (sgACC, BA 25). El grupo experimental mostró un incremento en rendimiento así como un incremento en velocidad de procesamiento medido por un test de memoria de trabajo después del NF, sugiriendo por tanto que los síntomas cognitivos de pacientes con depresión pueden aliviarse por medio de este procedimiento.

3. El tercer estudio investigó los efectos de 18 sesiones de NF en niños con TDAH (N = 20) en un estudio preliminar no controlado. Este estudio mostró un incremento en la potencia (relativa y absoluta) en alpha superior en la tarea activa (pre-post estudio). Mientras que los cambios pre-post estudio estuvieron restringidos mayormente a la banda alpha superior, los efectos dentro de la sesión mostraron un decremento en potencia absoluta en las bajas frecuencias (se debe notar que los niños con TDAH usualmente tienen un exceso de actividad en bajas frecuencias). Los padres indicaron una mejora clínica en los niños con respecto a inatención e hiperactividad/impulsividad, y los tests neuropsicológicos mostraron una mejora en memoria de trabajo.

En resumen, estos resultados muestran que la técnica de NF se adaptó a la gran variabilidad de los patrones cerebrales entre sujetos y sesiones. Además, estas tres poblaciones fueron capaces de auto-regular los patrones cerebrales con una consecuente mejora tanto en rendimiento cognitivo y como en escalas clínicas (en el caso de niños con TDAH). Aunque la principal contribución de esta tesis está en los métodos y en la implementación de una técnica individualizada de NF, los estudios de NF aquí presentados son novedosos en sí mismos y los resultados que se extraen de ellos constituyen una contribución añadida de esta tesis.

Abstract

Neurofeedback (NF) promotes the learning of the self-regulation of brain activity, where subjects can learn to shape (to a certain degree) some patterns of brain activity. A key practical point of NF is the recording technique of brain activity, where the electroencephalogram (EEG) is the most widely used one as it is non-invasive, portable and presents a good temporal resolution.

Neuroscience research has repeatedly reported the relation of cognitive functions and some psychiatric disorders to EEG oscillations. Thus, it is not surprising that the regulation of EEG oscillations yields behavioral effects. For instance, a large body of research has applied NF for the enhancement of cognitive functions such as working memory, attention and visuospatial abilities, usually applied to healthy subjects. NF has been also applied for the treatment of psychiatric disorders such as attention-deficit/hyperactive disorder (ADHD), depression, epilepsy and tinnitus, among others.

EEG is a non-stationary signal that presents an inherent variability among subjects in the EEG correlates of brain processes. However, the large majority of NF procedures developed to date are subject-generic in the sense that they are not adapted to the individual EEG patterns of each subject. In this direction, there has been a trend in recent years towards the use of subject-specific NF procedures by adapting some methods involved in that procedure. This thesis addresses the design of a subject-specific NF approach in a unified framework, and shows its feasibility by implementing three different NF studies of upper alpha up-regulation for cognitive enhancement in healthy subjects, patients with major depressive disorder and children diagnosed with ADHD.

One discipline that comes to mind when thinking about how to individualize EEG-based NF procedures is the brain-computer interfaces (BCIs). BCIs is a recent technology whose objective is to open a communication channel between a human and a device using only brain activity to improve the quality of life of people with severe motor disability. A key point of BCIs is that the signal processing methods are adapted for each subject and time of use of the technology. This is commonly achieved by a calibration phase

before the online operation. In this calibration phase, the subjects perform metal tasks that allow to measure some EEG correlates that are used to compute subject-specific filters, for example in terms of filtering the EEG artifacts and detecting the mental tasks. These filters are then applied during the online operation phase to the ongoing EEG to decode the mental tasks, actuating the devices accordingly.

Taking the BCI framework as a reference, we propose the following individualized methods: (1) a real-time artifact filtering method (using blind source separation) to remove the artifacts from the brain patterns of interest; (2) a novel method for the individualization of the brain patterns according to the combination of EEG recordings in two conditions (resting state and task-related activity); (3) a method for computing the baseline working level of the brain patterns per subject and session; and (4) a variety of methods and metrics to assess the effects of NF on the brain patterns (post-analysis).

In order to demonstrate the feasibility and experimental validity of this subject-specific NF approach, we carried out an implementation of a NF protocol of upper alpha up-regulation for cognitive enhancement, evaluated in three different NF studies involving healthy subjects, depressed patients and ADHD children. These studies investigated whether healthy, depressed and ADHD individuals could learn to increase the individual upper alpha power by means of NF, and whether these effects were related to behavioral effects on either cognition or clinical outcome.

1. The first study investigated the effects of a single NF session on healthy participants (N = 19) following a sham-controlled experimental design. This study showed increased upper alpha power in task-related activity (immediately after training), as well as increased pre-stimulus upper alpha power during the execution of a mental rotation task, apparent only for the experimental group. Both groups improved cognitive performance, with a more prominent improvement for the experimental group. However a single session seems to be insufficient to yield significant differences between groups.

2. The second study investigated the effects of eight NF sessions on depressed patients (N = 60) in a controlled study. This study showed increased upper alpha power in task-related activity (pre-post study) for the experimental group, not spatially or spectrally restricted to the trained parameter. A current density increase appeared at brain source level in alpha for the experimental group, localized in the subgenual anterior cingulate cortex (sgACC, BA 25). The experimental group showed increased performance as well as improved processing speed in

a working memory test after the training, thus suggesting that the cognitive symptoms of depressed patients could be alleviated by this type of procedure.

3. The third study investigated the effects of 18 NF sessions on ADHD children (N = 20) in a preliminary uncontrolled study. This study showed increased relative and absolute upper alpha power in task-related activity (pre-post study). While the pre-post study effects were mainly restricted to upper alpha, within-session analysis showed an absolute power decrease in slow-frequency oscillations (note that ADHD children commonly show an excess of slow-frequency activity). Parents rated a clinical improvement in children regarding inattention and hyperactivity/impulsivity, and neurophysiological tests showed an improvement in working memory.

In summary, these results show that the NF technique was able to accommodate the large variability of the brain patterns among subjects and over sessions. In addition, these three populations were able to self-regulate the targeted brain patterns with a consequent improvement in cognitive performance and clinical outcome (in the case of ADHD children). Although the main contribution of the thesis is on the methods and on the implementation of the subject-specific NF procedure, the NF studies herein presented are novel and the results extracted from them constitute an added contribution of this thesis.

Contents

Abbreviations

ACC	Anterior cingulate cortex
ADHD	Attention-deficit/hyperactivity disorder
BCI	Brain-computer interface
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
IAF	Individual alpha frequency
MDD	Major depressive disorder
NF	Neurofeedback
rTMS	Repetitive transcranial magnetic stimulation
SMR	Sensorimotor rhythm
UA	Upper alpha
WM	Working memory

1 | Introduction

No feedback, no learning. Feedback is the return of information an entity gets as a result of its actions, and it is a key factor to promote learning through operant conditioning (Skinner, 1938). Behavior can be reinforced or inhibited by means of positive and/or negative feedback evaluating the actual actions. These principles can be followed to promote the learning of the self-regulation of brain activity within a paradigm called neurofeedback (NF), where subjects can learn to shape (to a certain degree) some patterns of brain activity. The rationale of NF is to record the brain activity, to process the signal to decode the brain patterns of interest, and to provide the subjects with real-time feedback covarying with the brain patterns. A key practical point is the recording technique of brain activity, where the electroencephalogram (EEG) is the most widely used one as it is non-invasive, portable and presents a good temporal resolution.

Neuroscience research has repeatedly reported the relation of cognitive functions and some psychiatric disorders to EEG oscillations (Başar and Güntekin, 2008, Klimesch et al., 2007, Klimesch, 1999). Thus, it is not surprising that the regulation of EEG oscillations yields behavioral effects. For instance, a large body of research has applied NF for the enhancement of cognitive functions such as working memory, attention and visuospatial abilities, usually applied to healthy subjects (Gruzelier, 2013, Vernon, 2005). NF has been also applied for the treatment of psychiatric disorders such as attention-deficit/hyperactive disorder (ADHD), depression, epilepsy and tinnitus, among others (Niv, 2013, Gruzelier, 2013).

EEG is a non-stationary signal that presents an inherent variability among subjects in the EEG correlates of brain processes (Niedermeyer and da Silva, 2005). However, the large majority of NF procedures developed to date are subject-generic in the sense that they are not adapted to the individual EEG patterns of each subject. In this direction, there has been a trend in recent years towards the use of subject-specific NF procedures by adapting (individualizing) some methods involved in this procedure (Hanslmayr et al., 2005, Zoefel et al., 2011, Nan et al.,

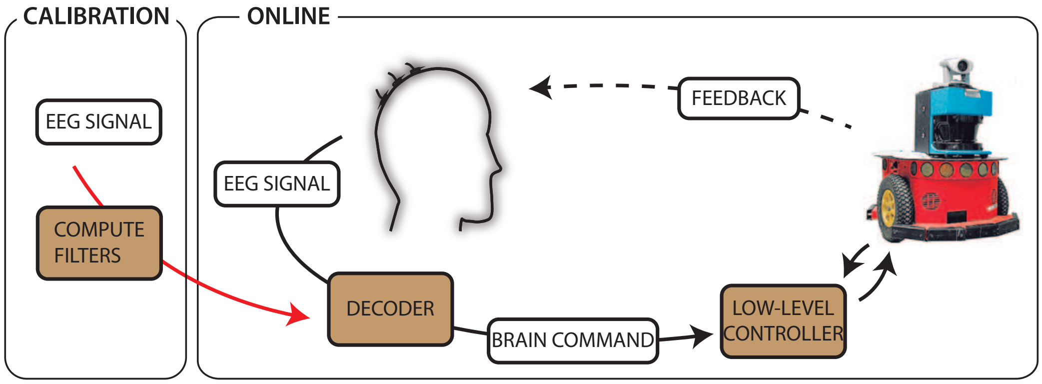

Figure 1.1: BCI for controlling of a robotic device. First, in the calibration phase a filter is computed according to the features of the subject's EEG signal. Subsequently, this filter is used during online operation to decode the ongoing EEG signal and finally the subject receives feedback (visual in this example) as the actions executed by the device.

2012, Alexeeva et al., 2012). This thesis addresses the design of a subject-specific NF approach in a methodological unified framework, and shows its feasibility by implementing three different NF studies of upper alpha up-regulation for cognitive enhancement in healthy subjects, patients with major depressive disorder and children diagnosed with ADHD.

One discipline that comes to mind when thinking about how to individualize EEG-based NF procedures is the brain-computer interfaces (BCIs). BCIs is a recent technology whose objective is to open a communication channel between a human and a device using only brain activity (Wolpaw et al., 2002) to improve the quality of life of people with severe motor disability (Millán et al., 2010). Some applications using the EEG as the recording technique include a speller for communication (Birbaumer et al., 1999), robotic devices for motor substitution (Iturrate et al., 2009) and neuroprosthetic devices for motor rehabilitation (Ramos-Murguialday et al., 2013).

A key point of BCIs is that the signal processing methods are adapted for each subject and time of use of the technology. This is commonly achieved by a calibration phase before the online operation. In this calibration phase, the subjects perform metal tasks that allow to measure some EEG correlates that are used to compute subject-specific filters, for example in terms of filtering the EEG artifacts and detecting the mental tasks. These filters are then applied during the online operation phase to the ongoing EEG to decode the mental tasks, actuating the devices accordingly (Figure 1.1). For instance, in a BCI application for controlling a robot, the system initially trains a classifier to detect the P300 event-related potential in the ongoing EEG, whose appearance is associated with a location of the space. During online operation the subject focuses on a location and a visual stimulation process elicits the P300 potential that enables the classifier to detect the subject's desired location to navigate to, finally sending the relevant movement commands to the robot (Escolano et al., 2012a)[1]. Note that this calibration process is carried out every time the BCI is used, thus the outcome of this phase are specific filters for each subject and session.

Taking the BCI framework as a reference, there are some issues that a subject-specific NF procedure might take into account:

1. EEG artifacts such as eye blinking and muscular artifacts may interfere with the brain patterns of interest (Delorme et al., 2007). The large majority of these artifacts are dependent on each subject and time of use of the technology (session in the context of NF).

2. EEG brain patterns present an inherent inter-subject variability (Haegens et al., 2014, Neuper et al., 2005). This inter-subject variability might be even higher in some clinical populations such as ADHD (Barry et al., 2003, Lansbergen et al., 2011b).

3. EEG brain patterns present an inherent inter-session variability within each subject (Haegens et al., 2014, Angelakis et al., 2004). This variability could be due to the non-stationary nature of the EEG (Niedermeyer and da Silva, 2005), to the physiological state of the subjects and the task being performed (Klimesch, 1999), or could be a consequence of the self-regulation (through NF) of these patterns.

4. As a consequence of addressing the three previous points with new signal processing methods, post-analysis methods that aggregate the EEG results in a subject- and session-specific way should be developed.

The objective of this thesis is to design a subject-specific NF approach addressing the previous issues in a unified framework. We propose the following individualized methods: (1) a real-time artifact filtering method (using blind source separation) to remove the artifacts from the brain patterns of

[1] In the initial stage of this thesis we developed a BCI telepresence system to provide subjects with presence in remote environments through a mobile robot (Escolano et al., 2012a). That system relied on a P300-based BCI and a mobile robot with autonomous navigation and camera orientation capabilities. We further extended this system to the teleoperation of multiple robots (Escolano and Minguez, 2011) and performed initial tests in patients with amyotrophic lateral sclerosis (Escolano et al., 2010).

interest; (2) a novel method for the individualization of the brain patterns according to the combination of EEG recordings in two conditions (resting state and task-related activity); (3) a method for computing the baseline working level of the brain patterns per subject and session; and (4) a variety of methods and metrics to assess the effects of the NF on the individualized brain patterns targeted by the NF, the effects on non-targeted brain patterns (specificity of the procedure), the effects during the execution of cognitive tasks, and the effects at brain source level.

In order to demonstrate the feasibility and experimental validity of this subject-specific NF approach, we carried out an implementation of a NF protocol of upper alpha up-regulation for cognitive enhancement, evaluated in three different NF studies involving healthy subjects, depressed patients and ADHD children. These studies investigated whether healthy, depressed and ADHD individuals could learn to increase the individual upper alpha power by means of NF, and whether these effects were related to behavioral effects on either cognition or clinical outcome.

1. The first study investigated the EEG and behavioral effects of a single NF session on healthy participants. Ten participants were assigned to the experimental group and nine to a sham-feedback control group. A NF protocol of upper alpha power enhancement over parieto-occipital locations was performed. This study showed increased upper alpha power in task-related activity (immediately after training), as well as increased pre-stimulus upper alpha power during the execution of a mental rotation task, apparent only for the experimental group. Both groups improved cognitive performance, with a more prominent improvement for the experimental group. However a single session seems to be insufficient to yield significant differences between groups.

2. The second study investigated the EEG and behavioral effects of eight NF sessions on depressed patients. 40 patients were assigned to the experimental group and 20 to a non-interventional control group. A NF protocol of upper alpha power enhancement over parieto-occipital locations was performed. This study showed increased upper alpha power in task-related activity (pre-post study) for the experimental group, not spatially or spectrally restricted to the trained parameter. A current density increase appeared at brain source level in alpha for the experimental group, localized in the subgenual anterior cingulate cortex (sgACC, BA 25). The experimental group showed increased performance as well as improved processing speed in a working memory test after the training, thus suggesting that the cognitive symptoms of depressed patients could be alleviated by this type of procedure.

3. The third study investigated the EEG and behavioral effects of 18 NF sessions on ADHD children. 20 children were assigned to the experimental group (preliminary uncontrolled study). A NF protocol of relative upper alpha power enhancement over fronto-central areas was performed. This study showed increased relative and absolute upper alpha power in task-related activity (pre-post study). While the pre-post study effects were mainly restricted to upper alpha, within-session analysis showed an absolute power decrease in slow-frequency oscillations (note that ADHD children commonly show an excess of slow-frequency activity). Parents rated a clinical improvement in children regarding inattention and hyperactivity/impulsivity, and neurophysiological tests showed an improvement in working memory.

In summary, this thesis proposes the design of a subject-specific NF approach, which was subsequently implemented in a NF protocol of upper alpha up-regulation targeting cognitive enhancement in three different populations (healthy users, depressed patients and ADHD children). The results show that the technique was able to accommodate the large variability of the brain patterns among subjects and over sessions. In addition, these three populations were able to self-regulate the targeted brain patterns with a consequent improvement in cognitive performance and clinical outcome (in the case of ADHD children). Although the main contribution of the thesis is on the methods and on the implementation of the subject-specific NF approach, the NF studies herein presented are novel and the results extracted from them constitute an added contribution of this thesis.

1.1 Structure and publications

The contents of the thesis are organized as follows.

- **Chapter 2** provides some background information. We provide an overview of the EEG focusing on alpha and the individual alpha frequency, and the link between alpha and cognitive performance. We also provide an overview of NF containing its historical perspective, current protocols for cognitive enhancement, and the technical and methodological limitations of current NF techniques.

- **Chapter 3** presents the subject-specific NF technique developed in this thesis, which is currently protected by an European patent (Escolano et al., 2014a).

- **Chapter 4** investigated the NF effects in healthy subjects. This work was presented in Escolano et al. (2012b) and extended for a journal publication (Escolano et al., 2014d).

- **Chapter 5** investigated the NF effects in depressed patients. This work was presented in Escolano et al. (2013) and extended for a journal publication (Escolano et al., 2014b).

- **Chapter 6** investigated the NF effects in ADHD children. This work was published in Escolano et al. (2014c).

- Finally, **chapter 7** presents the conclusions of this thesis.

2 | Background information

This thesis develops a NF technique in terms of subject-specific signal processing methods and implements a NF protocol of upper alpha up-regulation for cognitive enhancement. Section 2.1 provides an overview of the EEG, focusing on alpha activity and the individualization of alpha frequency due to its well-known inter- and intra-subject variability, and we then describe the link between alpha and cognitive performance. Finally, Section 2.2 describes the principles of NF, provides a brief historical perspective, reports an overview of current NF protocols for cognitive enhancement, and reports the technical and methodological limitations of current NF techniques.

2.1 EEG

The EEG reflects rhythmic fluctuations in the excitability of underlying neural populations (Niedermeyer and da Silva, 2005). EEG oscillations are commonly transformed to the frequency domain and divided into a set of frequency bands: delta, theta, alpha, beta and gamma (Figure 2.1). The activity in these frequency bands has been found to be related to brain states and functions (Niedermeyer and da Silva, 2005). As a brief summary, delta (0.5-4 Hz) mostly dominates deeper sleep states. Theta (4-7 Hz) displays characteristic patterns in states of drowsiness and sleep, and plays a maturational role in infancy and childhood (Niedermeyer and da Silva, 2005). Interestingly, an excess of theta activity in fronto-central sites is the most reliable EEG pattern in ADHD children (Barry et al., 2003). Alpha (8-12 Hz) is the dominant frequency in the human EEG and predominates during wakefulness relaxation (Klimesch, 1999). Beta (12-30 Hz) is associated with motor processing, showing a power decrease over sensorimotor areas during motor action (Pfurtscheller and Lopes da Silva, 1999). Low amplitude beta is associated with active cognitive engagement (Niedermeyer and da Silva, 2005). Faster oscillations as gamma ($>$ 30 Hz) have not been as much studied as slower oscillations. These oscillations are modulated by cognitive processes such as attention and memory, and they have been suggested to be linked to binding and feature integration mechanisms (Senkowski et al., 2007).

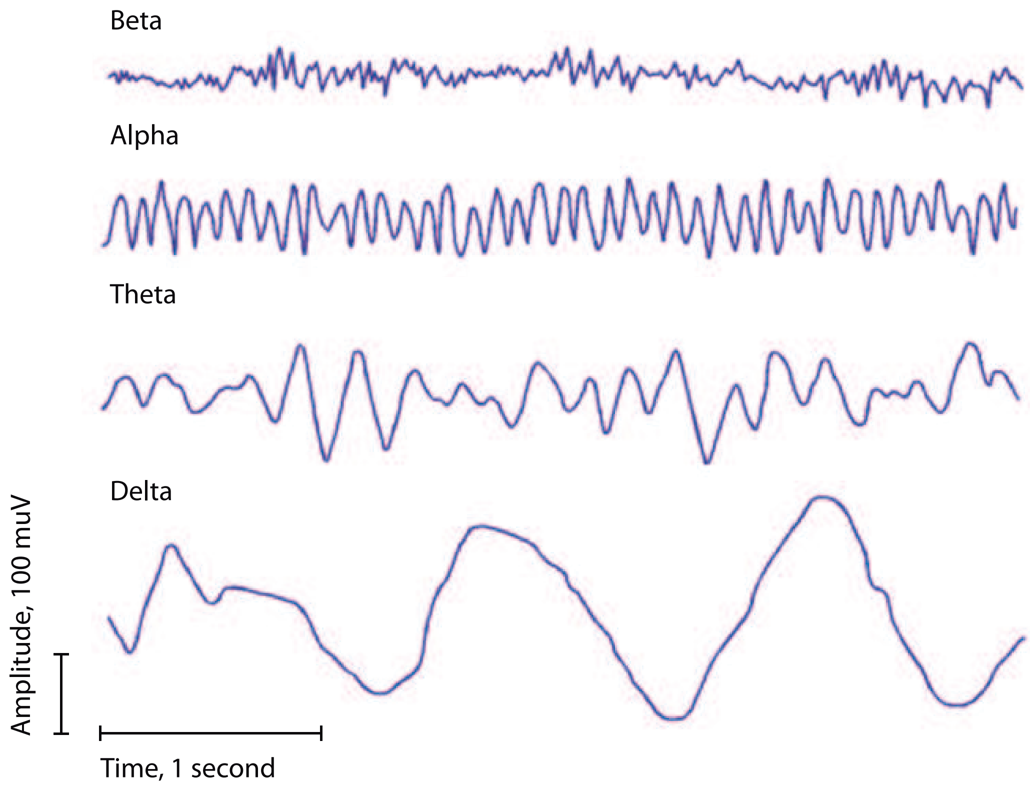

Figure 2.1: Common EEG frequency bands: delta activity during deep sleep, theta in drowsy state, alpha in wakefulness relaxation state, and beta in wakefulness state.

2.1.1 Alpha activity

Alpha rhythm is the dominant frequency in the human EEG, first recorded in the 1920s (Berger, 1929). This rhythm is characterized by a "peak" in the spectral analysis in the (8-12 Hz) frequency range, and predominates during wakefulness relaxation with closed eyes, best observable over posterior areas of the scalp (Klimesch, 1999). The parieto-occipital alpha rhythm is attenuated by eye opening, visual stimuli and by increased attentiveness (Palva and Palva, 2007). It also responds to motor tasks (Pfurtscheller and Lopes da Silva, 1999) and to different cognitive demands such as attention and memory tasks (Klimesch, 1999).

Although there is not an universally accepted theory about the functional role of alpha oscillations, the understanding of these oscillations has greatly advanced over the last decades. Initially, alpha activity was interpreted as a rhythm of “cortical idling” of areas that do not process sensory information or motor output. This was proposed due to the observation of increased alpha power in the primary hand area during visual processing or during foot movement (Pfurtscheller et al., 1996). However, this hypothesis was challenged due to the findings of increased alpha power (in posterior areas) with memory load during the retention interval in working memory tasks (Jensen et al., 2002, Jensen and Mazaheri, 2010).

One of the most accepted hypothesis to date is that alpha reflects the active inhibition of regions not relevant for the task being performed (Klimesch et al., 2007, Jensen and Mazaheri, 2010). Thus, the increased alpha power during the retention interval in the aforementioned example would prevent interference (according to this hypothesis) from posterior areas, usually involved in visual tasks and irrelevant during the retention interval in a working memory task (Jensen and Mazaheri, 2010).

2.1.2 Individual alpha frequency

Alpha frequency presents a hight inter- and intra-subject variability (Haegens et al., 2014, Angelakis et al., 2004). For instance, the alpha frequency has been shown to differentiate groups of adults with higher memory performance from those with lower performance (Klimesch et al., 1993). The alpha frequency has been found to be correlated to behavioral states and cognitive traits (Angelakis et al., 2004). It has also shown an increase (approximately 1 Hz) from resting state to the N-back working memory paradigm, thus suggesting an increase with cognitive demands (Haegens et al., 2014).

Several methods have been proposed to compute the alpha frequency (Goljahani et al. (2012) contains a review). The most used method is the peak frequency, which localizes the frequency at which the alpha peak occurs in the EEG power spectra, referred to as the Individual Alpha Frequency (IAF, Klimesch, 1999). Recent evidences suggest that the alpha band can be divided into three sub-bands (using the IAF as an anchor point) with different functional significance (Klimesch, 1999). Specifically the three sub-bands are lower alpha 1, (IAF-4, IAF-2) Hz; lower alpha 2, (IAF-2, IAF) Hz; and upper alpha, (IAF, IAF+2) Hz. Figure 2.2 displays these three alpha sub-bands. Lower alpha sub-bands were observed to respond to general attention demans, whereas upper alpha was observed to respond to cognitive performance in memory tasks. For instance, upper alpha has shown to be the most sensitive one to the encoding and processing of semantic information, distinguishing between good and bad performers in a semantic memory task

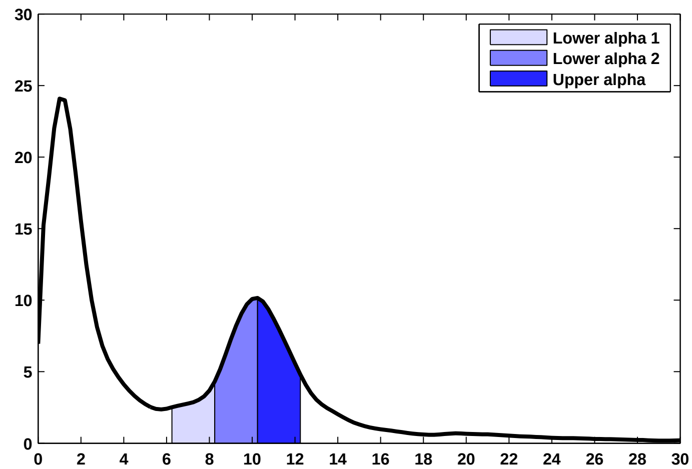

Figure 2.2: EEG power spectra. The three alpha sub-bands are depicted, which were individualized according to the Individual Alpha Frequency (IAF). In this example IAF is 10.25 Hz.

(Klimesch, 1999).

2.1.3 Alpha & cognitive performance

Alpha activity is hypothetized to be related to cognitive performance by actively inhibiting irrelevant information (Klimesch et al., 2007, Jensen and Mazaheri, 2010). This hypothesis has been experimentally validated by studies combining neuromodulation techniques (such as repetitive transcranial magnetic stimulation, rTMS) and EEG (Sauseng et al., 2009, Thut and Miniussi, 2009). rTMS is a neuromodulation technique that delivers magnetic pulses through a coil located above the head inducing electrical currents (at specific frequencies), thus stimulating cortical areas (Thut and Miniussi, 2009). For example, Sauseng et al. (2009) performed a visuospatial working memory task in which a memory array displayed either on the right or left visual hemifield had to be retained. During the retention interval of the task, rTMS was delivered (at 10 Hz to increase alpha amplitude) in either contralateral or ipsilateral parietal sites to the items to be retained. Increased performance was found when rTMS was applied ipsilaterally to the items to be retained, suggesting that enhanced alpha oscillations effectively suppressed irrelevant information. In addition, the relationship between alpha and working memory was recently proposed (Freunberger et al., 2011) due to the fact that the inhibition of irrelevant information (filtering efficiency to working memory contents) is a key factor in working memory performance (McNab and Klingberg, 2007, Vogel et al., 2005).

These evidences may explain the observed cognitive enhancement after alpha-based NF training (Zoefel et al., 2011, Hanslmayr et al., 2005, Nan et al., 2012, Ros et al., 2014) although certainly more research is needed to elucidate the mechanisms of action of NF. Similarly, recent SMR-based NF studies have proposed that increased SMR activity may reduce sensorimotor interference and thereby promote cognitive processing (Kober et al., 2014). In particular, the protocol implemented in this thesis targeted the upper alpha power. Recent alpha-based NF studies for cognitive enhancement are following this line (Hanslmayr et al., 2005, Zoefel et al., 2011, Nan et al., 2012). This trend towards targeting upper alpha (rather than the entire alpha band) seems to be due to evidences showing that upper alpha responds to cognitive performance in memory tasks (Klimesch, 1999). This decision may increase the specificity and replicability of the effects on the electrophysiology as well as to increase the behavioral effects with regard to generic alpha-based protocols. In this line, Klimesch et al. (2003) study reported the superiority of regulating upper vs lower sections of alpha in cognitive performance. They applied rTMS during the pre-stimulus interval of a mental rotation task in either upper or lower alpha, and improved performance was only found when stimulating upper alpha. To the best of our knowledge there are not studies performing such a comparison in NF literature.

2.2 Neurofeedback

The aim of neurofeedback (NF) is to allow the subjects to self-regulate brain activity. NF consists in measuring the brain activity and providing the subjects with real-time feedback covarying with the brain patterns of interest. Thus, the subjects may acquire a certain degree of awareness of the underlying brain processes and learn to regulate them (Congedo et al., 2004). EEG is the most used recoding technique in NF literature to date since it is non-invasive, portable and presents a good temporal resolution.

2.2.1 Historical perspective

The ability to self-regulate brain electrical activity in humans was first demonstrated in the 1960s, targeting alpha oscillations at occipital locations (Kamiya, 1969). At the end of the 1960s, the findings of Prof. Sterman in animal studies became a milestone in NF research (see Sterman (2000) for a review). He found that cats that learned to up-regulate SMR were resistant to seizures when exposed to a toxic (monomethylhydrazine). From that moment the term SMR was coined to refer to the activity recorded in the (12-15 Hz) frequency range over the sensorimotor cortex. These findings showed the physiological correlates of SMR and led to a series of human studies.

The first clinical study of NF was conducted in epileptic patients in 1972 (Sterman and Friar, 1972). Prof. Sterman also found that SMR was maximal during periods of quiet wakefulness and desynchronized during motor action (Sterman, 2000). In line with the latter finding, Prof. Lubar hypothetized that SMR up-regulation would lead to a reduction in hyperactive symptoms in ADHD (Lubar and Shouse, 1976). Since then, ADHD is the disorder that has received most attention in the field of NF (Arns et al., 2014). Due to the observations of abnormal brain oscillations in ADHD children when compared to controls, commonly an excess of theta activity and a reduction of beta activity (Barry et al., 2003), the SMR protocol rapidly evolved to suppress the theta/beta ratio simultaneously (Lubar, 1991). Protocols based on the theta/beta ratio have been used in ADHD for four decades, following many slight variations such as simultaneously enhancing SMR (Arns et al., 2013, Loo and Makeig, 2012, Monastra et al., 2006).

Despite the early beginnings of EEG-based NF, it was for many years mostly applied in clinical settings (e.g., by clinical practitioners in the USA) and largely abandoned by the research community due to a lack of scientific validation (Gruzelier, 2013). As an example, a recent paper (Keizer et al., 2010) states: "even though it is true that the widespread advertisement and application of NF methods in clinical domains is not always based on firm scientific grounds...". Nonetheless, there has been a regrowth of interest in the last decade, with the focus on the scientific validation using state-of-the-art engineering methods. Some examples include the use of high-quality acquisition devices, multisite recordings, deeper evaluation of the effects on the EEG (Gruzelier, 2014), novel techniques to compute the feedback (such as the activity at brain source level by EEG inverse solutions, Congedo et al., 2004) and the evaluation of the NF effects in brain function by the combination of neuroimaging techniques and EEG (Ros et al., 2010, 2013). In addition, NF is being re-discovered by the application of new recording methods such as real-time fMRI, which presents a high spatial resolution from the whole brain, including subcortical areas (Weiskopf, 2012).

2.2.2 NF protocols

The regulation of EEG oscillations has yielded behavioral effects on cognitive performance, as well as on clinical symptoms in some psychiatric disorders, due to the fact that cognitive functions and some psychiatric disorders are related to EEG oscillations (Başar and Güntekin, 2008, Başar et al., 2000, Klimesch et al., 2007, Klimesch, 1999). Thus many different NF protocols have been evaluated in NF literature, most of them targeting power spectral features (Gruzelier, 2013). The rationale behind NF in psychiatric disorders is commonly to "normalize" abnormal brain oscillations in comparison to a non-clinical population (Başar and Güntekin, 2008), which is hypothetized to improve the clinical outcome. As examples of the clinical populations included in this thesis, a frontal alpha asymmetry has been found in depressed patients (Henriques and Davidson, 1991), thus most of the NF protocols for depression try to reduce that asymmetry (Choi et al., 2011). Regarding ADHD, most of the NF protocols try to reduce the theta power (Arns et al., 2014) since an excess of theta activity is a commonly reported EEG pattern in ADHD (Barry et al., 2003).

Since we implemented a NF protocol of upper alpha up-regulation for cognitive enhancement, we below summarize a variety of protocols targeting cognitive enhancement. Note that the regulation of slow-cortical potentials is a well-known protocol (Birbaumer, 1999), which was mainly oriented to the treatment of ADHD (Strehl et al., 2006), and it will not be covered here.

Gamma is suggested to be related to local feature integration and top-down control of memory retrieval. Keizer et al. (2010) performed a protocol aimed at enhancing gamma (36-44 Hz) activity over an occipital location (Oz). Increased gamma activity was apparent, as well as increased flexibility in handling (selectively retrieving) episodic bindings (i.e., bindings between two features of visual objects, such as their shape and location).

Frontal midline theta is suggested as a correlate of executive functioning. Enriquez-Geppert et al. (2014) performed a protocol aimed at enhancing the frontal midline theta. Experimental group was compared to a sham-feedback control group. A theta enhancement was found, however the impact in cognitive performance was not assessed. Wang et al. (2013) performed a protocol aimed at enhancing the frontal midline theta. They investigated its effects in older and younger participants, and were compared to sham-feedback control groups. A significant increasing trend of theta amplitudes appeared. Both older and younger participants showed improved attention, whereas only the older participants showed improved working memory.

Theta/beta protocols with/without SMR enhancement are considered to be a clinically effective treatment for ADHD (Arns et al., 2014). The application of this kind of protocols to ADHD led to its evaluation in healthy users for cognitive enhancement (see Gruzelier (2013) and Vernon (2005) for reviews). Positive results in cognitive performance have been extensively reported elsewhere, however most of these studies relied on small sample sizes with unproper control conditions, reported controversial behavioral results across studies, and provided no clear evidence of the effects on the EEG.

SMR enhancement is being recently re-evaluated, advancing towards a scientific validation. Kober et al. (2014) performed a protocol aimed at enhancing SMR over a central location (Cz) in a sham-controlled study. The experimental group showed linear increases in SMR power over training runs, which was associated with behavioral improvements in memory and attentional performance. In addition, increasing SMR led to increased amplitude in N100 and P300 event-related potentials during a short-term memory task. Finally, reduced connectivity between motor and visual processing areas was found after training. Interesting similar studies have evaluated some psychological aspects of this protocol. Witte et al. (2013) showed that participants whose confidence in control over technical devices is high achieved lower control over SMR. Kober et al. (2013) evaluated the effect of different mental strategies on the ability to regulate SMR (and gamma, not reviewed here). They found the higher effects on SMR for those participants reporting no specific mental strategies at the end of the study, thus suggesting that SMR-based NF is associated with implicit learning mechanisms.

Alpha-based protocols have received much attention in the last decade. Hanslmayr et al. (2005) reported a single-session training in which the participants performed combined trials of theta suppression and upper alpha enhancement (within-subjects design). Those participants who succeeded in enhancing upper alpha activity improved performance in a mental rotation task. Zoefel et al. (2011) performed five sessions of upper alpha enhancement over parieto-occipital locations. Responders showed improved performance in a mental rotation task in comparison to a non-interventional control group. Nan et al. (2012) performed 20 sessions of upper alpha enhancement over a central location (Cz). Participants showed increased performance in a short-term memory task (digit span) in comparison to a non-interventional control group. Alexeeva et al. (2012) performed eight sessions of upper alpha enhancement over a parietal location (Pz). Participants were compared to a sham-feedback control group. Only participants in the experimental group with a low baseline alpha frequency showed improved cognitive performance in a variety of cognitive functions. Ros et al. (2014) performed a single-session training aimed at reducing the alpha (8-12 Hz) power in the right primary motor cortex (crossover experimental design). Shortly after training participants performed a serial reaction time task with their non-dominant (left) hand. Participants who received NF immediately prior the task exhibited faster reaction times, suggesting a faster rate of learning.

2.2.3 Technical and methodological limitations of NF

We next summarize some technical and methodological limitations of current NF techniques at both the online signal processing and the post-analysis of the effects on the EEG. Note that we do not intent to cover the extensive NF literature but rather to mention some of the major limitations.

Calibration and online signal processing

Some NF techniques record the EEG in only a reduced set of feedback locations (Nan et al., 2012, Alexeeva et al., 2012, Keizer et al., 2010). This restricts the potential signal processing methods to be subsequently applied to compute the feedback as well as the methods to be applied in the EEG post-analysis. Regarding the artifact filtering, some techniques do not have protection against artifacts or they implement a time-domain threshold for artifact detection, interrupting the feedback for some seconds when an artifact is detected (Zoefel et al., 2011). In the first case the accuracy of the feedback may be compromised and therefore hinder the learning of the self-regulation process, and in the second case the effective time of training may be reduced. In both cases it would be desirable filtering the artifacts rather than detecting them. Other techniques include either low frequency or high frequency oscillations (or both) as additional feedback for the subjects in order to try to reduce the blinking/eyes movement or muscular artifacts, respectively (Kober et al., 2014). This decision may make the task more complex for the subjects. A major concern of this thesis is the individualization of the signal processing methods to target subject-specific brain patterns. Traditional NF approaches use subject-generic filters to the decode the brain patterns of interest, commonly fixed frequency bands (Vernon, 2005). This approach may not to be able to deal with the EEG variability among subjects and sessions. Finally, some techniques set the baseline manually according to the trainer experience (Vernon, 2005), which may restrict the replicability of the results (training is dependent from the trainer).

Post-analysis of the effects on the EEG

NF literature lacks an extensive analysis of the electrophysiological effects, especially in non-trained EEG brain patterns, and during the execution of cognitive tasks. As already mentioned, some NF techniques record the EEG in only a reduced set of feedback locations (Nan et al., 2012, Alexeeva et al., 2012, Keizer et al., 2010). This restricts the potentials methods to be applied and reduces the spatial resolution of the post-analysis. In fact many studies assess the effects on the trained brain patterns only. In addition, few metrics are commonly used to assess these effects. A recent review (Gruzelier, 2014) encouraged the use of several metrics such as the effects after the study (pre-post study effects), the immediate effects after the training trials (within-session effects) and the effects over the sessions (trend or learning curve over sessions). There are few examples of studies assessing the specificity of the NF effects on the EEG by measuring the effects on non-trained patterns, and those studies commonly restrict the analysis to a small number of pre-determined frequency bands (Zoefel et al., 2011, Nan et al., 2012). Furthermore, there are few studies assessing the effects of the NF on the EEG recorded during the execution of cognitive tasks. Some examples include the analysis of the EEG power time-course during the execution of a mental rotation task (Hanslmayr et al., 2005) and the analysis of event-related potentials during a short-term memory task (Kober et al., 2014).

3 | The development of the neurofeedback technique

This chapter describes the developed subject-specific NF technique. We first present the related problems and common concerns regarding NF techniques with an overview of the state of the art. We then present the design and implementation of a NF protocol of upper alpha up-regulation. Note that slight variations of this protocol (feedback locations and whether feedback was computed in absolute or relative power) were used in the three NF studies included in this thesis. On one hand, the NF protocol applied to healthy and depressed participants aimed to increase the absolute upper alpha power over parieto-occipital locations (chapters 4 and 5). On the other hand, the protocol applied to ADHD children targeted the relative upper alpha power over fronto-central locations (chapter 6).

3.1 Common concerns

Artifact filtering. We refer as artifacts to the electrical signal recorded along with the EEG signal but that originates from non-cerebral sources. Biological artifacts such as eye blinks and muscular activity contaminate the EEG and can thus hinder the brain patterns of interest. This is the reason why artifact filtering is a common and important problem in EEG research (Delorme et al., 2007). The blinking artifact presents the stronger effects in low frequency oscillations (1-3 Hz) and may interfere higher frequencies as well, specially in frontal locations of the scalp, and is a natural body system with high occurrence rate. The muscular artifact induces strong (20-60 Hz) activity mainly at temporal locations (Delorme et al., 2007). In relation to NF literature, some techniques do not have protection against artifacts or they implement a time-domain threshold for artifact detection, interrupting the feedback for some seconds when an artifact is detected (Zoefel et al., 2011). Others include low and high frequency oscillations as additional feedback so the subjects can potentially learn to reduce the blinking and muscular artifacts, respectively (Kober et al., 2014). In the first case the accuracy of the feedback might be compromised, in the second case the effective time of training might be reduced, and in the third case it might make the task more complex for the subjects and seems not well suited for some artifacts (e.g., eye blinking is a natural body system).

Inter-subject variability of brain patterns. The EEG is a highly non-stationary signal that presents an inherent variability from subject to subject (Haegens et al., 2014, Neuper et al., 2005, Barry et al., 2003). As an example, Figure 3.1 displays the EEG power spectra of two subjects (depressed patient and ADHD child), illustrating the high variability in brain patterns, i.e., alpha frequency is around 10 Hz for the depressed patient and around 7.5 Hz for the ADHD child. This makes that most EEG systems need to adapt the technology to a particular subject as in BCIs, commonly executing a calibration step before the online operation (Pfurtscheller and Neuper, 2001). This individualization seems a "natural" approach to deal with the inter-subject variability. Most NF procedures do not target subject-specific brain patterns (Ros et al., 2014, Kober et al., 2013, Vernon, 2005), however there is a trend in alpha-based NF procedures in recent years towards the individualization of the alpha frequency (Zoefel et al., 2011, Hanslmayr et al., 2005, Nan et al., 2012, Alexeeva et al., 2012).

Inter-session variability of brain patterns over NF training. The NF seeks for the self-regulation of some brain patterns of interest. The temporal evolution of these patterns (dynamics) over training sessions presents a high variability. As an example, Figure 3.1 displays the EEG power spectra of two subjects over NF sessions, illustrating the high inter-session variability, i.e., alpha power (for each subject) shows an increase over the course of the training program. This variability could be due to the non-stationary nature of the EEG (Niedermeyer and da Silva, 2005), to the physiological state of the subject and the task being performed (Klimesch, 1999), or could be a consequence of the self-regulation of these patterns. In this line, some studies have investigated the NF outcome depending on the mental strategy (Kober et al., 2013, Nan et al., 2012) and the confidence in the technology (Witte et al., 2013). Similarly, there is a growing interest in BCIs for neurophysiological predictors of performance (Blankertz et al., 2010). However, in both BCI and NF the factors influencing the outcome are unclear to date. The inter-session variability has been taken into account by many NF procedures. For example, traditional techniques adapted the baseline manually

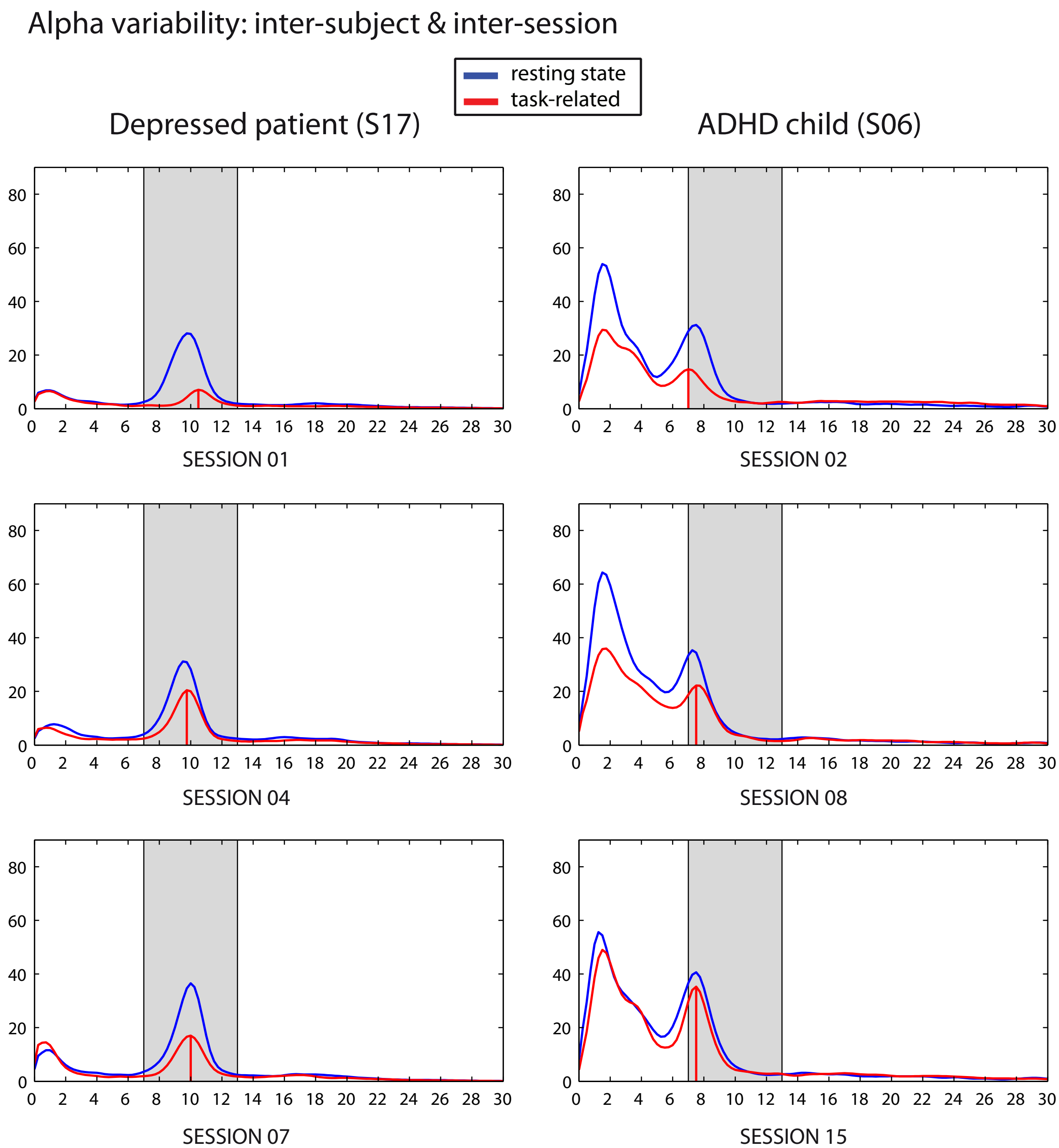

Figure 3.1: EEG power spectra of two subjects (a depressive patient and an ADHD child) over three NF sessions (at the beginning, middle, and end of the study). Blue line depicts resting state activity whereas red line depicts task-related activity. Gray area denotes the traditional alpha (7-13 Hz) range.

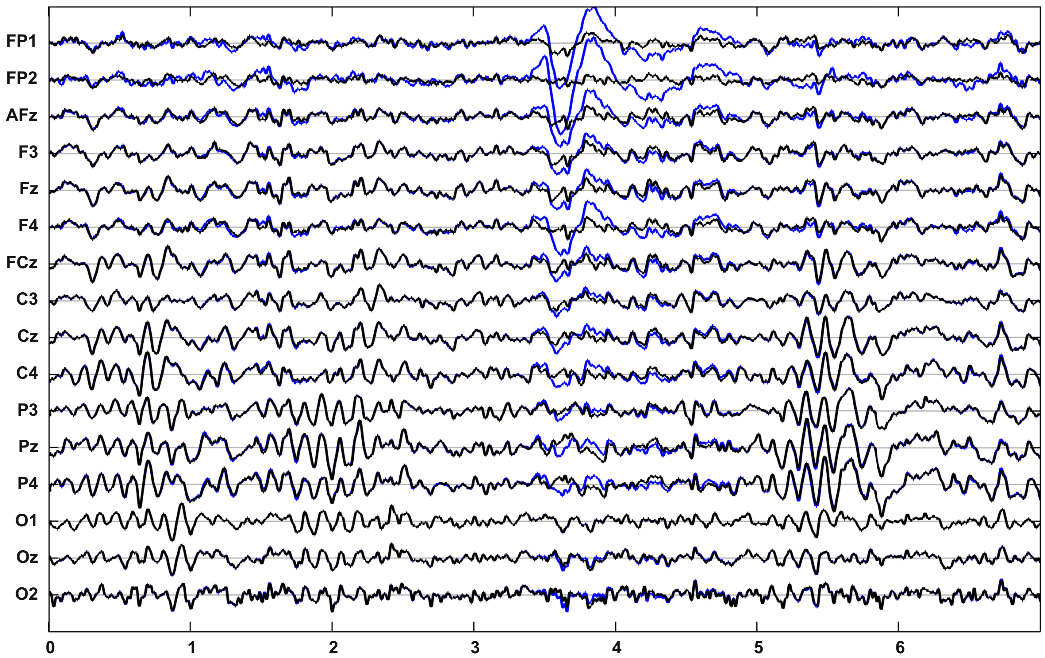

Figure 3.2: EEG signal (7 seconds) recorded from 16 electrodes. Raw signal is depicted in blue color, showing blinking artifacts, mostly apparent in anterior locations. ICA-filtered signal is superimposed in black color.

according to the trainer experience (Demos, 2005). This may restrict the replicability of the results (experimenter dependent) and it makes difficult to implement a double-blind experimental design. Recent NF procedures perform an automatic inter-session calibration within each session (Zoefel et al., 2011, Kober et al., 2014, Nan et al., 2012, Alexeeva et al., 2012).

3.2 Design

Artifact filtering. We designed an individualized real-time artifact filtering method using blind source separation (Hyvarinen, 1999). This method is well suited for blinking artifacts as they present a spatial pattern over the scalp. We re-computed this filter for each subject and session, this way the filter accommodates for not only the individual EEG patterns of each subject but also for other sources of variability such as slight differences in the sensors position. Figure 3.2 illustrates the result of this filtering. Filtering these artifacts can provide the subjects with more accurate feedback and more time of effective feedback (with regard to the detection strategy) in order to favor the learning of the self-regulation process.

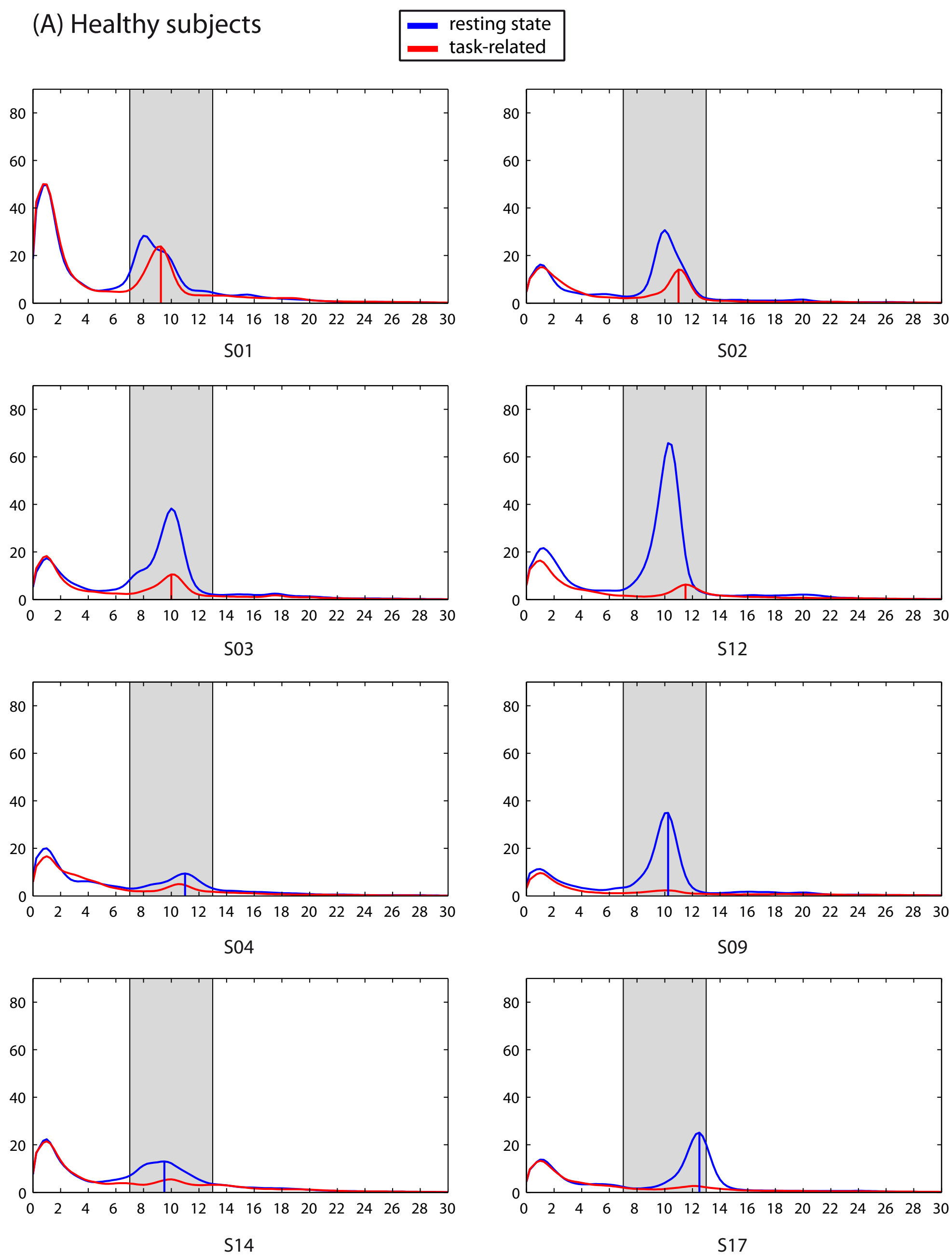

Figure 3.3: EEG power spectra over posterior locations of healthy subjects. Blue line depicts resting state activity whereas red line depicts task-related activity. Gray area denotes the traditional alpha (7-13 Hz) range. IAF was computed in alpha range, and it is shown as a vertical line, either in blue or red color, depending on whether it was computed in resting state or task-related activity, respectively.

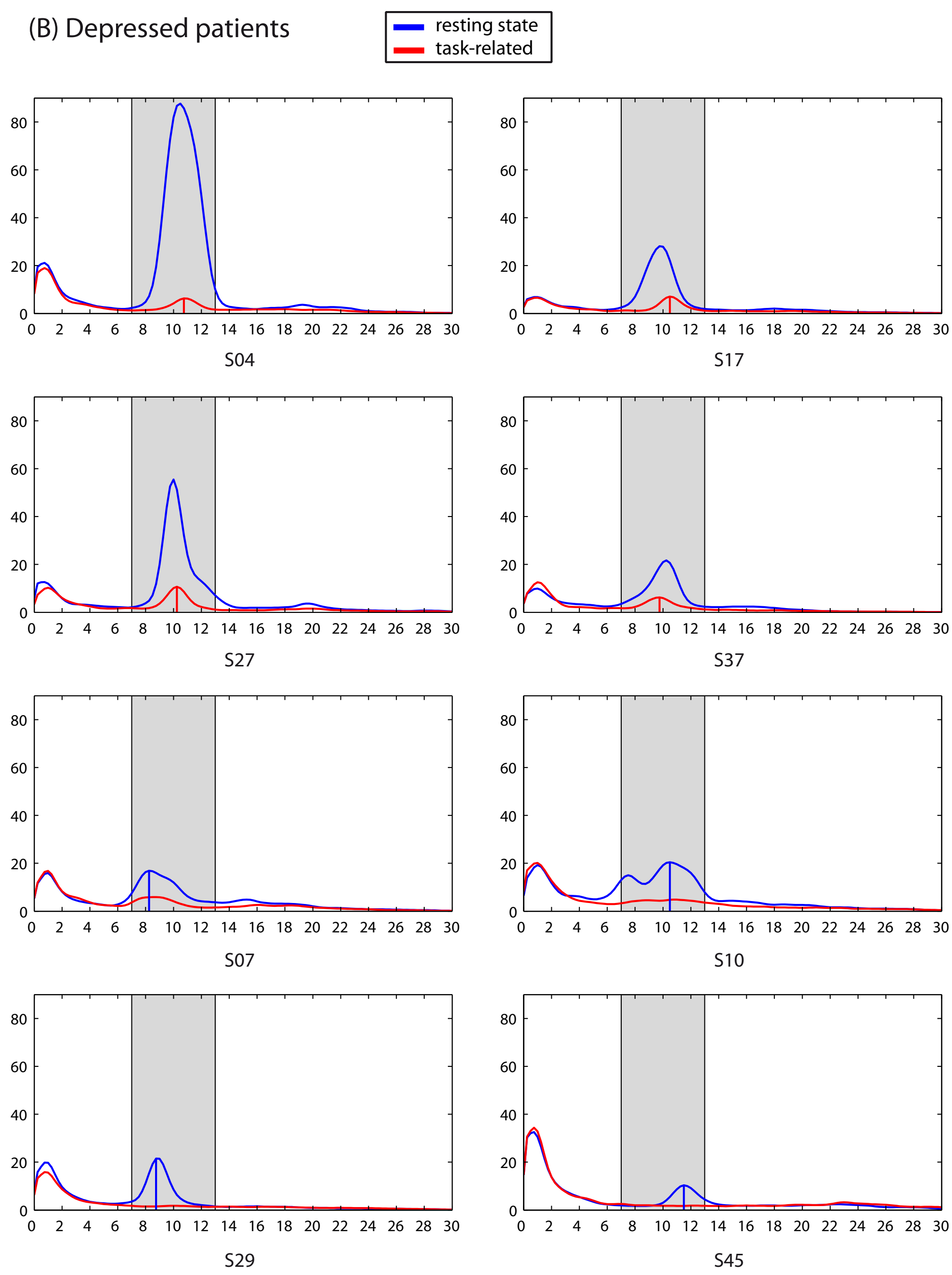

Figure 3.4: EEG power spectra over posterior locations of depressed patients.

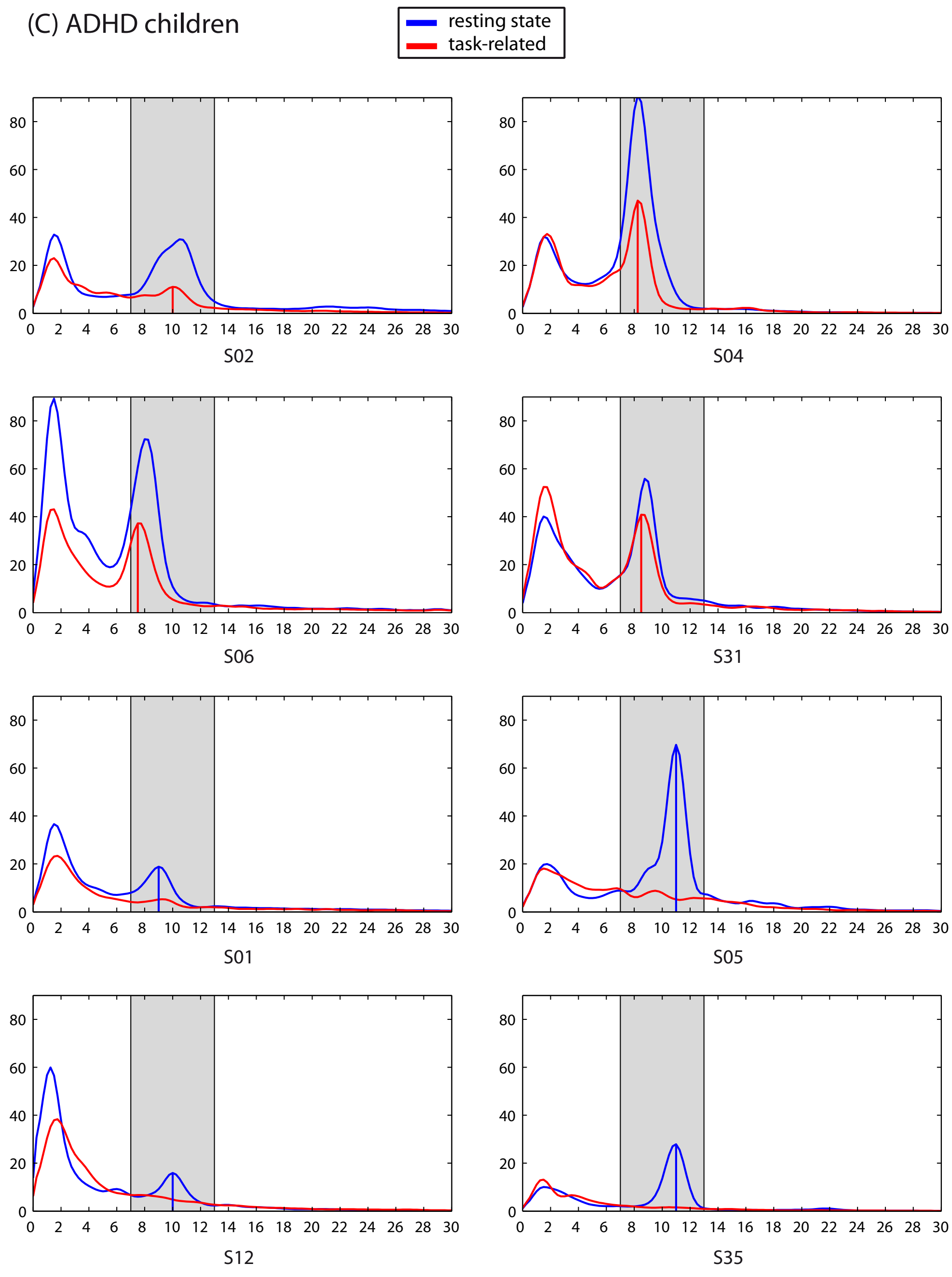

Figure 3.5: EEG power spectra over posterior locations of ADHD children.

Inter-subject variability of alpha frequency. Alpha frequency has shown a high inter-user variability (Haegens et al., 2014, Klimesch, 1999), which may be even higher when dealing with some clinical populations such as ADHD (Barry et al., 2003, Lansbergen et al., 2011b). We designed a novel method for the individualization of the alpha frequency according to the combination of EEG recordings in two conditions (resting state and task-related activity). This method first computes the alpha frequency in task-related activity and, in those cases in which a clear alpha peak is not shown in the EEG power spectra, the alpha frequency is computed in resting state activity instead. This method may better detect the alpha frequency in comparison to strategies used in literature either using resting state or task-related activity only. Some procedures compute the alpha frequency in resting state conditions (Hanslmayr et al., 2005, Nan et al., 2012, Alexeeva et al., 2012), which may not take into account the inter-task variability of alpha frequency (Haegens et al., 2014). Other procedures compute it in task-related activity (Zoefel et al., 2011), which may throw misleading errors in some subjects due to the well-known alpha attenuation phenomenon during active brain processing (Klimesch, 1999).

Figures 3.3, 3.4 and 3.5 illustrate this method. These figures show the EEG power spectra averaged across parieto-occipital locations, measured in resting state and task-related activity. EEG data from several participants of the studies are displayed, including healthy subjects, depressed patients and ADHD children. The first two rows (within each figure) show cases in which the alpha frequency could be accurately identified in task-related activity. Note that a subset of these subjects (e.g., healthy subjects 1, 2 and 12) display a high inter-task variability, showing faster alpha frequency in task-related activity than in resting state, which is in line with previous findings (Haegens et al., 2014). The last two rows show cases in which the alpha frequency was computed in resting state since no clear peak could be found in task-related activity. It is remarkable that some ADHD children showed a slow alpha peak (around 8 Hz) as found in other studies (Lansbergen et al., 2011b), suggesting that the individualization of brain patterns might be of special interest for this disorder.

Inter-session variability of upper alpha power. Alpha oscillations have shown to respond to many different physical or mental tasks (Klimesch, 1999). We designed a method for computing the baseline working level of the NF per subject at the beginning of each session. This way the technique can take into account the inter-session variability of the EEG (dynamics). This is in line with recent NF procedures performing an automatic adjustment of baseline activity (Zoefel et al., 2011, Kober et al., 2014, Hanslmayr et al., 2005, Nan et al., 2012, Alexeeva et al., 2012).

3.3 Implementation

We below describe the two phases that compose the NF technique: calibration and online training. Note that the calibration step was performed immediately before the online training within each session. As already mentioned, we implemented two slightly different NF protocols of upper alpha power upregulation. These protocols followed the same NF technique in terms of EEG acquisition process, artifact filtering, individualization method of the upper alpha band, power computation, and mapping between the power values and feedback. The only difference between them was the set of locations from which the feedback was computed, and whether the power was measured in absolute or relative units.

3.3.1 Phase 1: Calibration

Participants performed two EEG screenings at the beginning of each session. The first one was recorded in eyes closed resting state and participants were instructed to stay in a state of relaxed wakefulness. The second one (eyes open task-related activity) was recorded during the execution of a sustained attention task. During this task, participants faced a computer screen showing a square that changed saturation color randomly from gray to red or blue (gradually), and they were instructed to count the number of saturation changes from gray to red as a cognitive challenge.

The calibration step computed three elements from the two EEG screenings: (1) an ICA-based filter for the blinking artifacts, (2) the frequency range of the upper alpha band, and (3) the baseline for the online training (as well as the lower and upper limits). Recall that these elements were re-computed for each session to deal with the inter-session variability. This procedure is below detailed:

Artifact filtering. We automatically filtered out the blinking component from the task-related activity by Independent Component Analysis (ICA), using the FastICA algorithm (Hyvarinen, 1999). The blinking component was automatically detected by a time-domain threshold in the component space (the component with the most number of samples $> 75\mu V$ in prefrontal locations). We filtered out this blinking component and we then removed the 1-s epochs with amplitude larger than $200\mu V$ at any electrode.

Power computation. EEG power was then computed in each EEG screenings after the artifact filtering through a short-term fast Fourier transform (FFT) with 1 s hamming window, 30 ms of overlapping, and zero-padded to 1024 points (0.25 Hz resolution). Relative power was computed as the absolute power divided by the averaged power for each time window in the (1-30 Hz) range (for the NF protocol applied to ADHD children only).

Individual Alpha Frequency (IAF) computation. The IAF was computed for each electrode on the EEG power spectra of task-related activity as the frequency bin with the maximum power value in the extended (7-13 Hz) alpha range (Klimesch, 1999). Note that when no prominent alpha peak was found, the IAF was computed on resting state instead. We considered a prominent alpha peak in the (7-13 Hz) band when the maximum power value in that interval was higher than power in surrounding frequency bins. We finally defined the upper alpha (UA) band as the 2 Hz frequency interval starting in IAF, i.e., the (IAF, IAF+2) Hz interval (Klimesch, 1999).

Baseline. Finally, the baseline was computed in task-related activity as the mean upper alpha power averaged across the feedback electrodes, and $(5th - 95th)$ percentiles established the lower and upper limits, respectively.

3.3.2 Phase 2: Online training

Figure 3.6 displays the online training phase. First, the ongoing EEG data was online filtered from blinking artifacts through the aforementioned ICA filter, computed in the calibration phase. Please note that the calibration phase was performed at the beginning of each session, thus this ICA filter was re-computed for each session. An UA power value was computed each 30 ms through the same FFT algorithm and averaged across the feedback electrodes. Then, a linear mapping was used to convert between the UA power and the square color (see color scale in Figure 3.6). Power values above the baseline were displayed in a red color scale with increasing saturation. Similarly, power values below the baseline were displayed in a blue color scale. The color scales ranged from 0% saturation (baseline in gray color) to 100% saturation in both blue and red color scales set by the lower and upper limits, respectively. Finally, a visual feedback was displayed every 30 ms on a computer screen in the form of a square with changing saturation colors. No additional information was displayed during training.

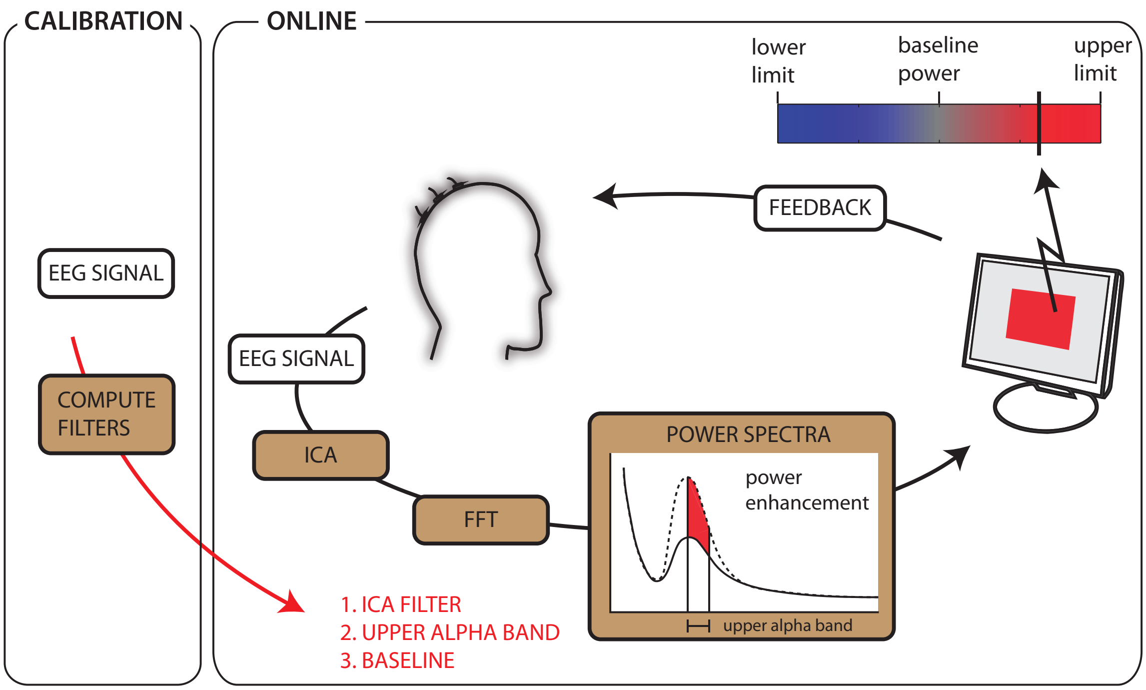

Figure 3.6: Online training. This technique gets three inputs from the calibration phase: ICA filter, the individual upper alpha band and the baseline. EEG data is ICA-filtered from blinking artifacts and FFT-transformed to the frequency domain. Then, the UA power is computed and compared to the baseline. If the current UA power is higher than the baseline a positive feedback is displayed on a computer screen in the form of a red-colored squared. UA power values lower than the baseline are displayed in a blue color scale.

4 | The effect of a single session of NF in healthy subjects

4.1 Introduction

This chapter investigates the effects of a single-session subject-specific NF procedure (25 minutes of training) for cognitive enhancement, which follows a double-blind sham-controlled experimental design with healthy subjects. The NF procedure focused on up-regulating the individual upper alpha power measured over the parieto-occipital area of the scalp. Non-specific factors were minimized by including a sham-feedback control group and by the short duration of the training. EEG analysis measured the effects on resting state and task-related activity immediately pre- and post- NF and one day after, as well as during training. Also, the effects on the event-locked EEG recorded during the pre- and post- executions of a mental rotation task were assessed. These effects were measured on the trained parameter (upper alpha), as well as in the surrounding frequency bands (lower alpha and lower beta) as an exploratory analysis. A series of psychological tests and a cognitive task measured the effects on cognitive functions (working memory, attention, executive functions and mental rotation abilities).

4.2 Methods

Participants and experimental design

19 engineering students of the University of Zaragoza participated in the study. Participants were randomly assigned either to the NF group (n = 10, 3 females, mean $\pm$ SD age: 25.8 ± 4.1 years) or control group (n = 9, 2 females, 24.3 ± 3.7 years). Participants were informed about the protocol of the study before signing the informed consent forms. They were told that all participants would perform a single session NF training to investigate the

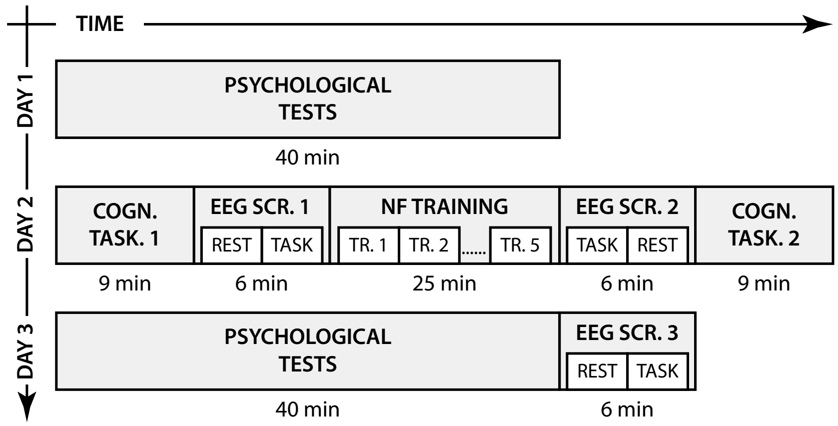

Figure 4.1: Experimental design of the study, executed in three consecutive days. The NF training was performed on Day 2, with an EEG screening and a cognitive task executed immediately before and after NF training. An EEG screening was also executed on Day 3. Each EEG screening recorded eyes closed resting state activity and eyes open task-related activity. Psychological tests were executed on Day 1 and Day 3. Note that there is a numerical code for each EEG screening, cognitive task and training trial.

effects on cognitive performance. Participants were not informed about the existence of two groups to avoid biases (lack of motivation or effort since NF requires the active engagement of participants). Both groups performed the same experimental design with the only difference that the control group received sham feedback. Finally, participants were debriefed at the end of the study. The study was approved by the regional Ethics Board.

The design of the study is shown in Figure 4.1. In the first and third days, the psychological tests were carried out. In the second day, the NF training was performed with a pre- and post- EEG screening, and a pre- and post-execution of the cognitive task (EEG was recorded during the cognitive task). Finally, an EEG screening was also performed on the third day to assess one-day lasting effects on the EEG. Note that we included EEG screenings recording both eyes closed resting state and eyes open task-related activity with a double objective: to identify the alpha peak using both recordings, and to assess the effects of the NF in both conditions.

Psychological tests and cognitive task

Psychological data collection comprised four tests: (*i*) Paced Auditory Serial Addition Task (PASAT, Gronwall, 1977) evaluated working memory and processing speed. This test is sensitive to minimal changes in neurocognitive performance and presents high levels of internal consistency and test-retest reliability (Tombaugh, 2006). The test scores were the number of errors and elapsed time. (*ii*) Rey Auditory Verbal Learning Test (RAVLT, Rey, 1964), Spanish version (Miranda and Valencia, 1997), evaluated retention and immediate evocation, verbal learning, remembering items after an interference task, and recognition (Lezak, 2004). The test score was the number of recognized words. (*iii*) Trail Making Test (TMT, Reitan, 1958) evaluated the information on visual search, scanning, processing speed, mental flexibility and executive functions. The test is composed of two parts: part A measured attention and concentration, and part B measured executive functions such as planning and mental flexibility. The scores were the elapsed time to complete each part of the test. (*iv*) Stroop Color-Word Test (STROOP, Stroop, 1992) evaluated attention, concentration, resistance to interference, and individual capacity to solve cognitive stress, inhibit interferences and process complex data (Lezak, 2004). The test score was the interference.

The cognitive task was adapted from a visuospatial Spanish test (Yela, 1969) and EEG was recorded during its execution. In each trial, a target and a test figure were presented one above the other, and the subjects had to indicate (by pushing a button) whether the test figure corresponded to a rotated version of the target. Subjects were instructed to answer as quickly and accurately as possible. The test consisted of two phases of 25 trials each, with an inter-trial interval of 2.5 s. Each trial lasted 7.5 s and was composed of two time intervals: rest interval (-1.5, 0) s, in which a fixation cross was displayed on the center of the screen, and task interval (0, 6) s, in which the figures were presented for 6 s. Note that (t=0) s denotes figures onset. The test scores were the number of correct responses and reaction time. Responses within the task interval plus the inter-trial interval were taken into account and reaction times were computed for the correct responses.

Two-way repeated-measures ANOVA was separately conducted for each score with the between-subject factor Group (NF, Control) and the within-subject factor Time (Pre, Post). Post-hoc paired samples t-tests were performed for within-group (pre vs post) comparisons.

EEG recording and neurofeedback procedure

EEG data was recorded from 16 electrodes placed at FP1, FP2, F3, Fz, F4, C3, Cz, C4, P7, P3, Pz, P4, P8, O1, Oz and O2 (subset of the 10/10 system), with the ground and reference electrodes on FPz and on the left earlobe, respectively. EEG was amplified and digitized using a g.tec amplifier (Guger Technologies, Graz, Austria) at a sampling rate of 256 Hz, power-line notch-filtered at 50 Hz and (0.5-60) Hz band-pass filtered. EEG recording and the

NF procedure were developed using software of *Bit&Brain Technologies, SL*.

EEG screenings

EEG screenings were carried out immediately before and after the NF training on Day 2, as well as on Day 3 in order to asses immediate and one-day lasting effects on the EEG. For each EEG screening we recorded three-min of eyes closed resting state activity and three-min of eyes open task-related activity. In the latter, subjects faced a computer screen showing a square that changed saturation color randomly from gray to red or blue (gradually). Participants were instructed to count the number of saturation changes from gray to red as a cognitive challenge (Zoefel et al., 2011).

Neurofeedback procedure

The NF training focused on the increase of upper alpha (UA) power averaged over parieto-occipital locations (P3, Pz, P4, O1 and O2, referred to as feedback electrodes). The procedure consisted of two phases: calibration to individualize the training for each subject, and online training (5 trials of 5 min each). The description of the NF technique can be found in Chapter 3. Note that the calibration phase was computed on the pre-NF EEG screenings of Day 2 (resting state and task-related activity).

Before the beginning of the study we recorded the EEG signal of a healthy subject performing the same NF procedure (i.e., pre- and post- EEG screenings and five training trials of the same duration), which was used as a "sham signal" for the control group. The software recorded the real EEG signal from the participants, but the signal processing methods were applied to the "sham signal" for the participants of the control group. Thus, all the participants in the control group received exactly the same feedback.

Note that all the signal processing methods at both the calibration and online training steps were fully automatic and they did not require any supervision from the trainers. Thus trainers could be easily blinded to the group assignment, they simply had to enter an ID number in the software for each participant (ranging from one to the number of participants in order of arrival), which was previously assigned to a group by a technician who did not participate in the recordings. Trainers were shown the real EEG signal of participants in a computer screen with no additional information, and thus they could not guess the group assignment.

EEG analysis

Offline EEG pre-processing

The EEG data of each Day was cleaned from artifacts using a three-step procedure: filtering of the blinking component by FastICA (Hyvarinen, 1999), epoch rejection by a time-domain threshold ($> 150\mu V$) at any electrode, and epoch rejection by a frequency-domain threshold. In the latter step, we computed the power values for each epoch in the bands (1-4) Hz and (20-30) Hz, commonly affected by ocular and muscular artifacts (Delorme et al., 2007), and outliers (z-score > 2) at any electrode were removed. In the case of the EEG collected during the cognitive task, we applied an ICA filter, and we further applied epoch rejection in both time and frequency domains on a trial basis (instead of on an epoch basis).

Analysis of EEG screenings and NF trials

Immediate and one-day lasting effects were assessed in resting state and task-related activity. Immediate effects were measured as the power comparison between the pre- vs post- EEG screening of Day 2 (SCR.1 vs SCR.2, Figure 4.1). One-day lasting effects were measured as the power comparison between the pre-NF EEG screening vs EEG screening of Day 3 (SCR.1 vs SCR.3). In addition, training progress evaluated the power enhancement during training, measured as the power comparison between the baseline (task-related activity in pre-NF EEG screening) vs training trial five. We performed the analysis in the trained parameter (i.e., UA power) and an exploratory analysis in the following bands, based on Klimesch (1999): lower alpha 1, LA_1 = (IAF-4, IAF-2); lower alpha 2, LA_2 = (IAF-2, IAF); and lower beta, LB = (IAF+2, IAF+4).

Analysis of event-locked EEG during the cognitive task

The power in the pre- and post- executions of the cognitive task was computed in rest interval (-1.5, 0) s, and task interval (0, 6) s. Note that (t=0) s represents the figures onset. Power was computed for each trial and averaged across trials. In addition, we computed the power desynchronization between rest and task intervals using two metrics: (*i*) absolute power desynchronization, computed as the power in task interval minus the power in rest interval, and (*ii*) event-related desynchronization (ERD), computed as the power in task interval minus the power in rest interval, normalized by the power in rest interval (Pfurtscheller and Lopes da Silva, 1999). Thus, the NF effects on the event-locked EEG were assessed by the pre- vs post-power comparison in rest and task intervals, and by the pre- vs post- power desynchronization comparison measured using the absolute metric and the relative metric (ERD). We performed the analysis in the trained parameter and an exploratory analysis in LA_1, LA_2 and LB bands.

Statistical analysis

Between-group statistical significance was assessed by independent samples t-tests on change scores. Paired samples t-tests were performed for within-group (pre vs post) comparisons. Power values were log-transformed prior statistical testing. Regarding the exploratory analysis in LA_1, LA_2, UA and LB bands, a non-parametric randomization method using the t-max statistic was used to correct for the number of bands, i.e., to control the familywise type I error rate (FWER, Holmes et al., 1996). Following this method, the null distribution of the maximum absolute t-value across all bands was estimated by 5000 random permutations. Then the absolute observed t-value for each band was tested against the $(1-\alpha)th$ percentile of the null distribution. The FWER was set at $\alpha = .05$.

4.3 EEG results

This section analyzes the NF effects on the EEG by two sub-analyses: (*i*) immediate and one-day lasting effects in the EEG screenings and during training trials, and (*ii*) the event-locked EEG effects during the execution of the cognitive task. For each sub-analysis we first performed a pre- vs post- comparison of the effects on the trained parameter (UA power) and we then assessed the effects on surrounding bands (LA_1, LA_2, and LB) as an exploratory analysis. The results of the exploratory analysis were corrected for the multiple comparisons (number of bands) by a t-max randomization procedure (Holmes et al., 1996).

Groups did not differ statistically in baseline IAF. Mean $\pm$ SD IAF in resting state was 9.8 ± 0.2 Hz for the NF group and 10.3 ± 0.3 Hz for the control group (independent samples t-test: $t_{17} = -1.50, p = .15$); and in task-related activity it was 10.2 ± 0.2 Hz for the NF group and 10.6 ± 0.3 Hz for the control group ($t_{17} = -1.05, p = .3$).

Analysis of EEG screenings and NF trials

We first assessed the NF effects in the trained parameter (UA power). Regarding the resting state, no significant difference appeared between groups

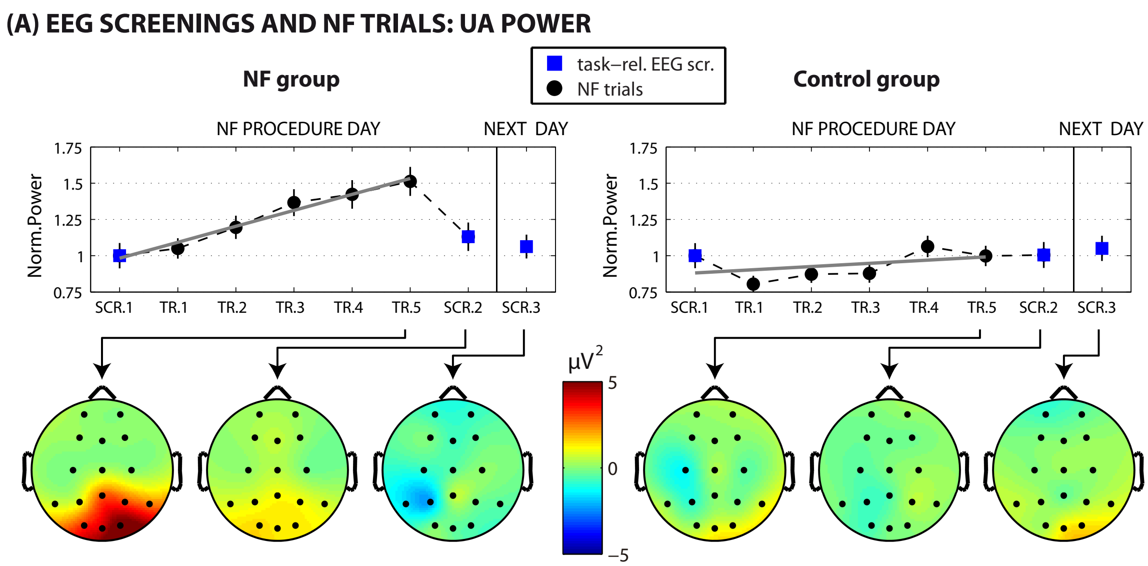

Figure 4.2: NF effects on the EEG screenings and NF trials. (A) displays the UA power in the task-related EEG screenings (blue squares) and training trials (black dots). Values are normalized per subject to the power in the pre-NF EEG screening. Vertical bars indicate SEM. The gray line represents the training progress. Topoplots display the power difference (μV^2) with regard to the pre-NF EEG screening.

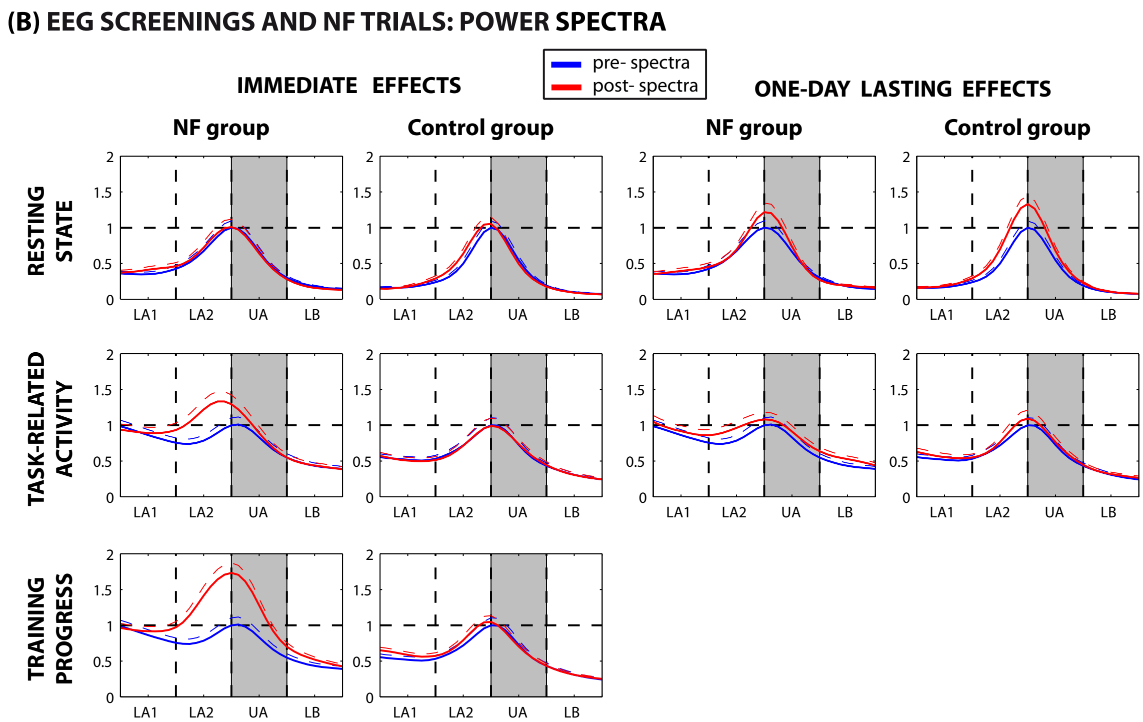

Figure 4.3: NF effects on the EEG screenings and NF trials. (B) displays the pre- and post- EEG power spectra for the immediate and one-day lasting effects on both resting state and task-related activity, as well as the training progress. Average and SEM power values are displayed (solid and dashed lines, respectively). Note that for illustration purposes, the pre- and post- power spectra were normalized per subject to the power in the pre-spectra IAF bin, and averaged across subjects. The (IAF-4, IAF+4) Hz frequency range is displayed (covering LA_1, LA_2, UA, and LB frequency bands). UA band is shaded in gray color.

(on change scores) either immediately after the training or the following day. Figure 4.2 displays the UA power in task-related activity and during training. Task-related activity showed a between-group difference at statistical trend immediately after the training ($t_{17} = 1.88, p = .077$). Post-hoc t-tests showed a significant increase for the NF group ($t_9 = 3.42, p < .01$), with an average increase of 13.08%. These effects were not significantly sustained the following day. Training progress showed a between-group difference at statistical trend ($t_{17} = 1.81, p = .089$). Post-hoc t-tests showed a statistical trend for the NF group ($t_9 = 1.94, p = .084$), with an average increase of 51.22%. The higher effects in the latter metrics were found in posterior areas of the scalp. In addition to that, we measured the training progress as the trend (slope of a fitted regression line) of the power values of the baseline and five NF trials (see Figure 4.2). The average slope was 0.11 for the NF group (significantly higher than zero, $t_9 = 1.86, p = .048$) and 0.02 for the control group (non significant, n.s.).

We assessed the EEG effects in three alpha sub-bands and lower beta (LA_1, LA_2, UA, LB). Figure 4.3 displays the pre- and post- EEG power spectra in immediate and one-day lasting effects, as well as the training progress. Note that the statistical results below reported were corrected for the multiple bands using a t-max randomization procedure (Holmes et al., 1996). No significant between-group differences (on change scores) appeared in resting state either immediately after training or the following day. Regarding the immediate effects in task-related activity, we found a significant between-group difference in LA_2 band (threshold $t = 2.80$[1], $t = 3.69, p = .01$). Post-hoc t-tests showed a significant increase for the NF group (threshold $t = 2.98$, $t = 4.06, p < .01$), with an average increase of 50.93%. No significant one-day lasting effects appeared in task-related activity. Finally, a between-group difference in training progress appeared in LA_2 band at statistical trend (threshold $t = 2.74$, $t = 2.45, p = .085$). Post-hoc t-tests showed a significant increase for the NF group (threshold $t = 2.69$, $t = 4.14, p < .005$), with an average increase of 74.55%. No significant pre- vs post- changes appeared for the control group.

Analysis of event-locked EEG during the cognitive task

We first assessed the NF effects in UA power. Figure 4.4 depicts the UA power time-course: absolute power time-course and ERD metric. Note that the absolute power time-course allows to observe the pre- and post- power

[1]The t thresholds reported throughout this study (for the t-max randomization procedure) were computed at ($\alpha = .05$).

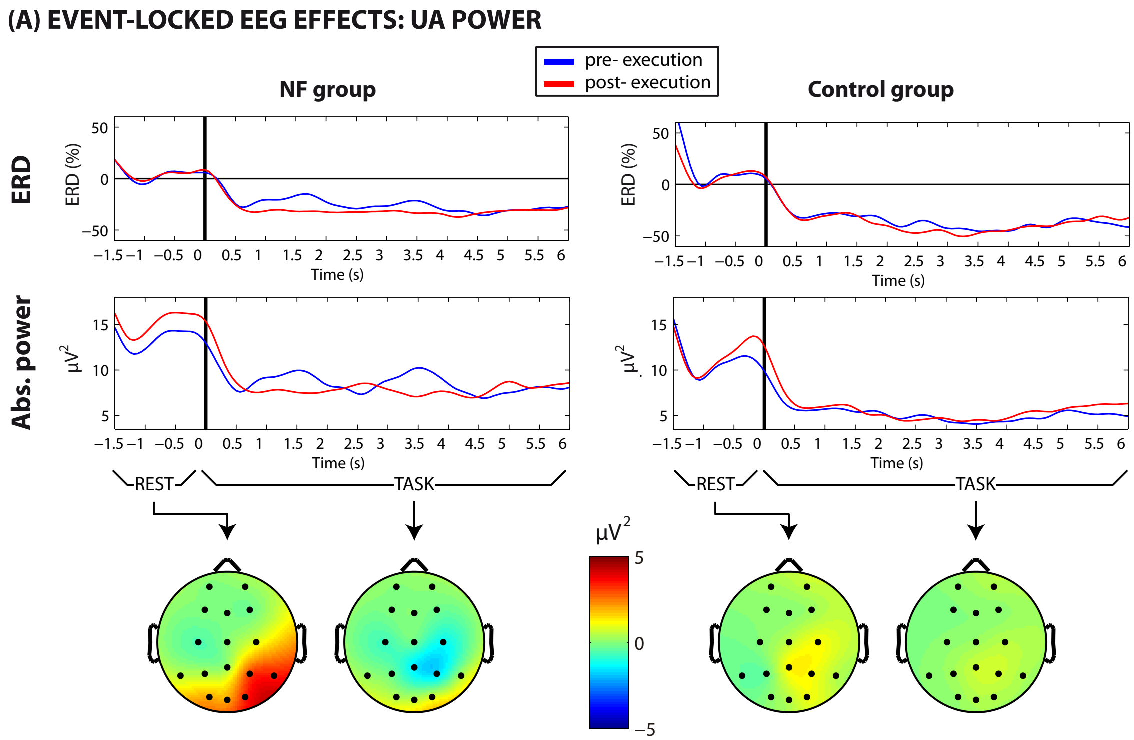

Figure 4.4: NF effects on event-locked EEG during the pre- and post- executions of a cognitive task. (A) displays the UA power time-course. Upper figures show the ERD measurement (Pfurtscheller and Lopes da Silva, 1999): UA power in each time instant was normalized to the power in rest interval. Bottom figures show the absolute UA power. Topoplots display the averaged pre- and post- power difference (μV^2) in both rest and task intervals.

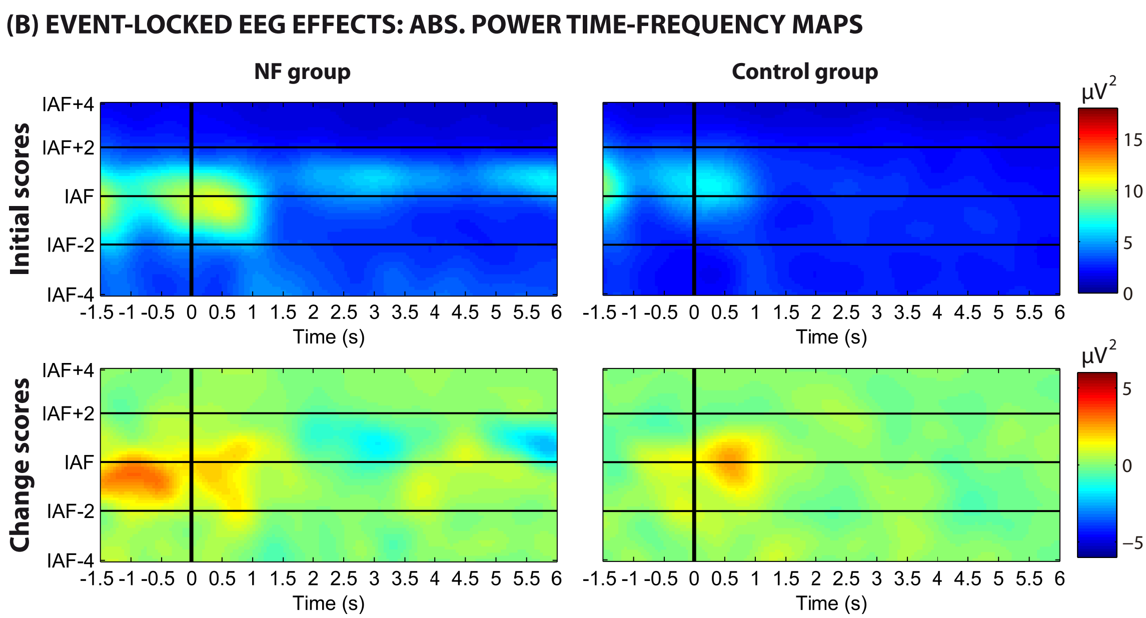

Figure 4.5: NF effects on event-locked EEG during the pre- and post- executions of a cognitive task. (B) displays the absolute power time-frequency maps in the initial (pre- execution) and change scores (pre- vs post- execution) for each group. The (IAF-4, IAF+4) Hz frequency range is displayed (covering LA_1, LA_2, UA, and LB frequency bands).

changes in each trial interval (rest, task). The UA power in rest interval showed a between-group difference (on change scores) at statistical trend ($t_{17} = 1.96, p = .067$). Post-hoc t-tests showed a significant increase for the NF group ($t_9 = 3.97, p < .005$), with an average increase of 16.61%. The higher effects were found in posterior areas of the scalp. No significant effects appeared for the task interval. A desynchronization pattern was apparent, showing an UA power decrease after the figures onset for both groups and pre- and post- executions of the cognitive task (Figure 4.4). This pattern is in line with other studies performing similar mental rotation tasks (Hanslmayr et al., 2005, Klimesch et al., 2003). A between-group difference at statistical trend was found in absolute power desynchronization ($t_{17} = -1.99, p = .063$). Post-hoc t-tests showed a significant increase for the NF group ($t_9 = -2.53$, $p = .032$), with an average increase of $2.2\mu V^2$. Note that a positive difference denotes an increase in desynchronization.

We assessed the EEG effects in three alpha sub-bands and lower beta (LA_1, LA_2, UA, LB). Figure 4.5 displays the time-frequency analysis in the (IAF-4, IAF+4) Hz range, showing the initial and change (pre vs post) absolute power values for each group. Note that the statistical results below reported were corrected for the multiple bands (Holmes et al., 1996). We did not found significant differences between groups (on change scores) in any band and metric. We further conducted pre- vs post- t-tests within each group. A significant increase appeared in LA_2 band for the NF group in rest interval (threshold $t = 3.17$, $t = 4.52, p = .006$), with an average increase of 29.9%; as well as in task interval (threshold $t = 3.01$, $t = 4.10, p = .007$), with an average increase of 12.1%. These effects in LA_2 power can be observed in Figure 4.5. No significant pre- vs post- changes appeared for the control group.

4.4 Behavioral results

This section analyzes the NF effects on cognitive performance measured by a battery of psychological tests (targeting functions such as working memory, episodic memory, attention, concentration, and executive functions) and the cognitive task (mental rotation abilities). Table 4.1 summarizes the scores in the psychological tests and cognitive task.

We assessed the between-group differences by the $Group \times Time$ interaction in the ANOVAs. A significant effect appeared in part B of TMT test ($F_{1,17} = 4.51$, $p = .049$). Post-hoc t-tests showed that both groups improved performance (NF: $t_9 = -4.26, p < .005$; Control: $t_8 = -3.52, p < .01$), with a higher improvement for the NF group. No significant between-groups dif-

Test scores	NF Pre mean (SEM)	NF Change mean (SEM)	Control Pre mean (SEM)	Control Change mean (SEM)	Paired-samples t-test NF t-val	NF p-val	Control t-val	Control p-val	ANOVA $G \times T$ F-val	p-val
PASAT										
# errors	6.70(1.03)	−3.10(1.02)	4.11(1.03)	−1.33(0.90)	**-3.05**	**.014**	−1.49	.176	1.67	.214
time (s)	199.93(18.12)	−42.09(7.97)	174.24(19.83)	−33.47(8.72)	**-5.28**	**<.001**	**-3.84**	**.005**	0.53	.475
RAVLT										
# recognized words	13.90(0.41)	0.90(0.35)	13.67(0.53)	0.89(0.54)	**2.59**	**.029**	1.65	.137	0.00	.986
TMT										
part A, time (s)	27.16(3.59)	−6.15(3.03)	27.07(3.92)	−6.64(2.69)	−2.03	.073	**-2.47**	**.039**	0.01	.905
part B, time (s)	53.98(4.11)	−17.24(4.04)	36.10(3.54)	−7.27(2.07)	**-4.26**	**.002**	**-3.52**	**.008**	**4.51**	**.049**
STROOP										
interference	3.17(1.94)	3.60(3.66)	10.54(3.07)	2.69(1.38)	0.98	.351	1.95	.088	0.05	.826
COGNITIVE TASK										
# correct responses	41.20(1.40)	4.00(1.20)	39.00(0.99)	2.33(0.65)	**3.33**	**.009**	**3.61**	**.007**	1.40	.253
reaction time (s)	4.49(0.32)	−0.68(0.13)	4.14(0.22)	−0.44(0.22)	**-5.18**	**<.001**	−2.02	.078	0.93	.349

Table 4.1: Pre- and change scores (mean ± SEM) on the behavioral results for each group. The t- and p-values of the paired-samples t-tests are shown for each group (pre vs post changes), as well as the F- and p-values of the $Group \times Time$ interaction in the ANOVAs. Significant effects are marked bold ($p < .05$). PASAT = Paced Auditory Serial Addition Task, RAVLT = Rey Auditory Verbal Learning Test, TMT = Trail Making Test.

ferences appeared for the other scores. We further conducted pre- vs post-t-tests within each group as an exploratory analysis. PASAT test showed a decrease in the number of errors for the NF group only ($t_9 = -3.05, p = .014$), whereas the time elapsed decreased for both the NF ($t_9 = -5.28, p < .001$) and control group ($t_8 = -3.84, p = .005$). The number of recognized words in the RAVLT test increased for the NF group only ($t_9 = 2.59, p = .029$). Part A of the TMT test improved for the control group only ($t_8 = -2.47, p = .039$). The interference score in the STROOP test did not significantly change for any group. Regarding the cognitive task, the number of correct responses increased for both the NF ($t_9 = 3.33, p < .01$) and the control group ($t_8 = 3.61, p < .01$). The reaction time decreased for the NF group only ($t_9 = -5.18, p < .001$).

4.5 Discussion

This study reports the effects of a single-session subject-specific NF procedure for cognitive enhancement in healthy subjects. The NF training aimed at enhancing the individual upper alpha power measured over parieto-occipital locations. A double-blind sham-controlled study was designed within a short procedure (25 minutes of training) to minimize the non-specific factors of the training. The NF sham training is considered as a genuine, blind placebo control (Brandeis, 2011), which can provide a better consideration of non-specific factors such as motivation, expectancy and practice effects (Enriquez-Geppert et al., 2013). Most of the NF studies use non-interventional control groups, which could lead to a misleading interpretation of the results due to the between groups differences in psychological factors (such as motivation and expectancy) or due to practice effects. Only very recent NF studies are including sham control groups (Alexeeva et al., 2012, Kober et al., 2014, Ninaus et al., 2013). To the best of our knowledge, there is not a standard procedure to compute/provide sham feedback. In the current study, all participants in the control group received the same feedback based on the EEG signal of a single subject (not included in the study). For instance, an alternative procedure for implementing the sham feedback would be to vary the order of appearance of the feedback for each subject in the control group by randomizing the training trials.

We performed an extensive evaluation of the effects on the electrophysiology and assessed the behavioral effects on several cognitive functions (working memory, episodic memory, attention, concentration, executive functions and mental rotation abilities). Note that the reliability and specificity of the NF effects at behavioral and electrophysiological level remain a common limitation (Gruzelier, 2014, Vernon, 2005), and NF literature still lacks an extensive evaluation of the electrophysiological effects, especially on non-trained EEG parameters and during the execution of cognitive tasks, although some studies have partially addressed these issues (Zoefel et al., 2011, Nan et al., 2012, Hanslmayr et al., 2005).

EEG results

The EEG analysis of the EEG screenings and NF trials showed that upper alpha power was enhanced for the NF group only, measured immediately after training in task-related activity, and during training. The higher effects were found in posterior areas of the scalp. These effects were not restricted to the upper alpha band: lower alpha 2 showed a higher increase than the corresponding increase in upper alpha (in the same metrics). These effects may be due to a 0.1 Hz decrease in the IAF immediately after training (independent samples t-test: $t_{17} = -2.33, p = .03$), which reduced the effects on upper alpha while increasing the effects on the lower sections (see Figure 4.3). Note that Escolano et al. (2011) also reported an IAF decrease immediately after training. The IAF decrease was not sustained one day after, which is consistent with previous studies (Escolano et al., 2011, Zoefel et al., 2011). No significant one-day lasting effects appeared for any group. Eyes closed resting state activity was not significantly modified for any group, which suggests that this procedure presents lower effects on resting state. In relation to other works, upper alpha NF studies reported no modifications in lower alpha and lower beta (Escolano et al., 2011, Zoefel et al., 2011), however they followed a different definition for the frequency bands (herein the most common definition was adopted, Klimesch, 1999).

Regarding the analysis of the event-locked EEG effects during the execution of the mental rotation task, the NF group showed higher upper alpha power in the initial execution for both the rest and task intervals (Figure 4.4). These between-group differences were not significant as assessed by independent samples *t*-tests (rest interval: $t_{17} = 0.23, p = .81$; task interval: $t_{17} = 0.75, p = .46$). This analysis showed that the NF group enhanced upper alpha power in the rest interval (pre-stimulus) immediately after training. Power in task interval was not significantly modified for any group. As a consequence, the NF group increased upper alpha desynchronization measured using absolute power measurements. Note that this desynchronization increase was already suggested to be positively related to cognitive performance (Klimesch et al., 2007). This increased pre-stimulus upper alpha activity may prevent interference from visual stimuli thus promoting cognitive processing (Freunberger et al., 2011, Klimesch et al., 2007). These results are in line with a previous study involving a mental rotation task (Hanslmayr et al., 2005). Similarly to the effects in the EEG screenings and NF trials, lower alpha 2 power showed a significant increase for the NF group (no significant between groups) in both rest and task intervals (Figure 4.5).

Behavioral results

The NF group performed better than the control group in all the scores (except for part A of TMT test), but with no significant difference between groups (except for part B of TMT test, in which the NF group performed significantly better). In addition to that, some scores were improved for the NF group only such as the number of errors in the PASAT test (working memory is suggested to be related to alpha rhythm, Freunberger et al., 2011), the number of recognized words in the RAVLT test and the reaction time in the mental rotation task. However, the improvement in these scores was not significantly superior to the improvement observed in the control group.

These effects in cognitive performance might be explained by a strong learning effect due to repeated measurements (30 min between test-retest in the cognitive task, and one day in the psychological tests) and by the short duration of the training, which might be insufficient to yield significant differences between groups. Note that NF effects on the EEG were not sustained at the post-NF administration of the psychological tests, which may have diminished the behavioral effects. In relation to other works, a previous study (Hanslmayr et al., 2005) comprising a single-session training of combined trials of theta suppression and upper alpha enhancement (within-subjects design) led to improved performance in a mental rotation task for the subjects that responded to the upper alpha NF. The difference to the results herein presented may be due to the fact that a within-subject design could have better dealt with the between-group variability in baseline scores.

Limitations

Deception was used to blind the participants to the experimental condition. When debriefing the participants we could have asked them to "guess" the condition they were assigned. This point should be considered in future studies. A limitation of the behavioral analysis was the high baseline scores (e.g., the number of correct responses in the cognitive task was 41.2/50 and 39/50 for the NF and control group), which left little margin for improvement. The degree of difficulty of the psychological tests or cognitive tasks should be adapted to the participants in future studies, and cut-off scores could be established. Finally, a larger sample size would be desirable to increase the statistical power.

4.6 Conclusions

This study showed that healthy participants can enhance upper alpha power (in task-related activity) after 25 minutes of NF training in comparison to a sham control group. These effects were not sustained one day after. The experimental group presented increased pre-stimulus upper alpha power during the mental rotation task and consequently higher event-locked power desynchronization. Regarding the behavioral results, the experimental group showed higher performance improvement than the control group, however no significant difference between groups was obtained. Thus, a single session of training seems not enough to produce sustained effects on the EEG and to reach significance level (between groups) in cognitive performance. A higher number of training sessions seem thus necessary to achieve long-lasting effects on the electrophysiology and to enhance the behavioral results.

In next chapter we report a NF study on depressed patients following the same subject-specific NF protocol of upper alpha up-regulation over parieto-occipital locations, including a higher number of participants to increase the statistical power of the analyses. Next study extends the analysis of the specificity on the power spectra to the (1-30 Hz) range and all the recording locations, covering frontal, central, and parieto-occipital areas. It will also assess the effects at brain source level.

5 | The cognitive effect of NF in major depression

5.1 Introduction

Major depressive disorder (MDD) is a severe, chronic, mood disorder characterized by episodes of sadness, loss of interest and motivation, pessimism, and suicidal thoughts (DeRubeis et al., 2008). Depression affects each year 13 to 14 million citizens in the United States, with a lifetime prevalence of 16.2% (Kessler et al., 2003). MDD is estimated to become the second cause of burden of disease in 2030 (Mathers and Loncar, 2006). The current standard treatment for depression is antidepressant medication. Unfortunately with this treatment about 33% of patients fail to achieve remission (Anderson et al., 2008). Moreover, the patient compliance to the treatment can decrease due to the side effects such as sexual dysfunction, gastrointestinal problems, and weight gain (Brunoni et al., 2009). For this reason, the development of new treatments is constantly explored. In particular, recently there has been a renewed interest on neuromodulation techniques such as repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and NF (DeRubeis et al., 2008, Brunoni et al., 2009).

Most of the NF protocols applied to date to depressed patients are based on EEG findings of frontal asymmetry in the alpha frequency band, with depressed patients showing left hypoactivation (Henriques and Davidson, 1991, Davidson, 1998, 2004, Coan and Allen, 2004). These findings are interpreted as a dysfunction of the prefrontal cortex (PFC) and a predisposition towards negative emotions and behavioral withdrawal (Davidson, 2004, DeRubeis et al., 2008). While some studies support this theory (Gotlib, 1998, Lubar et al., 2003), controversial results have also been reported (Reid et al., 1998). Furthermore, some studies found asymmetry changes over recording sessions not related to the clinical symptoms of the patients (Allen et al., 2004a), thus its consideration as a marker for depression remains unclear to date (Allen and Cohen, 2010). Some NF studies have tried to reduce the alpha asymmetry in an attempt to alleviate the depressive symptoms, reporting promising results (Baehr et al., 1997, 2001, Hammond, 2000, 2005). However, to the best of our knowledge, none of the early studies were appropriately controlled. The first controlled study of this kind reported a reduction in depressive symptoms and an improvement in executive functions (Choi et al., 2011).

The present work is based on a different rationale. Our objective is to alleviate the cognitive symptoms of depression. Cognitive deficits are core symptoms of depressive disorders with a clear-cut impact on social and occupational functioning, with patients showing decreased performance in working memory (WM) and attention, among others (Gotlib and Joormann, 2010, Castaneda et al., 2008, Austin et al., 2001). Furthermore, depressive patients show biases in the processing of emotional contents in WM (Gotlib and Joormann, 2010, Levens and Gotlib, 2010). For example, Levens and Gotlib (2010) performed an emotion n-back WM task in which depressed and control individuals had to match the valence of stimuli (happy, neutral or sad). Comparing the depressed vs control individuals they found in the 2-back task that depressed individuals were slower to match emotional stimuli in WM (regardless of the valence), and they integrated faster and removed slower the sad stimuli from WM. Recent evidences thus suggest that cognitive deficits may not only be correlates of depression, but they may also increase the risk for depression (Gotlib and Joormann, 2010, Levens and Gotlib, 2010).

We hereby explore WM entrainment by means of a subject-specific NF protocol aimed to up-regulate the individual upper alpha power in parieto-occipital locations. To the best of our knowledge, this is the first NF study exploring the cognitive effect of WM entrainment in patients with MDD. Eyes closed resting state and eyes open task-related activity were recorded before and after the training as well as pre- and post- the training trials within each session. A power EEG analysis and an alpha asymmetry analysis were conducted at the sensor level. Frequency domain standardized low resolution tomography (sLORETA) was used to assess the effect of training at the brain source level. Finally, a correlation analysis between the clinical/cognitive and EEG measurements was conducted at both the sensor and brain source level. The main cognitive variable was WM, measured along other variables such as attention, verbal memory and executive functions.

5.2 Material and Methods

Participants

74 participants diagnosed with major depressive disorder (MDD) were allocated to the NF group ($n = 50$) or to the control group ($n = 24$). Participants were not randomly allocated to groups (see discussion). Patients were recruited from different health centers in the city of Zaragoza (Spain). The inclusion criteria were age range (18-65 years), Spanish as the native language, diagnosis of MDD according to DSM-IV, and stable pharmacological/psychological treatment. Participants met DSM-IV criteria for MDD as assessed by their respective therapists. The exclusion criteria were diagnosis of comorbid disorders (e.g., schizophrenia, drug addiction, dementia). The experimental design was approved by the Ethical Review Board of the regional health authority and followed the Declaration of Helsinki. All participants signed an informed consent. Five participants dropped out the study due to the inability to perform the cognitive assessments or recording sessions, four of whom belonging to the NF group. Among the remaining participants who completed the study, six subjects in the NF group and three in the control group were excluded due to excessive artifacts in the EEG. Thus, the final sample consisted of 40 participants in the NF group and 20 in the control group. Demographic and clinical variables for both groups are reported in Table 5.1. There were no significant differences between groups in any variable.

	NF group $n = 40$	Control group $n = 20$	NF vs Control p-value
Gender (male/female)	15/25	4/16	0.24
Age, years (mean ± SD)	53.70 ± 10.87	49.50 ± 10.18	0.16
Antidepressant medication (yes/no)	37/3	18/2	1.00
Comorbidity of anxiety (yes/no)	33/7	15/5	0.51
BDI-II score (mean ± SD)	23.70 ± 13.51	22.25 ± 11.74	0.68
PHQ-9 score (mean ± SD)	13.33 ± 6.84	15.65 ± 5.96	0.21

Table 5.1: Demographic and clinical variables of the participants at study entry. Between-group differences were assessed by Fisher's exact test and independent samples t-tests for categorical and continuous variables, respectively. BDI-II = Beck Depression Inventory, Second Edition. PHQ-9 = Patient Health Questionnaire.

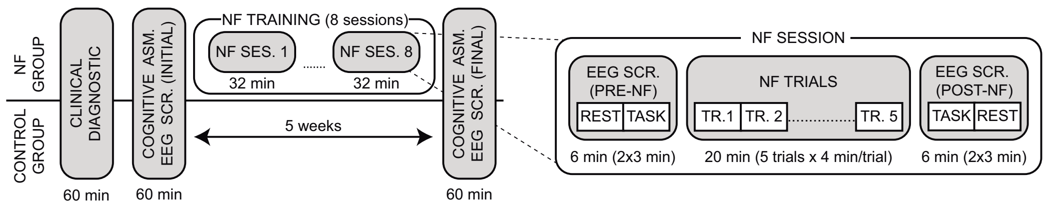

Figure 5.1: Experimental design of the study. After an intake diagnostic both groups executed a pre- and post- cognitive assessment and EEG screening within a five-week time interval. The NF group performed a total of eight NF sessions (two sessions per week), which were composed of a pre- and post-EEG screening (six min each) and five training trials (four min each). The EEG screenings included eyes closed resting state and eyes open task-related activity.

Experimental Design

The design of the study is shown in Figure 5.1. The severity of depressive symptoms was evaluated in a semi-structured interview using the Beck Depression Inventory (BDI-II, Beck et al., 1996) and the Patient Health Questionnaire (PHQ-9, Kroenke et al., 2001). After that, both groups performed a cognitive assessment and an EEG screening at the beginning and at the end of the study (five-week time interval). Cognitive assessments lasted approximately one hour. The NF group performed eight NF sessions over four weeks (two sessions per week). Each session was composed of five trials of four min each for a total of 20 min of training, and a pre- and post- EEG screening. For each EEG screening we recorded three-min of eyes closed resting state activity and three-min of eyes open task-related activity. In the latter, participants faced a computer screen showing a square that changed saturation color randomly from gray to red or blue (gradually). Participants were instructed to count the number of saturation changes from gray to red as a cognitive challenge (Zoefel et al., 2011).

Cognitive Performance

Pre- and post- cognitive assessments were carried out at the beginning and at the end of the study. The main outcome variable was WM, which was measured using the Paced Auditory Serial Addition Task (PASAT, Gronwall, 1977) along with the processing speed. This test is sensitive to minimal changes in neurocognitive performance and presents high levels of internal consistency and test-retest reliability (Tombaugh, 2006). The test scores were the number of errors and elapsed time. Episodic memory, attention and executive functions were also assessed using the following tests: (*i*) Rey Auditory Verbal Learning Test (RAVLT, Rey, 1964) evaluated episodic memory and the test score was the number of recognized words. (*ii*) Stroop Color-Word Test (STROOP, Stroop, 1992) evaluated attention and concentration. The test score was the interference, which was standardized across age groups. (*iii*) Trail Making Test (TMT, Reitan, 1958) evaluated executive functions and was composed of parts A and B. The scores were the elapsed time to complete each part of the test. (*iv*) Fluency Verbal Test (FAS, Benton and Hamsher, 1976) evaluated verbal phonetic fluency. The test score was the number of evoked words. To determine statistical significance, two-way repeated-measures ANOVA (rm-ANOVA) was separately conducted for each score with the between-subject factor Group (NF, Control) and the within-subject factor Time (Pre, Post). Paired samples t-tests were performed for within-group (pre vs post) comparisons.

EEG Recording and Neurofeedback Procedure

EEG data was recorded from 16 electrodes placed at FP1, FP2, F3, Fz, F4, C3, Cz, C4, P7, P3, Pz, P4, P8, O1, Oz and O2 (subset of the 10/10 system), with the ground and reference electrodes on FPz and on the left earlobe, respectively. EEG was amplified and digitized using a g.tec amplifier (Guger Technologies, Graz, Austria) at a sampling rate of 256 Hz, power-line notch-filtered at 50 Hz and (0.5-60) Hz band-pass filtered. EEG recording and the NF procedure were developed using software of *Bit&Brain Technologies, SL*.

The NF training focused on the increase of the individual upper alpha (UA) power averaged over parieto-occipital locations (P3, Pz, P4, O1 and O2, referred to as feedback electrodes). The description of the NF technique can be found in Chapter 3. Participants in the NF group were not given any mental strategy nor they were aware of the EEG trained parameter. Instead, they were encouraged to try different mental strategies guided by the feedback. To the best of our knowledge, the effect of different mental strategies in the ability to self-regulate brain activity is unclear to date, which is the focus of recent NF studies (Kober et al., 2013).

Offline EEG pre-processing

EEG data from the initial and final EEG screenings was carefully inspected for the presence of artifacts such as eye blinks, eye movements, body movements and EKG artifacts. Initially, the extended infomax ICA (Lee et al., 1999) was applied to the task-related activity to remove the eye blinking component. Then, both resting state and task-related activity were imported into

EureKa! software (Congedo, 2002) to reject the contaminated data by visual inspection. Participants with at least 30 s of artifact-free data were included in the analysis[1]. EEG spectrum was computed following the same procedure as in the NF procedure. The EEG data of each NF session was cleaned from artifacts using a three-step automatic procedure: filtering of the blinking component by the extended infomax ICA (Lee et al., 1999), epoch rejection by a time-domain threshold ($> 200\mu V$) at any electrode, and epoch rejection by a frequency-domain threshold. In the latter step, we computed the power values for each epoch in the bands (1-3 Hz) and (20-30 Hz), commonly affected by ocular and muscular artifacts (Delorme et al., 2007). Then, we converted the log-transformed power values to z-scores and removed the outliers (> 2.5) at any electrode. Note that the automatic procedure was only used to compute the alpha power in parieto-occipital locations, and no significant differences were found between the two procedures in either resting state (paired samples t-test: $t_{59} = -0.77, p = .44$) or task-related activity ($t_{59} = 0.26, p = .79$). EEG power was then computed through a short-term fast Fourier transform (FFT) with 1 s hamming window, 30 ms of overlapping, and zero-padded to 1024 points (0.25 Hz resolution).

Power EEG Analysis in the trained parameter

Power EEG analysis was conducted in the trained parameter: power in the individual UA band, averaged across the feedback electrodes (P3, Pz, P4, O1, O2). The pre-post enhancement was measured as the power change between the initial and final EEG screenings in resting state and task-related activity for both groups. The across- and within-session enhancement were also measured (for the NF group). Across-session enhancement was assessed by a linear trend analysis of the power values in the pre-NF screenings of all sessions and the final screening. The within-session enhancement comprised two measurements, computed in the power values averaged across the NF sessions: a power change comparison between the pre- and post- EEG screenings, and a linear trend analysis of the power values in the pre-NF task-related EEG screening and the five training trials. To determine statistical significance of pre- and post- comparisons, log-transformed power values were entered into a two-way rm-ANOVA with the factors Group (NF, Control) and Time (Pre, Post). Paired samples t-tests were performed for within-group (pre vs post) comparisons. Trend analysis consisted in the computation of the slope of a fitted regression line for each participant, and a t-test to test

[1] Some studies found reliable test-retest correlation coefficients in FFT frequency analysis performed on segments of 60, 40, or 20 s total length (Salinsky et al., 1991).

the hypothesis of a null slope. The type I error was set at $\alpha = .05$.

Power EEG Analysis in the Sensor x Frequency domain

Power analysis was conducted for all sensors and frequencies in the (1-30 Hz) interval, separately applied for the resting state and task-related activity. The NF training effects were measured as the log-transformed power spectra comparison between the initial and final EEG screening: a between-group comparison (NF vs control group) on the change power values, and a within-group comparison (pre vs post) for each group. A cluster-based non-parametric randomization method (Nichols and Holmes, 2002, Maris and Oostenveld, 2007) was used, as implemented in the Fieldtrip toolbox (FC Donders Centre for Cognitive Neuroimaging, Nijmegen, The Netherlands; see http://www.ru.nl/fcdonders/fieldtrip). This method first computes the difference between two conditions by performing t-tests in the (sensor, frequency)-pairs. Those pairs exceeding a threshold q are clustered on the basis of spatial and spectral adjacency, and then cluster-level statistics are calculated as the sum of the t-values within every cluster. The threshold was set to ($q = .05$) for resting state and to ($q = .01$) for task-related activity. Finally, the significance probability at the cluster-level was estimated by a permutation method (Pesarin, 2001). The distribution of the cluster values was constructed under the null hypothesis by 5000 random permutations and then the observed values were tested against the $(1 - \alpha)th$ percentile of the null distribution. This method controls for the type I error rate and corrects for multiple comparisons both across sensors and frequencies. The type I error at cluster-level was set to $\alpha = .05$.

Alpha Asymmetry Analysis

Initial and final scores of alpha (8-12 Hz) asymmetry were computed in resting state and task-related activity. EEG data was re-referenced to Cz and asymmetry scores were computed as the normalized power difference between homologous right- and left-side locations, (R-L)/(R+L). See Allen et al. (2004b) for a review on methodological considerations. This score indicates the relative activation of the left over right locations. Thus positive scores indicate left-lateralized activation, i.e., more power over right-side locations due to the inverse relation between alpha power and brain activation (Coan and Allen, 2004). Alpha asymmetry scores were computed in five areas of the scalp: prefrontal (FP: FP2-FP1), frontal (F: F4-F3), central (C: C4-C3), parietal (P: (P7+P3)/2-(P8+P4)/2) and occipital (O: O2-O1). Independent samples t-tests were conducted to test for between-group differences in initial scores. We applied t-tests on the initial scores (for each group and area of the scalp) to test for null asymmetry scores. Two-way rm-ANOVA with the factors Group (NF, Control) and Time (Pre, Post) was separately conducted for each area of the scalp to test for pre-post study changes. Bonferroni correction was applied to correct for multiple areas so as to keep the FWER at $\alpha = .05$.

EEG Analysis at the Brain Source Level

Frequency domain standardized low resolution tomography, sLORETA (Pascual-Marqui, 2002, 2007) was used to estimate the current density of brain sources in resting state and task-related activity. The current density changes were compared between groups (NF vs control group) as well as within groups (pre vs post) for each group. EEG data was re-referenced to a common average reference and Fourier cross-spectral matrices were computed for the following frequency bands: delta (1-4 Hz), theta (4.5-7 Hz), alpha (8-12 Hz), beta1 (12-15 Hz), beta2 (15-20 Hz) and beta3 (20-30 Hz). These bands were defined according to the results obtained in the clustering analysis at the sensor level (section 5.2). After that, sLORETA estimated the current density values in 6239 voxels (5 mm^3 spatial resolution). sLORETA applies the boundary element method on the MNI-152 (Montreal Neurological Institute, Canada) template of Mazziotta et al. (2001), and the anatomical labelling is based on probabilities returned by the Daemon Atlas (Lancaster et al., 2000). Finally, current density values were log-transformed and statistical significance of each voxel was determined by a non-parametric randomization procedure using the t-max statistic to control the familywise type I error rate (FWER, Holmes et al., 1996). Following this procedure, the null distribution was estimated by 5000 random permutations under the null hypothesis of the maximum absolute t-value across all voxels. Then the absolute observed t-value for each voxel was tested against the $(1-\alpha)th$ percentile of the null distribution. Bonferroni correction was applied to correct for multiple bands so as to keep the FWER at $\alpha = .05$.

Correlation Analysis: EEG vs behavioral variables

Spearman correlation was employed to test for a correlation in the initial scores between the clinical/cognitive and EEG variables, as well as in the change scores between the cognitive and EEG variables (clinical variables were not measured after NF training). A total of two clinical variables and seven cognitive variables were tested (section 5.2). The EEG variables were assessed in resting state and task-related activity and can be divided into

Test	NF		CONTROL		Paired-samples t-test		ANOVA
Scores	Pre mean (SEM)	Change mean (SEM)	Pre mean (SEM)	Change mean (SEM)	NF p-value	CONTROL p-value	$G \times T$ p-value
PASAT							
# errors	13.45(1.09)	−3.32(0.64)	11.59(2.22)	−0.41(1.23)	**<.001**	.742	**.024**
time (s)	253.23(13.25)	−39.55(8.05)	249.76(20.40)	−3.71(16.08)	**<.001**	.821	**.031**
RAVLT							
# recognized words	12.25(0.43)	0.90(0.27)	11.55(0.65)	0.35(0.65)	**.002**	.597	.363
STROOP							
interference	51.64(1.23)	1.74(1.20)	54.60(1.80)	0.20(1.52)	.154	.897	.443
TMT							
part A, time (s)	44.66(3.03)	−6.37(3.26)	41.35(3.02)	−3.40(2.43)	.059	.178	.543
part B, time (s)	101.50(14.57)	−16.63(5.83)	84.90(11.60)	−11.50(10.55)	**.007**	.289	.645
FAS							
# evoked words	43.74(1.87)	3.10(1.19)	38.70(2.68)	1.10(1.54)	**.013**	.482	.319

Table 5.2: Cognitive performance at the beginning and at the end of the study for each group. Mean ± SEM scores in pre- cognitive assessments are shown, as well as the change scores (post-pre). The p-values of the paired samples t-tests are shown for each group (pre vs post changes), as well as the p-values of the $Group \times Time$ interaction in the rm-ANOVAs. Significant effects are marked bold ($p < .05$), statistical trends are underlined ($p < .1$). PASAT = Paced Auditory Serial Addition Task, RAVLT = Rey Auditory Verbal Learning Test, TMT = Trail Making Test, FAS = Fluency Verbal Test.

two groups: power variables at the sensor level, and current density variables at the brain source level. In both cases, the analysis was conducted in the aforementioned frequency bands (delta, theta, alpha, beta1, beta2, beta3). In the case of the sensor level, power values in each band were averaged across five areas: prefrontal (FP: FP1, FP2), frontal (F: F3, Fz, F4), central (C: C3, Cz, C4), parietal (P: P7, P3, Pz, P4, P8) and occipital (O: O1, Oz, O2). In the case of the brain source level, a randomization procedure was used to control the FWER (Holmes et al., 1996). 5000 random permutations were performed to construct a distribution of the maximum of the absolute r-value across all voxels under the null hypothesis. In both cases the Bonferroni correction was applied to keep the FWER at $\alpha = .05$.

5.3 Results

Cognitive Performance

Table 5.2 summarizes the scores in the cognitive assessments. A significant $Group \times Time$ ANOVA interaction appeared in the PASAT test (# errors:

$F_{1,46} = 5.42, p = .024$; time: $F_{1,46} = 4.97, p = .031$), showing an improvement in WM performance and processing speed for the NF group only (# errors: $t_{30} = -5.21, p < .001$; time: $t_{30} = -4.91, p < .001$). Cohen's d effect size (Cohen, 1988) revealed a medium-large effect for both the number of errors ($d = .703$) and elapsed time ($d = .673$). Note that 9 participants in the NF group did not complete the PASAT test in the initial assessment due to excessive cognitive effort, 4 of whom completed the final assessment. 3 participants in the control group did not complete the PASAT test in both initial and final assessments. No significant ANOVA interaction appeared in the other variables. Regarding the within-group (pre vs post) changes, the number of recognized words increased in the RAVLT test for the NF group ($t_{39} = 3.28, p < .005$). Interference score in the STROOP test was not significantly modified for any group. Both parts of the TMT test improved for the NF group (part A: $t_{37} = -1.95, p = .059$; part B: $t_{37} = -2.85, p < .01$). The NF group also improved the number of evoked words in the FAS test ($t_{38} = 2.61, p < .05$). No significant changes were found for the control group.

Power EEG Analysis in the trained parameter

The analysis of the pre-post enhancement in the trained parameter (power in the individual UA band averaged across the feedback electrodes: P3, Pz, P4, O1, O2) revealed a no significant $Group \times Time$ ANOVA interaction for the resting state activity. However, a statistical trend between the pre and post measurements was found in the NF group ($t_{39} = -1.72, p = .093$), with an average increase of 22%. Regarding the task-related activity, a significant $Group \times Time$ interaction appeared ($F_{1,58} = 14.88; p < .001$). Post-hoc t-tests showed a significant pre vs post difference for the NF group only ($t_{39} = -5.44, p < .001$), with an average increase of 56%. No significant change was found for the control group in either resting state or task-related activity. Note that groups did not differ statistically in initial IAF. Mean $\pm$ SD IAF measured in resting state activity was 9.81 ± 0.17 Hz for the NF group and 9.79 ± 0.25 Hz for the control group (t-test for independent samples, $t_{58} = .075$, $p = .94$); in task-related activity it was 9.71 ± 0.19 Hz for the NF group and 9.64 ± 0.24 Hz for the control group ($t_{58} = .21$, $p = .83$). Furthermore, IAF did not change significantly after the NF training for either group. The across- and within- session enhancement was measured for the NF group (see Figure 5.2). Trend analysis revealed a significant UA power increase across the NF sessions in both resting state ($t_{39} = 2.56, p = .014$) and task-related activity ($t_{39} = 4.04, p < .001$). Regarding the within-session enhancement, a significant power increase between the pre- and post- NF screenings appeared in resting state ($t_{39} = -3.10, p < .005$), with an average

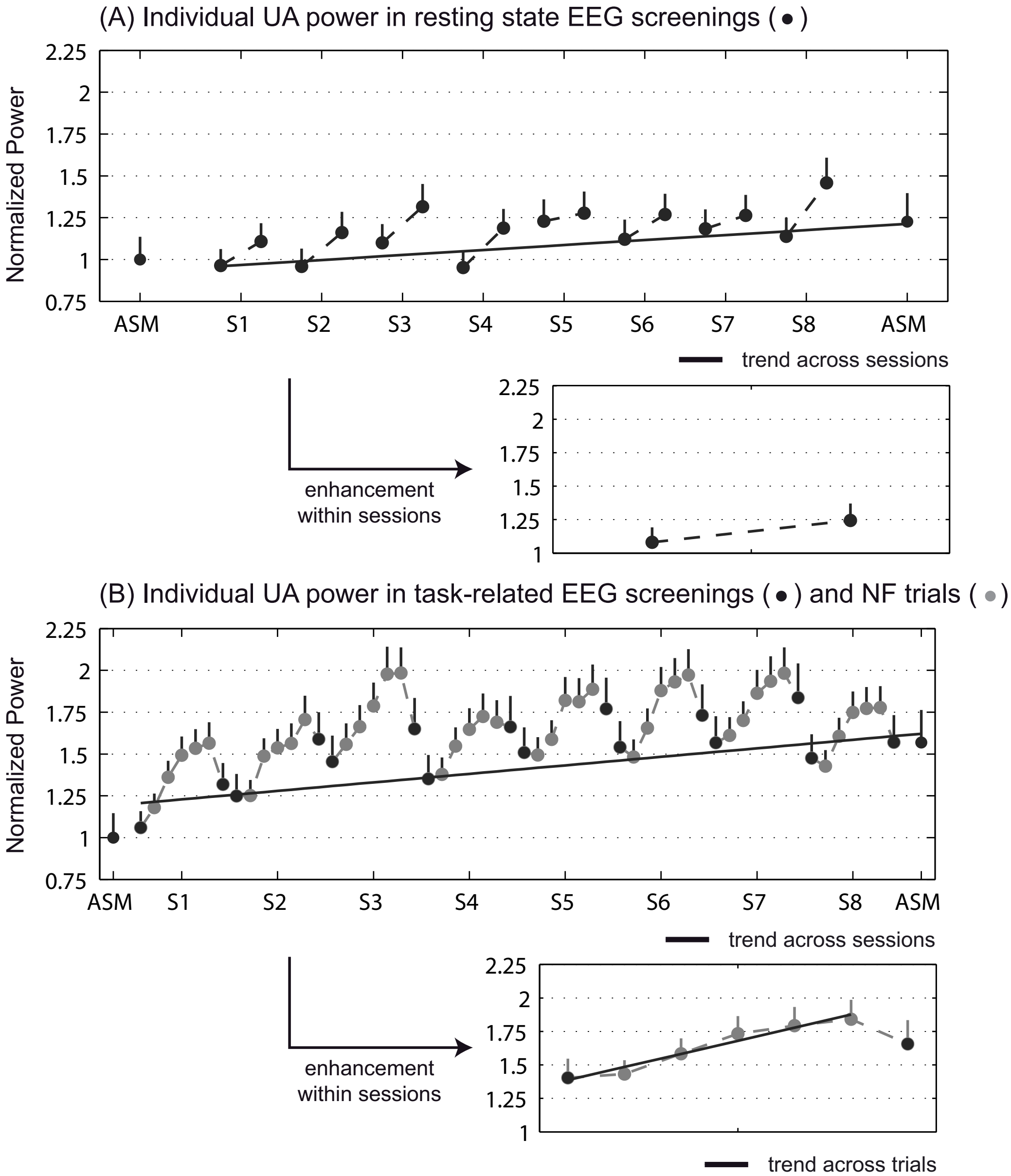

Figure 5.2: Individual UA power (mean + SEM) averaged across the feedback electrodes (P3, Pz, P4, O1, O2) for the NF group in the initial and final EEG screenings, and during the NF sessions. (A) displays the resting state EEG screenings, and (B) the task-related EEG screenings and NF trials. Data was normalized to the power in the initial screening. Right figures display the power enhancement within sessions, in which in the EEG data of the NF sessions was averaged across sessions. Dark and light gray dots depict EEG screenings and NF trials, respectively, and gray line the relevant trend measurements.

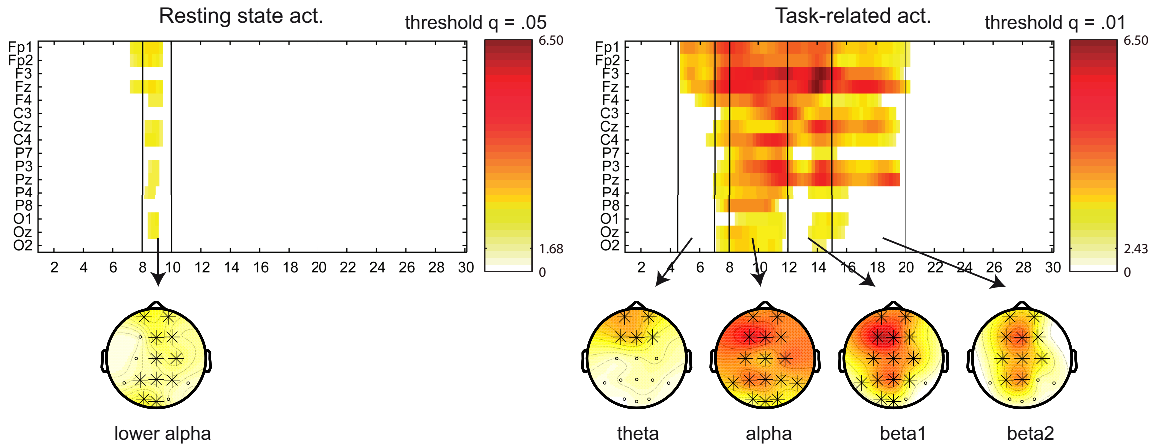

Figure 5.3: Sensor x frequency maps displaying the significant clusters (in the power spectra) for the NF group in the within-group (pre vs post) comparison. Left figure displays the resting state activity, and right figure the task-related activity. Significant clusters are shown at a given q threshold. X axis shows the frequency bins in the (1-30 Hz) frequency range, whereas Y axis shows the sensor locations. Topoplots are displayed in the frequency bands with power changes above the q threshold (in significant clusters), and the involved sensors are marked with a cross. Color scale represent t-values, indicating a power increase after the NF training.

increase of 15.1%; as well as in task-related activity ($t_{39} = -5.72, p < .001$), with an average increase of 16.1%. Trend analysis revealed a significant power increase across the NF trials ($t_{39} = 7.81, p < .001$).

Power EEG Analysis in the Sensor x Frequency domain

We have adjusted the frequency bands according to the results obtained in this analysis as follows: delta (1-4 Hz), theta (4.5-7 Hz), alpha (8-12 Hz), beta1 (12-15 Hz), beta2 (15-20 Hz) and beta3 (20-30 Hz). Regarding the power changes in the between-group (NF vs control) comparison, a cluster appeared in the (5-9 Hz) frequency range for the resting state activity ($p = .008$), indicating a power increase for the NF group in theta, apparent in frontal and central locations, and lower part of alpha (8-10 Hz), in frontal, central and parietal locations. A cluster was also found in task-related activity covering the (5.5-12 Hz) range ($p < .0001$), indicating a power increase for the NF group in theta, apparent in frontal locations, and alpha, in frontal, central and parietal locations. Figure 5.3 displays sensor x frequency maps of the power changes (pre vs post NF training) for the NF group (note that no significant clusters were found pre vs post for the control group). Resting state activity showed a cluster in the (7-9.5 Hz) range at a trend level (p = .073), indicating a power increase in lower alpha in all the scalp areas. A cluster in the (4.5-20 Hz) range appeared for the task-related activity ($p < .0001$), indicating a power increase in theta, apparent in frontal locations, alpha and beta1 in all the scalp areas, and beta2, apparent in frontal, central and parietal locations.

Alpha Asymmetry Analysis

No significant differences were found between groups in the initial asymmetry scores. We applied t-tests on the initial scores (for each area of the scalp) to test for null asymmetry scores within each group. No significant results appeared after strict control of the type I error (see discussion). Regarding the pre-post changes in asymmetry scores, no significant $Group \times Time$ ANOVA interaction was found in any area of the scalp, as well as no significant pre vs post differences within each group.

EEG Analysis at the Brain Source Level

A significant effect was found for the NF group only (pre vs post NF training) in task-related activity, measured in the alpha band (8-12 Hz), see Figure 5.4. 42 voxels showed a current density increase (threshold $t = 3.37$, $\alpha = .05$). The current density increase was localized in the subgenual anterior cingulate cortex, sgACC (BA 25; XYZ[2] $= 0, 5, -5$; $t = 4.54$), subcallosal gyrus (BA 34; XYZ $= -10, 5, -15$; $t = 4.35$), parahippocampal gyrus (BA 28; XYZ $= -15, -5, -15$; $t = 4.13$), anterior cingulate cortex, ACC (BA 32; XYZ $= -5, 20, -10$; $t = 4.11$) and rectal gyrus (BA 11; XYZ $= -5, 15, -20$; $t = 4.02$).

Correlation Analysis: EEG vs behavioral variables

No significant correlation was found between the clinical and EEG variables at study entry. Significant correlations were found (on change scores) between the elapsed time variable of the PASAT test and EEG variables at both the sensor and source space level for the NF group only, measured in task-related activity. Regarding the sensor level, a positive correlation appeared in the initial scores between the beta2 (15-20 Hz) power in parietal area (P: P7, P3, Pz, P4, P8) and the elapsed time ($r_{29} = 0.64, p = .029$),

[2]MNI (Montreal Neurological Institute, Canada) coordinates are used in this chapter.

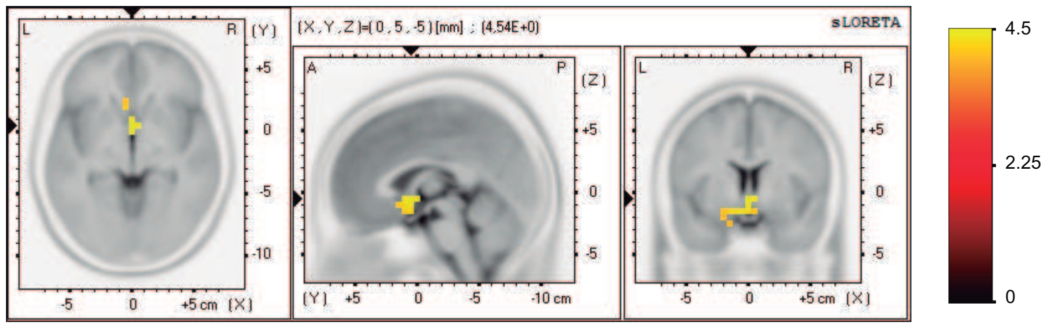

Figure 5.4: Effect of the NF training at brain source level for the NF group. Voxels showing a significant current density increase (pre vs post NF training) are displayed, measured in alpha band (8-12 Hz) in task-related activity. Axial (left), sagittal (middle) and coronal (right) sections of sLORETA are displayed through the voxel with maximal t-value. Color scale represent t-values, indicating a current density increase after NF training.

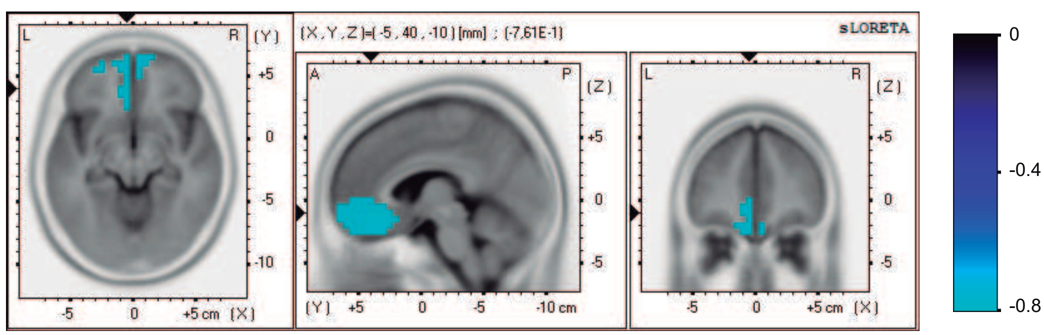

Figure 5.5: Correlation analysis for the NF group at the brain source level between the pre vs post increase in the elapsed time variable of the PASAT test and the increase in current density, measured in beta3 band (20-30 Hz) in task-related activity. Axial (left), sagittal (middle) and coronal (right) sections of sLORETA are displayed through the voxel with maximal absolute r-value. Color scale represent r-values, with negative values indicating a positive correlation between the current density increase and the improvement in processing speed (note the inverse relation between the elapsed time in the PASAT test and processing speed).

i.e., higher beta2 power in parietal locations correlated with slower processing speed. The analysis of the pre vs post change scores revealed negative correlations between the power increase in each beta sub-band in prefrontal area (FP: FP1, FP2) and the increment in elapsed time: beta1 (12-15 Hz, $r_{29} = -0.68, p = .007$), beta2 (15-20 Hz, $r_{29} = -0.65, p = .019$) and beta3 (20-30 Hz, $r_{29} = -0.79, p < .0001$). Thus, the beta enhancement in prefrontal locations correlated with the improvement in processing speed. Regarding the brain source level, the analysis of the pre vs post change scores revealed a negative correlation between the current density increase measured in the beta3 band (20-30 Hz) and the increment in elapsed time, see Figure 5.5. 133 voxels were significant ($\alpha = .05$), which were localized in the ACC (BA 32; XYZ $= -5, 40, -10$; $r = -0.761$), medial frontal gyrus (BA 11; XYZ $= -5, 35, -15$; $r = -0.757$), medial frontal gyrus (BA 10; XYZ $= -10, 40, -10$; $r = -0.755$), pregenual ACC, pgACC (BA 24; XYZ $= -5, 30, -5$; $r = -0.747$) and subgenual ACC, sgACC (BA 25; XYZ $= -5, 25, -20$; $r = -0.741$). Thus, the current density increase in the aforementioned regions correlated with the improvement in processing speed. No significant correlations were found for the control group.

5.4 Discussion

The objective of the current work was to explore whether the cognitive symptoms of patients with major depressive disorder (MDD) can be alleviated by EEG-based NF training. Depression is associated with cognitive deficits such as decreased working memory (WM) and attention, among others, which have a clear-cut impact on social and occupational functioning (Gotlib and Joormann, 2010, Castaneda et al., 2008, Austin et al., 2001). We hereby explored the application of a subject-specific NF protocol based on upper alpha up-regulation to improve WM performance in patients with MDD. The rationale beyond this protocol consists in evidences showing the relation between alpha oscillations and WM performance through inhibitory mechanisms (Freunberger et al., 2011, Klimesch et al., 2007). This NF protocol has obtained promising results in healthy users (Escolano et al., 2011, Nan et al., 2012). Recent evidences suggest that the WM deficits in depression (biases towards negative emotions) may not only be correlates of depression but also increase the vulnerability and recurrence to depression (Gotlib and Joormann, 2010, Levens and Gotlib, 2010). Thus this NF protocol has potential to improve depressive symptoms.

Cognitive performance

WM performance and processing speed (PASAT test) were significantly improved for the NF group in comparison with the control group, showing medium-large effect sizes. While positive findings had been already reported in healthy users (Escolano et al., 2011, Nan et al., 2012) this study supports the effectiveness of such a protocol in improving WM performance in patients with MDD. Episodic memory, executive functions and verbal fluency were also improved for the NF group only as revealed by the RAVLT, TMT and FAS tests. However the improvement in these cognitive functions was not significantly superior to the improvement observed in the control group. These results suggest that the stronger effect of the NF training is specifically found in WM performance and processing speed, whereas the improvement in the latter cognitive functions is marginal and may be explained by an enhancement of cognitive processing as a whole.

EEG analysis

A pre-post enhancement was found in the trained parameter: power in the individual upper alpha band averaged across parieto-occipital locations. The NF group showed an average increase of 56% in task-related activity after the NF training. Resting state activity was also increased for the NF group, with an average increase of 22%, but failed to reach statistical significance in comparison to the control group. No significant changes were found for the control group. In addition to that, upper alpha power in both resting state and task-related activity showed an increase with the number of sessions, as well as an increase (pre vs post) within each session. Bruder et al. (2008) showed alpha power differences between responders and non-responders to selective serotonin reuptake inhibitor (SSRI), with responders showing greater alpha power in resting state at study entry, specifically measured at occipital locations. While these findings show the potential utility of the present NF protocol in improving the responsiveness to antidepressant medication, it should be confirmed in future studies directly assessing that.

Some NF studies assess the effects of the training not only in the trained parameter, but typically in a small number of pre-determined frequency bands (Escolano et al., 2011, Zoefel et al., 2011, Nan et al., 2012). Here we extended that analysis to assess the power changes in all sensors in the (1-30 Hz) frequency range by a clustering analysis, obtaining sensor x frequency maps of the power changes. We believe that the present analysis can offer a clearer insight of the electrophysiological effects. This analysis was separately applied for the two recording conditions: resting state and task-related activ-

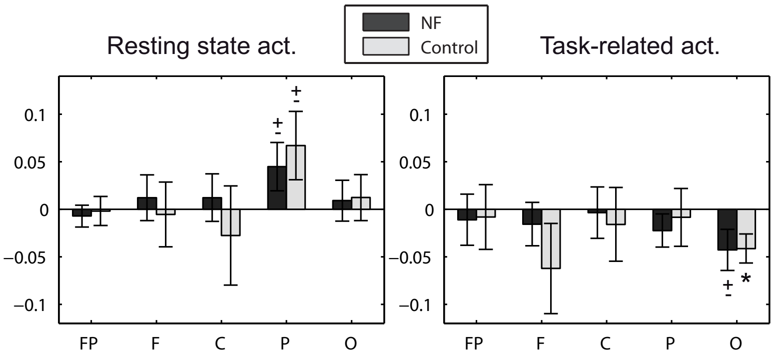

Figure 5.6: Alpha asymmetry scores measured in prefrontal (FP: FP2-FP1), frontal (F: F4-F3), central (C: C4-C3), parietal (P: (P7+P3)/2-(P8+P4)/2) and occipital (O: O2-O1) areas of the scalp. Positive asymmetry scores denote left over right activation, i.e., more alpha power in right hemisphere locations. $*$ significant effect ($p < .05$), $\pm$ statistical trend ($p < .1$). Note that statistical results are not corrected for the multiple areas.

ity. Since stronger effects were found in task-related activity in comparison to resting state, we adapted the q threshold to each recording condition to get clearer sensor x frequency maps. Please note that q threshold does not determine the type I error at cluster-level, which was set to ($\alpha = .05$) for both conditions. Significant clusters were found for the NF group only, showing a power increase after the NF training. The strongest effect in resting state activity appeared in the lower part of alpha (8-10 Hz). Task-related activity showed stronger effects in the (4.5-20 Hz) range, covering theta, alpha and the lower part of beta. These effects were apparent in anterior, central and posterior locations. Our results show the common finding that the effects of the NF training on the spectral power are not spatially or spectrally restricted to the trained locations and frequency bands, instead the training engenders profound changes of the homeostatic properties of the brain involving several locations and frequencies (Hughes and John, 1999). The strong effect in task-related activity illustrates the importance of recording EEG in several conditions to provide additional information of the underlying brain processes. This is in contrast to the common practice to study only the resting state, either eyes closed or eyes open.

Alpha asymmetry scores did not differ between groups at study entry and it did not change pre-post the study for any group. While previous studies have found a frontal asymmetry in depression (Davidson, 2004) the current study can-not assess this finding since we would need to compare our results to a control group of non-depressed participants. We investigated the initial alpha asymmetry scores for null scores, measured in five areas of the scalp (prefrontal, frontal, central, parietal and occipital). Strong asymmetry scores were found although they failed to reach statistical significance after strict control of the type I error (Bonferroni correction). Here we summarize the significant results when not correcting for the multiple areas (see Figure 5.6). Significant scores were found in posterior areas (parietal and occipital). Left-lateralized activation (more alpha power over right locations) was found in resting state in the parietal area at a trend level for both the NF group ($t_{39} = 1.76, p = .086$) and the control group ($t_{19} = 1.86, p = .077$). These results are in line with previous studies (Kemp et al., 2010). Interestingly, the opposite effect was found in task-related activity. Right-lateralized activation (more alpha power over left locations) was found in task-related activity in the occipital area at a trend level for the NF group ($t_{39} = -1.98, p = .054$), significant for the control group ($t_{19} = -2.71, p = .014$). Please note that EEG data was recorded using a single earlobe reference, but re-referenced offline to Cz. The most common approach to measure brain asymmetry to date is the use of computer-averaged ears/mastoids reference, or Cz reference (Davidson, 1998, Coan and Allen, 2004, Allen and Cohen, 2010). Although there is no agreement about a preferred montage, reference placement might be a critical issue (Hagemann et al., 2001, Allen et al., 2004a, Davidson, 2004), with unilateral references being discouraged. Thus, the alpha asymmetry effects herein reported should be taken with caution and confirmed in future studies using one of the aforementioned recording approaches.

The analysis at the brain source level (using sLORETA) revealed significant changes in current density after the NF training for the NF group only. The stronger effect was found in task-related activity for the alpha band (8-12 Hz), localized in the subgenual ACC (sgACC, BA 25) extending to the entorhinal cortex (BAs 28, 34), ventromedial prefrontal cortex (BA 32) and orbitofrontal cortex (BA 11). Notice that we are controlling for the family-wise type I error rate using a conservative method for correcting also for the multiple frequency bands (t-max permutation tests were further corrected using a Bonferroni correction for the multiple bands). Strong effects were also found in other brain structures although they failed to reach statistical significance after such a strict control of the type I error. Here we summarize the significant results when not correcting for the multiple frequency bands, which appeared for the NF group only. Regarding the resting state activity, a current density increase appeared in the pregenual ACC, pgACC (BA 24; XYZ $= -5, 35, 10$; $t = 3.25$) measured in alpha band. Regarding the task-related activity, a current density increase appeared in the sgACC (BA 25; XYZ $= 0, 5, -5$; $t = 3.03$) measured in delta (1-4 Hz), in the pgACC (BA

24; XYZ $= -5, 30, 0$; $t = 3.01$) in theta (4.5-7 Hz), and in the pgACC (BA 24; XYZ $= -5, 25, 15$; $t = 3.27$) in beta1 (12-15 Hz).

Correlation Analysis: EEG vs behavioral variables

A strong correlation was found between the processing speed (elapsed time variable in the PASAT test) and the power in task-related activity measured in the beta frequency band. The power EEG analysis revealed that higher power in beta2 band (15-20 Hz) in parietal locations positively correlated with slower processing speed at study entry. We also found that the power increase in beta band (specifically in each one of the three beta sub-bands analyzed, ranging from 12 to 30 Hz) in prefrontal locations positively correlated with the improvement in processing speed (pre vs post NF training). These results suggest that beta band is related to processing speed in different ways according to the area of the scalp involved. Furthermore, a strong correlation was found at the brain activity recorded in different scalp locations: the increase in current density measured in beta3 band (20-30 Hz) positively correlated with the improvement in processing speed (pre vs post NF training). This correlation was localized in the pgACC (BA 24) and sgACC (BA 25) extending to the ventromedial prefrontal cortex (BA 32) and further into the orbitofrontal cortex (BA 11) and frontopolar cortex (BA 10).

Beta band activity has been traditionally linked to somatosensory and motor functions but its functional role is not well understood to date (see Engel and Fries, 2010, for a review). Regarding its perceptual-cognitive role, it has been recently associated with the active continuation of the current cognitive set in tasks involving a strong top-down component (Engel and Fries, 2010). According to this theory, the brain makes predictions in beta oscillations about what it will encounter in the internal and external environment, and updates this by measuring prediction errors, which are encoded by gamma oscillations (Arnal and Giraud, 2012). A large body of research has highlighted the relation of the ACC in error monitoring and prediction of errors (Holroyd et al., 2009, Rushworth and Behrens, 2008). The improvement in processing speed after NF training may be thus explained by this relation.

The involvement of the Anterior Cingulate Cortex

The ACC is known to be linked to cognitive and emotional processes (Bush et al., 2000). Based on cytoarchitecture, lesion and electrophysiological studies the ACC has been divided into two major functional sub-divisions: a cognitive and an affective sub-divisions (Bush et al., 2000). The cognitive division is localized in the dorsal ACC (areas 24', 32'), and the affective one is localized in the rostral-ventral ACC (rostral areas 24 and 32, and ventral areas 25 and 33). Functional differences in the ACC between depressed and non-depressed subjects have been repeatedly reported (Davidson et al., 2002, Mayberg, 1997, Pizzagalli et al., 2001). On one hand, decreased activation has been reported in the dorsal ACC (dorsal region of area 32; areas 24', 32'). On the other hand, increased pre-treatment activation has been found in responders (vs non-responders) to antidepressant medication in the rostral and ventral ACC (including pregenual areas 24 and 32), and it has been suggested as a predictor of treatment response (Pizzagalli et al., 2001, Mayberg et al., 1999). Pizzagalli et al. (2001) compared depressed participants showing better response to nortriptyline treatment to responders showing worse response. Participants showing a better response had higher pre-treatment theta (6.5-8 Hz) activity localized in the rostral ACC (BA 24, 32), estimated using sLORETA. In this line, the current study showed a current density increase in the rostral ACC (BA 24; XYZ $= -5, 30, 0$; $t = 3.01$) measured in the theta band (4.5-7 Hz), suggesting that the present NF protocol may increase the response to antidepressant medication. Regarding the correlation between the cognitive and EEG variables, the pregenual ACC (BA 24) and subgenual ACC (BA 25) were positively correlated with the improvement in processing speed. Interestingly, the subgenual ACC has not been traditionally linked to cognitive processing. However, recent studies demonstrate that there is an overlap of autonomic, sensorimotor, affective and cognitive processing in the midcingulate gyrus (Beissner et al., 2013) suggesting that the functional-anatomical parcellation of the cingulate gyrus is not as simple as has been assumed. The present study suggests that the subgenual ACC, apart from its well-known involvement in autonomic (Beissner et al., 2013) and emotional (Bush et al., 2000, Mayberg et al., 1999) regulation, it also is implicated in cognitive processing. Thus analogous to the midcingulate gyrus also the subgenual ACC may be involved in multiple overlapping functions.

Limitations

Due to the novelty and the exploratory character of the study, the control group designed in the present study was not optimal. On one hand, the number of subjects in the NF and control group was not balanced. We decided to use an allocation ratio 2:1 between the NF and control group since we were mainly interested on evaluating the effects of the NF on the EEG. On the other hand, participants were not randomly assigned to the experimental condition nor they were blinded with respect to the experimental condition. No randomization was used because the study was conducted in three different phases according to the participants and researchers availability (two phases for the experimental group, one phase for the control group, with each phase involving around 25 participants). Regarding the demographic characteristics, around 90% of the participants of the study followed a stable pharmacological antidepressant treatment during the study, 75% of whom consisted either on selective serotonin reuptake inhibitors (SSRI), benzodiazepines or serotonin-norepinephrine reuptake inhibitors (SNRI). Also, 80% of the participants presented comorbidity with anxiety. Further research is needed to elucidate to what extent the obtained results can be translated to a drug-free population or to a population without anxiety symptoms. The averaged severity of depression was “moderate” for both the NF and control group according to the BDI-II. However, the averaged PHQ-9 scores were slightly lower for the NF group (“moderate”) than for the control group (“moderately severe”). Nonetheless, there were no significant differences between groups in severity of depression as measured by either BDI-II or PHQ-9. The current study estimated the effects at brain source level using sLORETA (MNI-152 template) with only 16 electrodes. The spatial resolution and precision of sLORETA method could be improved by computing individual head models based on magnetic resonance imaging (MRI). A comparison of the cognitive performance with healthy subjects would have been an interesting analysis to estimate the significance of the observed effects. This analysis should be taken into account for future studies. Finally, although we have stated that the present NF protocol has the potential to improve depressive symptoms, such hypothesis can-not be corroborated in the present study since clinical variables were not assessed after NF training. While the control group used in the present study can account for practice effects in the cognitive assessments and for electrophysiological changes before and after the study, the motivation and expectations might be higher for the experimental group. Thus, the placebo effect can-not be ruled out with this experimental design. Due to the positive cognitive effects, the present NF protocol should be evaluated in future studies using stricter control conditions such as active control conditions (e.g., psychotherapy) or sham feedback. However, a sham feedback control condition may lead to ethical concerns when effective standard treatments are available (La Vaque and Rossiter, 2001).

5.5 Conclusions

This study showed that depressed patients can enhance upper alpha activity through NF training in comparison to a non-interventional control group. These effects in the power spectra were not spatially or spectrally restricted to the trained parameter, instead stronger effects appeared in the (4.5-20 Hz) range for task-related activity, covering anterior, central and posterior scalp locations. The experimental group showed a current density increase in task-related activity for the alpha band (8-12 Hz), localized in the subgenual ACC (sgACC, BA 25). A positive correlation was found for the experimental group between the improvement in processing speed and the increase of beta power at both the sensor and brain source level. Finally, the experimental group showed improved WM performance as well as processing speed, thus suggesting that the cognitive symptoms of depressed patients could be alleviated by this type of procedure.

Up to now, we have investigated the effects of the subject-specific NF protocol (upper alpha up-regulation) over parieto-occipital locations in healthy and depressed participants. Next study will investigate the effects of relative upper alpha up-regulation over fronto-central location in ADHD children. This study will extend the current analysis of the specificity by considering the subject-specific frequency bands (i.e., analysis centered to the IAF) and by assessing its within-session effects.

6 | The effect of NF in ADHD children

6.1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a behavioral disorder characterized by symptoms of inattention, impulsivity and hyperactivity according to DSM-IV (American Psychiatric Association, 1994). This disorder is one of the most common psychiatric disorders of childhood, affecting up to 5% of children worldwide (Polanczyk et al., 2007), presenting about 40-60% persistence in adolescence and adulthood (Faraone et al., 2006). Deficits in executive functioning, working memory and response inhibition have been repeatedly reported (Barkley, 1997, Martinussen et al., 2005, Castellanos and Tannock, 2002).

The most accepted treatments for ADHD are stimulant medication and behavior therapy (Barkley, 1997). Stimulant medication has emerged as the primary treatment for the core symptoms of ADHD, however some children do not respond to medication or suffer from side effects such as headache, dizziness, insomnia, anxiety and gastroenterological problems (Graham et al., 2011). In addition to that, the long-lasting effects of both stimulant medication and behavior therapy are uncertain, with some studies reporting limited effects (Wang et al., 2013, Molina et al., 2009). NF is a promising alternative treatment for ADHD (Arns et al., 2014, Loo and Makeig, 2012).

The rationale behind NF training in ADHD is the electrophysiological evidence collected over the last decades of abnormal brain oscillations in comparison to normal controls (see Barry et al. (2003), Loo and Makeig (2012) for reviews). The most reliable EEG pattern in ADHD to date is an excess of theta activity (4-8 Hz) in fronto-central sites, measured in resting state (Barry et al., 2003, Snyder and Hall, 2006, Clarke et al., 2001). Reduced alpha (8-13 Hz) and beta activity (13-30 Hz) have been commonly reported as well, thus theta/beta and theta/alpha ratios have been traditionally considered reliable measures to discriminate between ADHD and normal individuals (Barry et al., 2003, Snyder and Hall, 2006). In this direction, NF studies have mostly used standardized protocols to "correct" the aforementioned abnormal EEG patterns. The most used protocol is theta suppression/beta enhancement, usually enhancing SMR simultaneously (Loo and Makeig, 2012, Monastra et al., 2006, Arns et al., 2009).

An extensive evaluation of standardized NF protocols has been performed during the last 40 years in ADHD children, with recent reviews pointing out their effectiveness (Arns et al., 2014, Loo and Makeig, 2012, Heinrich et al., 2007). Despite the positive results, these protocols may not be able to account for the large EEG heterogeneity in ADHD (Loo and Makeig, 2012, Arns et al., 2008). In addition, recent findings challenge the theta/beta ratio as a marker for ADHD, which was found increased in only 20-30% of ADHD individuals (Arns et al., 2013, 2012). This may be partially due to a subgroup of 10-15% ADHD individuals showing increased (rather than decreased) beta activity (Clarke et al., 2013, 2001). Thus, individualized approaches may better cope with the EEG heterogeneity and improve the clinical outcome (Arns et al., 2014), which is the direction followed by some recent NF studies (Arns et al., 2012, Lansbergen et al., 2011a, Logemann et al., 2010).

The current study evaluates a subject-specific NF protocol for ADHD children. This NF protocol aims at enhancing the relative upper alpha power in fronto-central sites, individually determined for each child using the individual alpha frequency (IAF, Klimesch, 1999) as an anchor point. On one hand, this protocol has the potential to decrease the excess of absolute theta power (most reliable EEG pattern in ADHD to date) and the excess of slow frequency oscillations in general. On the other hand, this protocol builds upon the positive results of alpha-based protocols in cognitive enhancement, mainly evaluated in healthy users (Gruzelier, 2013). Thus, this NF protocol is meant to target the cognitive deficits of ADHD individuals. This study reports an open-label pilot study with 20 ADHD children who underwent 18 NF sessions. EEG was recorded pre- and post- training, and pre- and post- the training trials within each session, in both eyes closed resting state and eyes open task-related activity. A power EEG analysis assessed pre-post study and within-session effects, in the trained parameter and in all the sensors in the (1-30) Hz spectral range. Learning curves over sessions were assessed as well. Clinical and neurophysiological variables were measured pre- and post- training.

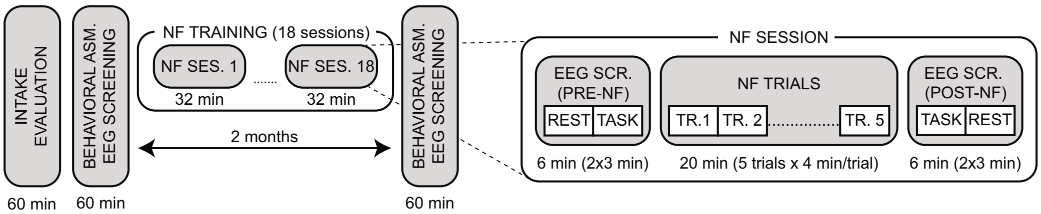

Figure 6.1: Experimental design of the study. After an intake evaluation, the children carried out an initial and final behavioral assessment (clinical and neuropsychological tests) and EEG screening within a two-months time interval. The NF training consisted of 18 sessions, which were composed of five training trials (four min each) and a pre- and post- EEG screening. The EEG screenings included eyes closed resting state activity (three min) and eyes open task-related activity (three min).

6.2 Methods

Participants

20 children with ADHD participated in the study. All children fulfilled DSM-IV[1] criteria for ADHD (American Psychiatric Association, 1994). Diagnoses were based on a semi-structured interview with the parents using the Structured Developmental History of the BASC (Reynolds, 2004). WISC-IV (Wechsler, 2003) was administered to estimate IQ. All children were drug-free and without concurring psychotherapy for at least one month before starting the NF training. Children with comorbid neurological or psychiatric disorders, or IQ < 80 were excluded from the study. Three children did not complete the study, thus the final sample consisted of 17 children (mean $\pm$ SD age: 11.8 ± 2.2 years, one girl). Seven children were diagnosed with inattentive type, ten with combined type. Families were informed about the study from local professionals in the city of Zaragoza (Spain). The experimental design was approved by the Ethical Review Board of the regional health authority and followed the Declaration of Helsinki. Parents and children signed informed consent.

Experimental design

An open-label pilot study was designed (Figure 6.1). After an intake evaluation, an initial and final behavioral assessment and EEG screening were carried out. The NF training was composed of 18 sessions, executed for two

[1]DSM was recently updated to the fifth edition (DSM-5).

months (two or three sessions per week). Each session was composed of five trials of four min each for a total of 20 min of training, and a pre- and post-EEG screening. For each EEG screening we recorded three-min of eyes closed resting state activity and three-min of eyes open task-related activity. In the latter, children faced a computer screen showing a square that changed saturation color randomly from gray to red or blue (gradually). Children were instructed to count the number of saturation changes from gray to red as a cognitive challenge (Zoefel et al., 2011).

Behavioral assessments

Parents rated the clinical conditions of the children pre- and post- the training using the following scales: (*i*) Parent Rating Scales of the BASC (BASC-PRS, Reynolds, 2004). The scores were the externalizing and internalizing problems, and adaptive skills. (*ii*) Conners' Parent Rating Scales-Revised (CPRS-R, Conners et al., 1998). The scores were the global index and DSM-IV items (inattention, hyperactivity/impulsivity and total score).

A battery of neuropsychological tests was administered to the children: (*i*) Two tests of the WISC-IV (Wechsler, 2003) evaluated working memory. Digit span consisted of sequences of numbers that had to be repeated, either in same or reverse order. Letter-number sequencing consisted of sequences of letters and numbers that had to be repeated in both numerical and alphabetical order. The test scores were the number of correct responses. (*ii*) D2 test (Brickenkamp and Zillmer, 1998) evaluated focussed and selective attention. Children crossed out target letters on a working sheet, working line by line with 20 s for finishing each line. The score was the concentration index. (*iii*) Conners' continuous performance test (CPT II, Conners and Staff, 2000) is a computerized assessment of attention-related problems. The CPT displayed letters on a computer screen, and children had to press the space bar except when the letter "X" was displayed. The test scores were the number of omission and commission errors. Paired samples t-tests were performed for pre vs post comparisons.

EEG recording and neurofeedback procedure

EEG data was recorded from 16 electrodes placed at FP1, FP2, AFz, F3, Fz, F4, FCz, C3, Cz, C4, P3, Pz, P4, O1, Oz and O2 (subset of the 10/10 system), with the ground and reference electrodes on FPz and on the left earlobe, respectively. EEG was amplified and digitized using a g.tec amplifier (Guger Technologies, Graz, Austria) at a sampling rate of 256 Hz, power-line notch-filtered at 50 Hz and (0.5-60) Hz band-pass filtered. EEG recording and the

NF procedure were developed using software of *Bit&Brain Technologies, SL*.

The NF training focused on the increase of the relative upper alpha power, averaged over fronto-central sites (AFz, F3, Fz, F4, FCz and Cz, referred to as feedback electrodes). The description of the NF technique can be found in Chapter 3.

Offline EEG pre-processing

EEG data from the EEG screenings and training trials was filtered from artifacts using a semi-automatic method based on Riemannian geometry (Barachant et al., 2012, 2013). This method was separately applied to each recording session, applied on the one hand to the resting state activity and on the other hand to the task-related activity and training trials. We first selected 15-20 artifact-free 1-s epochs by visual inspection. Covariances matrices were computed in each artifact-free epoch, and the geometric mean was computed. The remaining EEG data was then parsed into 1-s epochs using a sliding window algorithm with 30 ms overlapping. The distribution of the Riemannian distances between the geometric mean and the covariance matrix of each epoch was computed. Epochs with an absolute z-score higher than 2.5 were removed. A slight variation of this method was applied to the task-related activity and training trials to be more sensitive to non-blinking artifacts such as eyes and body movements. Initially, the extended infomax ICA (Lee et al., 1999) was applied to remove the eye blinking component and artifact-free epochs were selected by visual inspection in the sensor space. The semi-automatic method was then applied on the source space ($n - 1$ components) and clean EEG data was projected to the sensor space.

EEG analysis

Pre-post study effects assessed the power changes after the study, measured as the power comparison in the initial vs final EEG screening in both resting state and task-related activity. We performed a direct comparison in the trained parameter and an exploratory absolute/relative power spectral analysis in all the sensors in the ($\approx$ 1-30) Hz range (section 6.2).

Learning curves over sessions assessed the power changes as a function of the number of sessions, measured as the Spearman correlation between the power computed in the pre-NF EEG screening of each session (recorded before the training trials) vs the session number. We assessed the effects in resting state and task-related activity. We performed the analysis in the trained parameter and an exploratory analysis in absolute/relative power in the feedback sites and parieto-occipital sites (P3, Pz, P4, O1, Oz and O2) in the following bands: delta = (1, 3.5), theta = (IAF-6, IAF-4), lower alpha = (IAF-4, IAF), upper alpha = (IAF, IAF+2), beta1 = (IAF+2, IAF+8), beta2 = (IAF+8, IAF+14) and beta3 = (IAF+14, 30). A non-parametric randomization method using the r-max statistic was used to correct for the number of bands, i.e., to control the familywise type I error rate (FWER, Holmes et al., 1996). Following this method, the null distribution of the maximum absolute r-value across all bands was estimated by 5000 random permutations. Then the absolute observed r-value for each band was tested against the $(1-\alpha)th$ percentile of the null distribution. Bonferroni correction was further applied to control for the comparisons in absolute/relative power and the number of sensor clusters. The FWER was set at $\alpha = .05$.

Within-session effects assessed the power changes immediately after the training trials (in both resting state and task-related activity) and during training. First, the power values computed in the pre- and post-NF EEG screenings of each session were averaged across sessions. The power in the training trials were averaged across sessions as well, and further averaged across the five trials (averaged training power). Within-session effects in resting state and task-related activity were measured as the averaged pre- vs post-NF power comparison. We measured the effects during training as the averaged pre-NF power value in task-related activity (baseline) vs the averaged training power. We performed a direct comparison in the trained parameter and an exploratory absolute/relative power spectral analysis (section 6.2).

Cluster-based method for EEG spectral analysis

A cluster-based non-parametric randomization method (Nichols and Holmes, 2002, Maris and Oostenveld, 2007) was used to assess pre vs post power changes in all the sensors in the ($\approx$ 1-30) Hz range. This method is implemented in the Fieldtrip toolbox (FC Donders Centre for Cognitive Neuroimaging, Nijmegen, The Netherlands; see http://www.ru.nl/fcdonders-/fieldtrip). First, the power spectra of each subject was centered to the IAF and the (IAF-8, IAF+18) Hz range was considered. Since mean $\pm$ SD IAF was 9.25 $\pm$ 1.22 Hz, the (1.25-27.25) Hz range was covered on average. The clustering method computed the pre vs post difference by performing paired samples t-tests in the (sensor, frequency)-pairs. Those pairs exceeding a threshold ($q = .05$) were clustered on the basis of spatial and spectral adjacency, and cluster-level statistics were calculated as the sum of the t-values within every cluster. Finally, the significance probability at the cluster-level was estimated by a permutation method (Pesarin, 2001). The null distri-

	pre training	post training	t-stat	p-value	ES
Clinical scales					
BASC-PRS (T-scores)					
externalizing problems	61.44(2.94)	55.94(2.01)	$t_{16} = 3.52$	**.003**	0.85
internalizing problems	57.50(2.92)	50.41(2.23)	$t_{16} = 4.12$	<**.001**	1.00
adaptive skills	41.12(2.14)	41.53(1.92)	$t_{16} = -0.21$	.833	0.05
CPRS-R (T-scores)					
global index	68.38(2.65)	60.62(1.97)	$t_{16} = 4.86$	<**.001**	1.18
inattention (DSM-IV)	71.12(1.99)	62.65(1.82)	$t_{16} = 4.78$	<**.001**	1.16
hyperactivity/impulsivity (DSM-IV)	73.88(2.43)	64.32(1.71)	$t_{16} = 4.74$	<**.001**	1.15
total score (DSM-IV)	74.38(1.91)	64.50(1.57)	$t_{16} = 6.30$	<**.001**	1.53
Neuropsychological tests					
Digit span (WISC-IV)					
# correct responses	13.53(0.65)	15.76(0.85)	$t_{16} = -5.16$	<**.001**	1.25
Letter-number sequencing (WISC-IV)					
# correct responses	16.00(0.65)	17.65(0.66)	$t_{16} = -2.26$	**.038**	0.55
D2					
concentration index	48.76(6.44)	62.06(5.66)	$t_{16} = -3.29$	**.005**	0.80
CPT					
# omission errors	4.42(0.94)	4.79(0.98)	$t_{16} = -0.44$	.664	0.11
# commission errors	58.57(5.65)	45.10(5.51)	$t_{16} = 2.68$	**.016**	0.65

Table 6.1: Results of the clinical and neuropsychological tests pre- and post- training. BASC Parent Rating Scales (BASC-PRS) with the composite scales. Conners' Parent Rating Scales (CPRS-R) with global index and DSM-IV items. Two tests of the WISC-IV evaluating working memory: digit span and letter-number sequencing, with the number of correct responses. D2 test with concentration index. Conners' Continuous Performance Test (CPT) with the number of omission and commission errors. t- and p-values for the t-tests are provided, as well as Cohen's d effect size (ES). Significant values are marked bold (p < .05). p-values are not corrected for multiple comparisons.

bution of the cluster values was constructed by 5000 random permutations. The observed values were then tested against the $(1 - \alpha)th$ percentile of the null distribution. This method controls for the type I error rate and corrects for multiple comparisons across sensors and frequencies. The type I error at cluster-level was set to $\alpha = .05$.

6.3 Results

Behavioral assessments

The scores of the clinical and neuropsychological variables are summarized in Table 6.1. Regarding the clinical variables, BASC-PRS showed a significant decrease in both the externalizing ($t_{16} = 3.52, p = .003$) and internalizing problems scores ($t_{16} = 4.12, p < .001$), showing large effect sizes ($d \geq .85$). No significant change appeared in adaptive skills. CPRS-R showed a significant decrease in the global index ($t_{16} = 4.86, p < .001$) and in the three DSM-IV items (inattention: $t_{16} = 4.78, p < .001$; hyperactivity/impulsivity: $t_{16} = 4.74, p < .001$; total score: $t_{16} = 6.30, p < .001$), showing large effect sizes ($d \geq 1.15$).

Regarding the neuropsychological variables, a significant improvement in working memory performance appeared as measured by both the digit span test ($t_{16} = -5.16, p < .001$), showing a large effect size ($d = 1.25$), and by the letter-number sequencing test ($t_{16} = -2.26, p = .038$), which showed a medium effect size ($d = .55$). D2 test showed a significant increase in the concentration index ($t_{16} = -3.29, p = .005$), showing a large effect size ($d = .8$). The number of omission errors in the CPT test did not show a significant change. However, the number of commission errors decreased significantly ($t_{16} = 2.68, p = .016$), showing a medium-large effect size ($d = .65$).

Pre-post study effects

Mean ± SD IAF was 9.25 ± 1.22 Hz at study entry. No significant change in IAF appeared after the NF training. Trained parameter (relative upper alpha power in fronto-central sites) showed a pre-post increase in task-related activity (paired samples t-test: $t_{16} = -2.44, p = .026$), with an average increase of 13.4%. Figure 6.3A displays the results of the exploratory analysis. Significant clusters were only found in task-related activity, both in relative and absolute power. A relative power increase appeared in (IAF+1, IAF+3) Hz ($p = .039$), partially covering upper alpha and beta1. An absolute power increase was marginally significant in the same frequency range, apparent in central and parieto-occipital sites ($p = .07$). No significant effects were found in resting state.

Learning curves over sessions

Children with less than 30 s of artifact-free data in a given EEG screening of a session (in either resting state or task-related activity) were excluded from the analysis of that session. The mean ± SD number of children per session was 13.8 ± 1.3. Trained parameter (relative upper alpha power in fronto-central sites) showed a positive learning curve over sessions in task-related activity ($r_{17} = 0.62, p = .008$), see Figure 6.2. The exploratory analysis in relative power revealed a marginally significant negative learning curve in parieto-occipital sites for delta power, measured in task-related activity

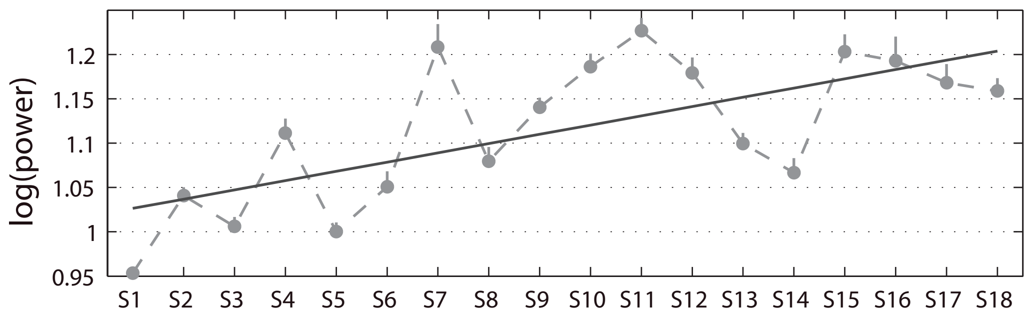

Figure 6.2: Relative upper alpha power in fronto-central sites (trained parameter) over sessions, measured in task-related activity. Dots depict the mean ± SEM power value in each session, computed in the EEG screenings recorded immediately before the training trials. Data was normalized per subject to the power in the initial EEG screening.

($r = -0.65, p = .083$). Absolute power analysis revealed a positive learning curve in parieto-occipital sites for upper alpha power, measured in task-related activity ($r = 0.75, p = .01$). No significant learning curves were found in resting state. Note that we are strictly controlling the FWER in the exploratory analysis by a randomization procedure plus Bonferroni correction.

Within-session effects

Trained parameter (relative upper alpha power in fronto-central sites) showed a within-session decrease in task-related activity (paired samples t-test: $t_{16} = 2.66, p = .017$), with an average decrease of 4.4%. No significant effects in the trained parameter appeared either in resting state or during training. Figure 6.3B displays the results of the exploratory analysis. Regarding the resting state, a relative power decrease was found in lower alpha, (IAF-2, IAF) Hz, apparent in fronto-central and parietal sites ($p = .063$), and a power increase in beta1, (IAF+2, IAF+4) Hz ($p = .083$). An absolute power decrease was found in slow frequencies (delta and theta) and lower alpha, (IAF-8, IAF) Hz ($p < .001$), and a power decrease in beta1, (IAF+4, IAF+9) Hz, in central and parieto-occipital sites ($p = .003$). Regarding the task-related activity, a power decrease was found in upper alpha measured in relative ($p = .005$) and absolute power ($p = .001$). A relative power increase was found in beta3, (IAF+12, IAF+18) Hz, apparent in parieto-occipital sites ($p = .007$), and an absolute power decrease in theta and lower alpha, (IAF-6, IAF-2) Hz ($p = .005$). During training, slow frequencies and lower alpha, (IAF-8, IAF-

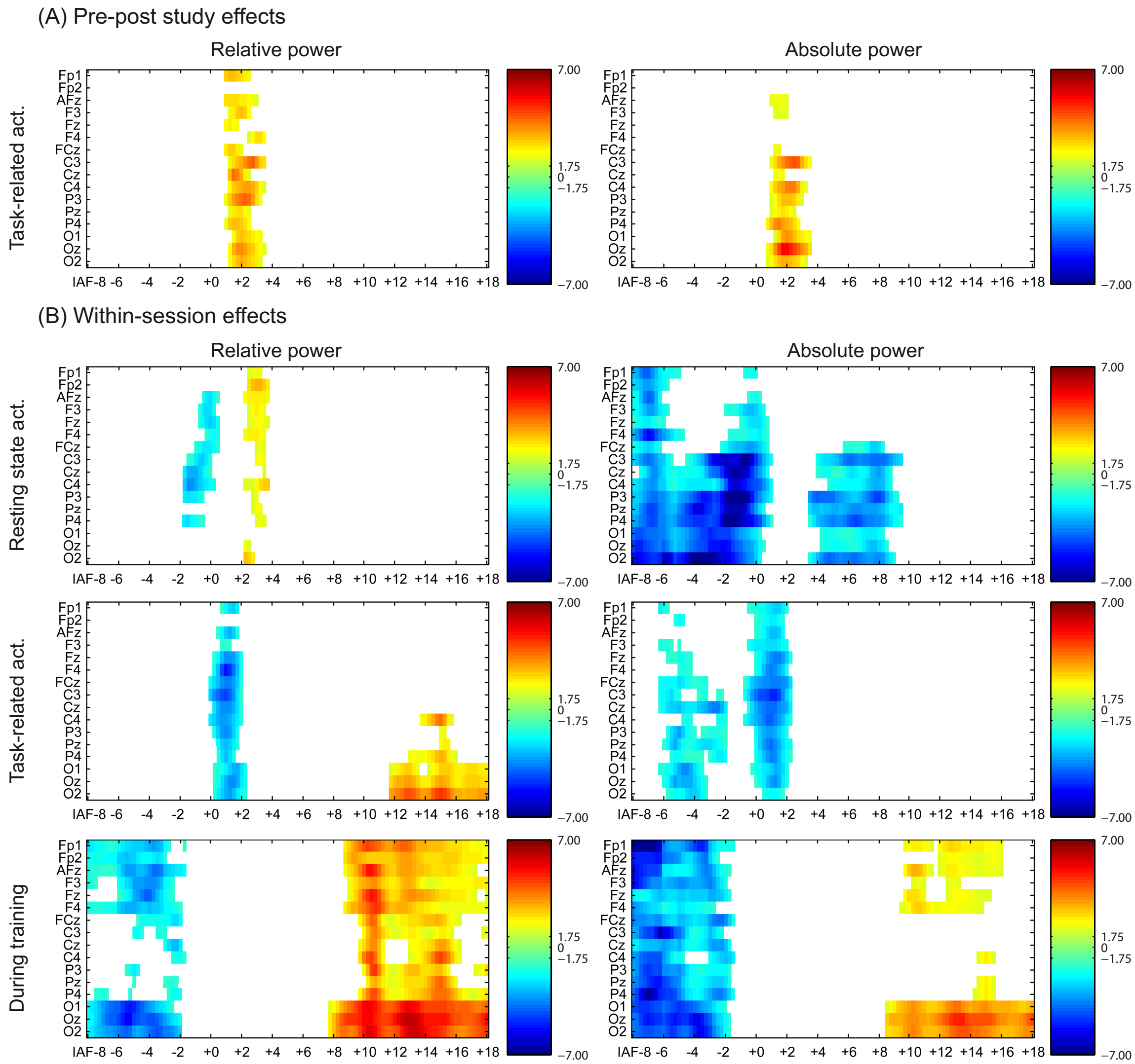

Figure 6.3: Sensor x frequency maps displaying the (A) pre-post effects and (B) within-session effects. Significant clusters (pre vs post power changes) are displayed. Left figures display the effects on relative power and right figures the effects on absolute power. Power spectra was centered per subject to the IAF. X axis shows the frequency bins in the (IAF-8, IAF+18) Hz range, whereas Y axis shows the sensor locations. Color scale represent *t*-values, with positive and negative values indicating a power increase or decrease, respectively.

2) Hz, showed a power decrease measured in relative ($p = .008$) and absolute power ($p < .001$). A power increase appeared in beta2 and beta3, (IAF+8, IAF+18) Hz, in relative ($p < .001$) and absolute power ($p = .01$).

6.4 Discussion

The current study evaluated a subject-specific NF protocol in children diagnosed with ADHD. Individualized approaches may better cope with the large EEG heterogeneity in ADHD and improve the clinical outcome (Arns et al., 2014). Recent NF studies have followed this direction (Arns et al., 2012, Lansbergen et al., 2011a, Logemann et al., 2010). Please note that in our study, "individualized NF approaches" refers to studies determining the EEG trained parameter according to the EEG activity of the individual rather than using a fixed EEG parameter for all the participants of the study. For instance, Arns et al. (2012) classified the individuals into a set of EEG clusters by a comparison to a normative database, and performed different protocols according to the cluster (e.g., theta/beta, alpha or beta suppression, SMR enhancement). Lansbergen et al. (2011a) and Logemann et al. (2010) performed a theta/beta protocol combined with SMR enhancement, in which the feedback sensors and range of frequency bands were determined by a comparison to a normative database.

The NF protocol herein proposed aimed at enhancing the relative upper alpha power in frontro-central sites, individually determined using the individual alpha frequency (IAF) as an anchor point. To the best of the authors knowledge, this is the first NF study evaluating such a protocol in ADHD individuals. In comparison to the aforementioned approaches, this NF protocol does not rely on a normative database comparison and it can address recent concerns of children with slow IAF. For example, Lansbergen et al. (2011b) found that children showing slow IAF may be clustered as an excess of theta activity. In addition to that, the use of an unique NF protocol makes possible to perform an homogenous group-level EEG analysis. On one hand, this protocol has the potential to deal with the excess of absolute theta power, which is the most reliable EEG pattern in ADHD to date (Barry et al., 2003, Snyder and Hall, 2006). Due to the $1/f$ distribution of EEG power spectra, we hypothetized stronger effects in slow frequencies (power decrease) and upper alpha (power increase). On the other hand, this protocol builds upon the positive results of alpha-based protocols in cognitive performance, mainly evaluated in healthy users (see Gruzelier (2013) for a review on NF studies on cognitive enhancement). Thus, this NF protocol has the potential to alleviate the cognitive deficits of ADHD individuals. Note that deficits in executive functioning, including working memory, and response inhibition have been repeatedly reported (Barkley, 1997, Martinussen et al., 2005, Castellanos and Tannock, 2002).

EEG analysis

An extensive power EEG analysis was conducted. We assessed pre-post study and within-session effects in all sensors in the ($\approx$ 1-30) Hz frequency range by a cluster-based randomization method, obtaining sensor x frequency maps of the power changes. Furthermore, the learning curve over sessions was assessed in fronto-central and parieto-occipital sites for a set of frequency bands covering the (1-30) Hz range. We believe that the present analyses can offer a clearer insight of the electrophysiological effects rather than traditional analyses only in the trained parameter.

Children showed pre-post effects in the trained parameter: relative upper alpha power in fronto-central sites was significantly enhanced after the NF training, measured in task-related activity. An average increase of 13% was found, as well a significant positive learning curve over sessions. In line with these results, Nan et al. (2012) performed a similar NF protocol of relative upper alpha enhancement in healthy users, obtaining a positive learning curve over sessions. We also found a significant absolute upper alpha power enhancement in parieto-occipital sites, and a learning curve over sessions. The increase of absolute upper alpha power in NF literature has been related to improvements (in healthy users) in working memory (Escolano et al., 2011) and visuospatial rotation (Zoefel et al., 2011, Hanslmayr et al., 2005). The pre-post effects in task-related activity were mainly restricted to the upper alpha band, with no significant effects in resting state. The stronger effects in task-related activity illustrate the importance of recording EEG in several conditions to provide additional information of the underlying brain processes. This is in contrast to the common practice to study only the resting state, either eyes closed or eyes open. Note that a correlation analysis was conducted between the behavioral and EEG variables, both in the initial and change scores, but no significant results were found.

The within-session effects measured the immediate effects after training in resting state and task-related activity, and the effects during training. To do so, EEG data was collected over sessions, and we compared the EEG screenings recorded immediately before vs after the training trials, and the EEG screenings recorded before vs the EEG during the training trials. A significant decrease in absolute and relative upper alpha power appeared in task-related activity, instead of the expected increase. This may be explained by an alpha “rebound” effect. While that kind of effect had been previously reported in EEG literature mainly related to motor acts in alpha or beta activity (Pfurtscheller and Lopes da Silva, 1999), a recent alpha-based NF study with post-traumatic stress disorder (PTSD) patients reported that effect in alpha activity immediately after a single session of training, pointing to homeostatic/compensatory brain mechanisms (Kluetsch et al., 2013). Regarding the resting state, an absolute power decrease was found in slow-frequency oscillations (delta and theta) and lower alpha, as well as a power decrease in lower part of beta. No significant effects in the trained parameter were found during training, however an absolute and relative power decrease appeared in slow-frequency oscillations and lower alpha, as well as an increase in upper part of beta. Thus, although the children were not able to increase the relative upper alpha during training, they showed a strong effect in slow frequencies (as hypothetized) and in upper part of beta to a lower extent. The latter effect was unexpected and should be further explored in future studies.

Behavioral assessments

Parents reported a significant reduction in the clinical symptoms of the children after the NF training. The externalizing and internalizing problems scores in the BASC test showed a significant improvement, as well as the inattention and hyperactivity/impulsivity scores in the CPRS test. The effect sizes in inattention and hyperactivity/impulsivity were 1.16 and 1.15, respectively. Regarding the neurophysiological tests, children showed a significant improvement in working memory as measured by the digit span and letter-number sequencing tests of the WISC-IV. We found a significant improvement in concentration as assessed by the D2 test. The number of commission errors in the CPT test was significantly decreased, thus suggesting an improvement in impulsivity. No significant change in the number of omission errors was found.

Interesting, slightly superior effect sizes in hyperactivity/impulsivity ($d = 1.15$) were found in comparison to literature (see Arns et al. (2009) meta-analysis). In this direction, a large body of research has hypothetized that the neuronal substrates of inhibitory mechanisms are related to alpha oscillations (Sauseng et al., 2009, Freunberger et al., 2011, Klimesch et al., 2007). Although it should be interpreted with caution, the upper alpha power enhancement herein reported may target mechanisms of behavioral inhibition, thus leading to higher outcomes in hyperactivity/impulsivity symptoms. SMR enhancement also has been traditionally hypothetized to alleviate hyperactivity. Due to the similitudes between these two protocols, the aforementioned relation may account for the clinical improvements and cognitive enhancement in ADHD. It was already pointed out by Hanslmayr et al. (2005) that the results in cognitive enhancement obtained after SMR-based NF (in healthy users) might be in part influenced by upper alpha activity. However, certainly more research is needed to elucidate the mechanisms of action underlying this protocol.

Limitations

Due to the novelty of the NF protocol in ADHD individuals an open-label pilot study was designed. The number of NF sessions was small in comparison with ADHD literature (30 to 40 sessions are usually executed). Furthermore, non-specific effects of the treatment cannot be ruled out due to the lack of a control group. The positive results of this NF protocol suggest that it should be further explored in a controlled study with a higher number of sessions and a larger sample size. Note that diagnosis was based on DSM-IV (American Psychiatric Association, 1994) since it was the more recent edition at the beginning of our study, however it was recently updated to the fifth edition (DSM-5, American Psychiatric Association, 2013).

6.5 Conclusions

This study showed that ADHD children can enhance relative and absolute upper alpha activity through NF training (preliminary uncontrolled study). These effects were mainly restricted to upper alpha. Within-session analysis showed a power decrease("rebound" effect) in task-related activity, with no significant effects during training. In addition, an absolute power decrease appeared in slow-frequency oscillations (note that ADHD children commonly show an excess of slow-frequency activity). Regarding the behavioral measurements, parents rated a clinical improvement in children regarding inattention and hyperactivity/impulsivity, and neurophysiological tests showed an improvement in working memory, concentration and impulsivity (decreased number of commission errors in a continuous performance test). These results suggest that the current protocol is effective in improving several measures of clinical outcome and cognitive performance in ADHD, thus a controlled evaluation seems warranted.

7 | Conclusions

This thesis has addressed the design of a subject-specific NF approach in a unified framework, and has shown its feasibility by implementing three different NF studies of upper alpha up-regulation for cognitive enhancement in healthy subjects, depressed patients and ADHD children.

7.1 A subject-specific NF approach

In order to design of a subject-specific NF approach, we first identified some "methodological principles" applied in the field of BCI in terms of signal processing methods. Note that BCIs have extensively make use of individualized methods for each subject and time of use of the technology. We consider that the main issues that a subject-specific NF approach should take into account are the artifact filtering, the individualization of the EEG brain patterns of interest (both among subjects and over sessions) to deal with the inherent large inter-subject and inter-session variability, and the development of post-analysis methods that take into account these individualized EEG patterns.

Below we describe an overview of the state of the art concerning these issues (within NF techniques) and the solutions developed in this thesis. Since we implemented a NF protocol of individual upper alpha up-regulation, these solutions are oriented towards alpha activity. However it is important to keep in mind that this approach could be adapted to other brain patterns, although this may require different implementations.

Artifact filtering. Few NF techniques deal with the artifact filtering. For example, Zoefel et al. (2011) performed a threshold-based detection in time domain, stopping the feedback when a blinking artifact was detected. This may reduce the effective time of training. Other techniques include low and high frequency oscillations as additional feedback so the subjects can potentially learn to reduce them (Kober et al., 2014). This may make the training more complex for the subjects and seems not well suited for some types of artifacts (e.g., eyes blinking is a natural body system). We developed a real-time artifact filtering method for the blinking artifacts based on Independent Component Analysis (ICA, Hyvarinen, 1999). Note that eyes blinking is a natural body system with high occurrence rate and may distort the alpha activity, specially in frontal electrodes (Delorme et al., 2007). This filter is re-computed per subject and session to deal with the different spatial distribution of this blinking (inter-subject variability) and, for example, to deal with the slight changes in electrode positions over sessions (inter-session variability). Thus this filter might favor the learning of the self-regulation process by proving the subjects with more accurate feedback and/or more time of effective training. Finally, this filter might be of special interest for NF studies targeting frontal locations such as our study with ADHD children.

Individualization of brain patterns. The signal processing methods should consider subject-specific EEG brain patterns. In addition, these methods should adapt to the temporal evolution of the brain patterns of each subject, which is commonly implemented in NF literature as a baseline computation before online training. While many NF techniques re-compute the baseline activity of the rhythms over the sessions (Zoefel et al., 2011, Nan et al., 2012, Kober et al., 2013), there is a trend in alpha-based NF procedures in recent years towards the individualization of the alpha frequency by using the Individual Alpha Frequency (IAF, Klimesch, 1999). Some of them compute IAF in resting state conditions (Hanslmayr et al., 2005, Nan et al., 2012, Alexeeva et al., 2012), which may not take into account the inter-task IAF variability (Haegens et al., 2014). Others compute it in task-related activity (Zoefel et al., 2011), which may not be accurate in some subjects due to the well-known alpha attenuation phenomenon during active brain processing. We developed a novel procedure combining resting state and task-related activity which might better deal with the inter-subject variability. We also re-computed the baseline working level of individual upper alpha for each session, measured in task-related activity, in order to accommodate to the temporal evolution of alpha (e.g., dependent on psychological state, outcome of the self-regulation process).

Post-analysis of the effects on the EEG. Due to the individualization of brain patterns the developed post-analysis (applied to the EEG data of the three NF studies) measured the effects on the subject-specific brain patterns in both resting state and task-related activity, systematically investigating the effects after the study (pre-post study effects), the immediate effects after the training trials (within-session effects) and the effects over the sessions (trend or learning curve over sessions). Note that a recent review encouraged the use of these metrics (Gruzelier, 2014).

In addition to this, we performed an extensive evaluation on the EEG by measuring the effects in non-trained patters (specificity of the training), the effects during the execution of a mental rotation task (transfer effects) and the effects at brain source level. We below outline some methods used throughout the manuscript in the different NF studies. We proposed to use an offline artifact filtering method based on Riemannian geometry (Barachant et al., 2012, 2013). Following this method, the EEG data (of a given session) can be filtered from artifacts by manually selecting a small of artifact-free epochs (15-20 epochs). This may be a robust method which seems less time-consuming than traditional visual inspection in clinical practice. We proposed the use of a cluster-based randomization procedure to assess the EEG power changes in all the spectral range and sensors, obtaining sensor-frequency maps of the power changes (Nichols and Holmes, 2002, Maris and Oostenveld, 2007). Note that traditional NF studies assess the effects of the training in a small number of pre-determined frequency bands (Zoefel et al., 2011, Nan et al., 2012). While this analysis has been extensively used in BCIs to obtain time-frequency maps (e.g., in motor imagery tasks), its application in NF could provide insights of the specificity of the training in the electrophysiology. We used sLORETA to study the effects at brain source level (Pascual-Marqui, 2002, 2007). The effects at brain source level are not typically assessed, however they might be of special interest for some clinical disorders in which abnormal regulation of brain structures is known, for example the ACC disregulation in depressed patients (Pizzagalli et al., 2001).

7.2 NF studies for cognitive enhancement

We implemented a subject-specific NF protocol of upper alpha power upregulation for cognitive enhancement, and performed three studies including healthy and clinical population: patients with major depressive disorder and children with ADHD. We were interested in evaluating whether upper alpha power could be enhanced by means of NF training, and if so, whether it could lead to either enhanced cognition or improvements in clinical outcome. Below we summarize the studies with the main results and contributions.

NF study on healthy subjects This study investigated the NF effects on healthy participants following a single session of training (25 minutes) and controlling for non-specific factors (double-blind sham-controlled study). A

NF protocol of individual upper alpha up-regulation over parieto-occipital locations was performed. Ten participants were assigned to the experimental group and nine to a sham-feedback control group. We assessed immediate effects after the training and one-day lasting effects on the EEG. In addition, we assessed the changes in the EEG power time-course between the pre- and post- execution of a mental rotation task. The objective of the latter task was to investigate whether the NF training increased pre-stimulus upper alpha power (increasing the desynchronization as well), which is suggested to be related to cognitive performance (Klimesch et al., 2007). These metrics were computed in the trained parameter (upper alpha power) as well as in the (IAF-4, IAF+4) Hz range, thus covering lower alpha 1, (IAF-4, IAF-2) Hz; lower alpha 2, (IAF-2, IAF); and lower beta (IAF+2, IAF+4) Hz.

Only the experimental group showed increased upper alpha power (in task-related activity) immediately after the training, as well as increased lower alpha 2 power. The stronger effects appeared in posterior areas of the scalp. Resting state activity was not significantly modified for any group, which suggests that this protocol presents lower effects on resting state. In addition to that, the experimental group presented higher pre-stimulus upper alpha power during the post- execution of the mental rotation task, and consequently higher desynchronization. In relation to other single-session NF studies, Hanslmayr et al. (2005) showed increased pre-stimulus during the execution of a similar mental rotation task after one training session. Ros et al. (2010) also showed EEG changes after alpha-based training over the sensorimotor cortex and an increase in corticospinal excitability. Taken together, these studies suggest that one session of NF training can produce significant effects at electrophysiological level immediately after training. Behavioral analysis showed a more prominent improvement for the experimental group in some cognitive functions (working memory, episodic memory and executive functions), however this improvement was not superior to the one observed for the control group, with the exception of executive functions, which was significantly improved for the experimental group. These results might be explained by a strong learning effect due to repeated measurements and by the short duration of the training. A higher number of training sessions seems thus necessary to yield significant behavioral differences between groups and to increase the effects on the EEG.

NF study on depressed patients This study investigated the NF effects on patients with major depressive disorder (MDD). A NF protocol of individual upper alpha up-regulation over parieto-occipital locations was performed. 40 patients were assigned to a eight-session training program and were compared to 20 participants in a non-interventional group. A power EEG analysis and an alpha asymmetry analysis were conducted at the sensor level. sLORETA was used to assess the effect at brain source level. Correlation analysis between the clinical/cognitive and EEG measurements was conducted at both the sensor and brain source level.

The experimental group showed increased upper alpha power pre-post study, measured in task-related activity. These effects were not spatially or spectrally restricted to the trained parameter. We extended the EEG power analysis to all sensors in the (1-30 Hz) frequency range by a clustering analysis (Maris and Oostenveld, 2007), obtaining sensor-frequency maps of the power changes. These maps showed significant clusters for the experimental group only, with a power increase after the NF training. The strongest effect in resting state activity appeared in the lower part of alpha (8-10 Hz). Task-related activity showed stronger effects in the (4.5-20 Hz) range, apparent in anterior, central and posterior locations. Regarding the effects at brain source level, a current density increase appeared in the alpha band (8-12 Hz) for the experimental group, localized in the subgenual anterior cingulate cortex (sgACC, BA 25). A positive correlation was found for the experimental group between the improvement in processing speed and the increase of beta power at both the sensor and brain source level. Regarding the behavioral effects, we found an improvement in working memory performance and processing speed for the experimental group in comparison to the control group, showing medium-large effect sizes.

The objective of this study was to evaluate whether this NF protocol could improve working memory performance in depressed patients, thus alleviating the cognitive deficits of these patients (Gotlib and Joormann, 2010, Castaneda et al., 2008, Austin et al., 2001). To the best of our knowledge, this is the first NF study exploring the cognitive effect of working memory entrainment in depressed patients. Note that recent evidences suggest that the working memory deficits in depression may not only be correlates of depression but also increase the vulnerability and recurrence to depression (Gotlib and Joormann, 2010, Levens and Gotlib, 2010). Thus this NF protocol has potential to improve depressive symptoms.

NF study on ADHD children This study investigated the NF effects on children diagnosed with ADHD. We performed a NF protocol of relative upper alpha power enhancement over fronto-central locations. 20 children underwent 18 training sessions (preliminary uncontrolled study). A power EEG analysis assessed pre-post study and within-session effects. Learning curves over sessions were assessed as well. Clinical and neurophysiological variables were measured pre- and post- training.

Children showed increased relative and absolute upper alpha power pre-post study, measured in task-related activity, as well as a positive learning curve over sessions. The analysis of within-session effects showed an upper alpha power decrease ("rebound" effect) in task-related activity, similarly to other NF studies (Kluetsch et al., 2013), with no significant effects during training. We further assessed pre-post and within-session power changes in all sensors in the (1-30 Hz) frequency range by a clustering analysis, in both absolute and relative power. While the pre-post effects were mainly restricted to upper alpha band, within-session analysis showed an absolute power decrease in slow-frequency oscillations (delta and theta) in both resting state and task-related activity. Parents rated a clinical improvement in children regarding inattention and hyperactivity/impulsivity. Neurophysiological tests showed an improvement in working memory, concentration and impulsivity (decreased number of commission errors in a continuous performance test).

This protocol seems effective in improving several measures of clinical outcome and cognitive performance for ADHD. This is the first NF study evaluating such a protocol in ADHD. This protocol has the potential to deal with the excess of absolute theta power (Barry et al., 2003, Snyder and Hall, 2006) and to target cognitive performance. Note that ADHD individuals show cognitive deficits (Barkley, 1997, Martinussen et al., 2005, Castellanos and Tannock, 2002). This study is in line with individualized NF protocols in children diagnosed with ADHD, which are proposed to better cope with the large EEG heterogeneity in ADHD with regard to traditional/standard approaches (Arns et al., 2012, Lansbergen et al., 2011a, Logemann et al., 2010). A controlled evaluation seems warranted due to the positive results obtained in the current study.

7.3 Summary & future work

The results show that the subject-specific NF technique was able to accommodate the large variability of the brain patterns. One important aspect of the NF framework developed is that all the steps of the procedure are fully automatic, thus this approach might be used by non-expert personnel in home settings. This fact could also be used to easily implement double-blind experimental designs. This framework could be seen as a personalized approach in line with the current trend of personalized medicine. It is important to keep in mind that this approach could be adapted towards other brain patterns (different than alpha) which thus may require a different implementation. For example, one might think about comparing the EEG power spectra of an individual (suffering from a clinical disorder) to a non-clinical population to find brain patterns deviating from the "normal" patterns. An individualized NF procedure targeting these patterns could be then performed thus hypothetizing that the "normalization" of these patterns leads to an improvement in the clinical outcome.

While the motivation for this subject-specific approach is the well-known inherent variability of EEG patterns, taking BCI discipline as a reference in terms of EEG signal processing methods, this thesis does not provide an answer about whether a subject-specific NF outperforms a generic one. A direct comparison between the two approaches (at both the behavioral and electrophysiological level) would be certainly an interesting future work.

The field of NF presents several limitations to date such as the lack of specificity and replicability of the effects at both the electrophysiological and behavioral level (Gruzelier, 2014, Vernon, 2005). We consider that these limitations might be derived (at least partially) from the use of a subject-generic approach that may not be able to deal with the inherent variability of EEG patterns. However, this hypothesis cannot be answered by this thesis (in the same line as the above discussion).

Finally, our studies show that the subject-specific NF protocol of upper alpha power up-regulation effectively enhanced upper alpha power (even in a single session of training) in healthy and clinical population, thus showing the replicability of the effects on the EEG. Note also that NF literature lacks an extensive evaluation of the EEG effects, thus the results herein presented may be of interest in the field of NF and cognitive enhancement. In addition, these studies add more evidence of the effects of this protocol at behavioral level, showing an enhancement in cognitive performance, and an improvement in clinical measures of attention/hyperactivity in ADHD children.

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